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## A Prospective Cohort Study of Patients with Peripheral T-Cell Lymphoma in the United States

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## Abstract

**Background**—Long-term survival in patients with aggressive peripheral T-cell lymphoma (PTCL) is generally poor and there is no clear consensus on initial therapy used for these diseases. We analyzed treatment patterns and outcomes in a prospectively collected cohort of patients with a new diagnosis of nodal PTCL in the United States.

**Methods**—Comprehensive Oncology Measures for Peripheral T-cell Lymphoma Treatment (COMPLETE) is a prospective multicenter cohort study designed to identify the most common prevailing treatment patterns used for newly diagnosed PTCL patients in the United States. Patients with nodal PTCL and completed records on baseline characteristics and initial therapy were included in this analysis. All statistical tests were two-sided.

**Results**—Of a total of 499 patients enrolled, 256 (51.3%) had nodal PTCL and completed treatment records. Patients received as initial therapy: doxorubicin-containing regimens (41.8%), doxorubicin + etoposide-containing regimens (20.9%), other etoposide regimens (15.8%), other single agent or combination regimens (19.2%), and gemcitabine-containing regimens (2.1%). Survival was statistically significantly longer for patients who received doxorubicin (log-rank  $P = .03$ ). After controlling for disease histology and International Prognostic Index, results showed a

trend toward significance in mortality reduction in patients who received doxorubicin compared to those who did not (hazard ratio = 0.71, 95% confidence interval = 0.48 to 1.05,  $P = .09$ ).

**Conclusion**—There is no clear standard of care in the treatment of PTCL in the United States. While efforts to improve front-line treatments are necessary, anthracyclines remain an important component of initial therapy of curative intent.

### Keywords

prospective studies; cohort studies; lymphoma; T-cell; peripheral; drug therapy; anthracyclines; treatment outcome

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## Introduction

The peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of aggressive malignancies derived from mature (post-thymic) T-lymphocytes that comprise between 5% and 10% of all non-Hodgkin lymphomas (NHLs) in Western countries.<sup>1,2</sup> Nodal PTCLs are the most common of the PTCL subtypes and include: peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL).<sup>3,4</sup> While PTCL-NOS is the most common of the nodal PTCL subtypes, representing roughly 25% of all PTCLs, it is largely a diagnosis of exclusion that is made when typical features of better defined PTCL subtypes are not present.<sup>5</sup> Less common PTCLs include extranodal and leukemic PTCLs such as extranodal NK/T-cell lymphoma, T-cell prolymphocytic leukemia, and hepatosplenic T-cell lymphoma, among others.<sup>6</sup>

Most clinical practice guidelines recommend initial treatment of the nodal PTCLs either on a therapeutic clinical trial or with regimens that were initially developed for patients with B-cell lymphoma, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).<sup>6–8</sup> However, the use of CHOP in PTCL has been associated with suboptimal 5-year overall survival rates ranging from 32% to 43% for PTCL-NOS, and 32% to 36% for AITL.<sup>4,9–11</sup> A notable exception to the poor long-term prognosis associated with CHOP treatment in PTCL is ALK+ ALCL, which is associated with 5-year overall survival up to 70% after CHOP.<sup>4,12</sup> In an effort to improve upon the poor results seen in PTCL-NOS and AITL, hematopoietic stem cell transplantation (HSCT) has been proposed for patients achieving complete remission after induction therapy; however, there are no randomized trials demonstrating a survival benefit for HSCT in this setting.<sup>13–15,16</sup>

To better understand the clinical characteristics, treatment patterns, and outcomes in patients with PTCL, the Comprehensive Oncology Measures for Peripheral T-cell Lymphoma Treatment (COMPLETE) study was initiated in 2010 (NCT01110733). Herein, we present the first publication of the treatments administered to COMPLETE study enrollees, focusing on those with aggressive nodal PTCL subtypes.

## Methods

### Study Design

COMPLETE is a prospective multicenter cohort study of patients with newly diagnosed PTCL in the United States. The primary objective of the study was to describe, in detail, patterns of care for PTCL patients. Secondary objectives were to document outcomes, identify factors influencing treatment decisions, determine incidence and severity of selected treatment toxicities and identify supportive care received (protocol available online).

### Ethics

The protocol was approved by the institutional review board (IRB) of each participating institution. All study participants or participants' guardians gave written informed consent before study entry.

### Study Eligibility

Patients with a new diagnosis of histologically confirmed PTCL were eligible for enrollment in the COMPLETE study until 30 days after initiation of the first lymphoma directed therapy. The following T- and NK-cell malignancies were excluded from COMPLETE: Precursor T/NK neoplasms, T-cell large granular lymphocytic leukemia, mycosis fungoides (other than transformed mycosis fungoides), Sézary syndrome, and primary cutaneous CD30+ disorders. Patients participating in clinical trials were not excluded from participation in COMPLETE. No specific target for enrollment was pre-specified given the lack of prior studies to inform such projections.

### Data Collection and Review for Accuracy

De-identified data were regularly uploaded onto the study server from each enrolling site, as new data became available. Data entered on the web-based server were subjected to automated error checking that looked for logical inconsistencies, out of range values and missing data. Verification of data accuracy was performed by either the treating physician or site principal investigator, after which the data was locked. Central review of the locked data was performed by a steering committee of experts in PTCL and queries were generated to verify any data inconsistencies. A separate analysis was performed to verify the accuracy of the histologic data entered at each site through comparison of the uploaded histologic data to the diagnostic pathology reports.<sup>17</sup>

### Cohort Selection

Due to the variable natural history and treatments used for the various PTCL subtypes, the study population presented herein was confined to the nodal PTCL population with a poor prognosis: AITL, PTCL-NOS, and ALCL (ALK-, and ALK+ with international prognostic index [IPI] 2–5). For patients with ALCL, we excluded patients with ALK+ disease and a low IPI score from our analyses given their superior prognosis compared to the other nodal PTCLs in the cohort.<sup>18</sup> The remaining patients were stratified into initial treatment groups based on the type of therapy received. The primary outcomes of interest were response rates and overall survival.

## Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics of the study cohort. For categorical and ordinal variables, frequencies and percentages were calculated. For continuous variables, descriptive statistics (number of patients, mean, median, standard deviation and range) were provided. Null hypothesis testing utilized chi-square, t-test and other non-parametric tests as required, with a two tailed p value of 0.05 to reject the null hypothesis. Survival-based analyses were performed using Kaplan-Meier methodology with censoring as appropriate and evaluated using a log rank test with a two tailed p value of 0.05 to reject the null hypothesis. Multivariable Cox regression was used to assess the relationship between pre-specified variables and overall survival. Hazard ratios and their 95% confidence intervals were also calculated. Non-significant variables (e.g.  $p > 0.05$ ) were not removed from the final models. The assumption of proportional hazards for the multivariable Cox regression models was assessed using a test based upon weighted Schoenfeld residuals versus log(time). All analyses were performed using R version 3.1.0 or greater (The R Foundation for Statistical Computing - <http://www.r-project.org/>).

## Results

A total of 499 patients were enrolled in the COMPLETE study between February 2010 and February 2014 from 55 academic and community sites located throughout the United States. Locked baseline records were available for 440 patients (88.2%). Patients with a diagnosis of ALCL, AITL, or PTCL-NOS comprised roughly two-thirds of the overall cohort of patients with locked baseline records ( $n = 287$ , 65.2%). After excluding patients with ALCL, AKL+ disease with an IPI of 0–1 and patients who discontinued the study for reasons other than death, locked baseline records and treatment records were available for 275 and 256 patients, respectively. The principal reason patients were removed from the baseline and treatment analyses was due to other PTCL histology ( $n = 150$  patients). A total of 198 patients had year one follow-up records, and 119 patients had year two follow-up records (Figure 1).<sup>19</sup>

### Patient Characteristics

Baseline characteristics of the patients with nodal PTCL are presented in Table 1. Consistent with data from the Surveillance, Epidemiology, and End Results (SEER) Program,<sup>20</sup> a sizable proportion of patients were 65 years of age or older (45.1% and 44.7% for COMPLETE and SEER patients, respectively); the majority were male (66.3% and 58.9%, respectively), white (77.3% and 76.2%, respectively), and had advanced stage (Ann Arbor stage III/IV) disease (76.5% and 61.4%, respectively). The diagnosis of PTCL-NOS was roughly twice as frequent as ALCL or AITL (51.3% and 49.9%, for COMPLETE and SEER patients, respectively). Characteristics of COMPLETE patients were also comparable to patients enrolled in the International T-Cell Lymphoma Project<sup>4</sup> (ITCP): median age (63.1 vs. 62), Stage III/IV (76.5% vs. 74.0%) and male sex (66.3% vs. 61.9%).

### Treatment Patterns

The intent of therapy, as defined by the treating investigator, was cure in 86.9% of the patients, while palliation was the intent in the remaining 13.1%. A slightly higher proportion

of patients given doxorubicin were treated with curative intent (94.4%), compared to those who did not receive doxorubicin (83.3%), but a substantial majority in both sub-groups were treated with curative intent. The top reasons for selection of a specific first-line regimen by the treating physicians were: PTCL subtype (62.5%), clinical data from the literature (55.3%), and patient age (37.9%). Cost or insurance coverage was a factor in treatment decisions for only two patients (<1.0%).

Initial treatment strategies included doxorubicin in 41.8% and doxorubicin + etoposide in 20.9% (Figure 2). The remaining patients received a variety of etoposide-based combination or single agent regimens (15.8%), other single agent or combination regimens (19.2%), or gemcitabine-based regimens (2.1%). Eight patients received rituximab as part of their PTCL treatment, half of whom were diagnosed with AITL. HSCT was performed in 52 patients (47 autologous and 5 allogeneic) as part of initial therapy, representing 20.6% of the overall study cohort. The proportion of patients receiving doxorubicin was comparable between those who received a transplant vs. those who did not (64.0% vs. 62.7%,  $P = .87$ ). Radiotherapy was administered to 16 patients. Eleven patients were followed initially with observation/supportive care. First-line therapy was completed as planned in 64.3% of patients.

## Outcomes

Response assessment was undertaken by the treating investigator according to the Revised Response Criteria for Malignant Lymphoma.<sup>21</sup> Complete response (CR) was reported in 57.1%, partial response in 13.3%, and stable or progressive disease in 19.1%. An additional 10.4% of patients were not evaluable for response. Best response was observed a median of 132 days after PTCL diagnosis, which approximated when 6 cycles of chemotherapy administered every 3 weeks would be completed. When responses were stratified by doxorubicin vs. non-doxorubicin treatment, a higher CR rate was seen in patients receiving doxorubicin treatment (Table 2). A higher CR rate was also reported in patients treated with curative vs. palliative intent: 60.6% vs. 24%.

Median follow-up in the cohort was 26.0 months (interquartile range 14.4 to 37.7 months). Estimated median survival was 43.0 months (95% confidence interval [CI]: 34.5 months to not reached; Figure 3A), with 12- and 24-month survival rates of 71.7% and 58.7%, respectively. PTCL subtype and IPI score had a significant impact on overall survival. Patients with ALCL had statistically significant better overall survival compared to those with AITL and PTCL-NOS (log-rank  $P = .01$ ) (Figure 3B), and patients with lower IPI scores had statistically significant longer survival compared to those with higher scores (log-rank  $P = .0002$ ) (IPI 0/1 vs. 2/3 vs. 4/5; Figure 3C). Survival by doxorubicin use is shown in Figure 4. Survival was statistically significantly longer for patients who received doxorubicin (log-rank  $P = .03$ ). Cox proportional hazards analysis was performed to evaluate doxorubicin use, etoposide use, and overall survival, while controlling for IPI score and PTCL histology (Table 3); results showed a trend toward significance in reduction in mortality among those treated with doxorubicin (hazard ratio [HR] = 0.71, 95% confidence interval [CI] 0.48 – 1.05,  $P = .09$ ), but no association was observed for those treated with



etoposide (HR = 1.00, 95% CI 0.66 – 1.53,  $P = .99$ ). Analyses surrounding HSCT and survival were not performed based on limited follow-up.

Grade 3 and 4 or clinically significant adverse events were common among nodal PTCL patients. Roughly one third of patients (32.3%,  $n = 82$ ) were hospitalized at some point during initial treatment. The most common reported adverse events were neutropenia (33.9%), thrombocytopenia (24.0%), anemia (18.9%), and febrile neutropenia (18.5%). The most common supportive care measures administered were myeloid growth factors (57.1%) and blood/platelet transfusions (21.3%).

## Discussion

COMPLETE is the largest-ever prospective cohort study of patients with PTCL in the United States. As with other aggressive NHLs,<sup>21</sup> the intent of therapy in a substantial majority of patients was cure. Treatment regimens were selected primarily based upon clinical considerations, with cost or insurance coverage concerns exerting little influence. Treatment-related toxicities occurred at a rate expected for aggressive NHL patients receiving multi-agent chemotherapy.

Over the past decade, the role of doxorubicin in the initial treatment of nodal PTCLs other than ALCL has come into question, as evidenced by the fact that more than one third of patients in COMPLETE did not receive anthracyclines in the front line.<sup>4,23,24</sup> However, we observed that patients who received non-anthracycline regimens had inferior response rates and worse overall survival compared to patients treated with anthracyclines. Confirmation of reduced mortality associated with anthracycline use on multivariate analysis (controlling for IPI score and disease histology) argues against confounding by indication as the primary source of this observation. Of note, two recent clinical trials using combination chemotherapy regimens without doxorubicin also did not improve response rates.<sup>23,24</sup> Our findings support the use of anthracyclines as an important part of the induction regimen for patients with nodal PTCL who are being treated with curative intent.<sup>25</sup> Among those expected to tolerate anthracycline treatment, removal of anthracyclines should be attempted only under the auspices of a clinical trial.

The inclusion of etoposide as a component of initial therapy was not significantly associated with survival in our study after controlling for disease histology and IPI (HR = 1.00). While the German high-grade non-Hodgkin lymphoma study group has presented evidence supporting the addition of etoposide to the CHOP regimen (CHOEP) in PTCL patients, this was a post-hoc analysis of clinical trial data and the benefit was confined to an improvement in event-free survival among patients younger than age 60 with normal LDH.<sup>26</sup> Furthermore, the majority of the benefit was observed in patients with ALCL. (We did not compare CHOP to CHOEP due to small numbers of patients.) While it is conceivable that residual confounding or small patient numbers limited our ability to detect a survival difference, consideration of our data in conjunction with the German data (which also did not demonstrate an improvement in overall survival) suggests that any overall survival benefit associated with etoposide use in PTCL is at best modest.

Despite the fact that a majority of the patients in this study were enrolled at academic institutions, only 20.6% of the nodal PTCL patients received HSCT. A recent retrospective analysis of PTCL patients in the United States demonstrated a transplant frequency of only 10%.<sup>27</sup> Our findings highlight that regardless of the survival benefit that may be conferred by HSCT, in practice this treatment modality is utilized in only a small minority of the PTCL patient population. As a result, efforts to improve overall survival for the majority of PTCL patients must focus on improvement in outcomes with induction and salvage therapies.

The use of rituximab in patients with nodal PTCL deserves special attention. Half of the patients in the cohort who received rituximab had AITL, a disease in which abnormal T-cells are histologically associated with reactive B-cells that express CD20.<sup>28</sup> While it was initially thought that rituximab induced B-cell reduction in patients with AITL would improve outcomes, a trial by GELA showed no difference in outcomes compared to CHOP alone.<sup>29</sup>

Front-line studies in PTCL remain challenging to perform, largely due to the rarity of PTCL. Nearly all of the recently completed large therapeutic studies in PTCL were in relapsed and refractory patients who were fit to enter clinical trials and were designed to support drug approvals. As a result, there may be differences between patients studied in clinical trials and the overall population of patients with PTCL.<sup>30</sup> Moving forward, consideration should be given to pragmatic clinical trials to compare the effectiveness of front-line treatments in PTCL patients with both favorable and unfavorable clinical manifestations. Such an approach would enhance enrollment through broader enrollment criteria.<sup>31</sup> In addition, more widespread adoption of the National Cancer Institute Central IRB process may streamline the opening of multicenter PTCL trials at a sufficient number of sites to allow completion of trials of comparative effectiveness.<sup>32</sup>

The limitations of this study should be highlighted. Although we cannot rule out selection bias, the similarity of characteristics of the patients enrolled in COMPLETE compared to what has been reported in SEER<sup>20</sup> and the ITCP<sup>4</sup> suggest this patient cohort is representative of the overall PTCL patient population. Furthermore, the prospective design of the study should reduce the risk of bias and confounding compared to retrospective studies of patients with PTCL. Data quality is also a concern in observational studies. While we did not perform onsite monitoring, the steering committee reviewed the collected data on an ongoing basis to uncover clinical inconsistencies, prompting clarification. Additionally, the level of missing data was low, with few patients discontinuing the study for reasons other than death (n = 27, 5.4%). The high proportion of patients enrolled in academic sites (86.0%) is likely a reflection of the referral patterns for rare diseases. Finally, like any analysis of data that is not randomized, we cannot rule out residual confounding from unmeasured variables as a contributor to our findings.

According to the NCCN guidelines, there is no standard of care for nodal PTCL and many regimens have been used for induction therapy. The data from COMPLETE support the concept that anthracycline-containing regimens should be utilized over non-anthracycline regimens for patients with common nodal subtypes. The lack of significant improvement in



overall survival in COMPLETE compared to historical data underscores the need for further studies of novel agents and approaches for PTCL.

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**Condensed abstract**

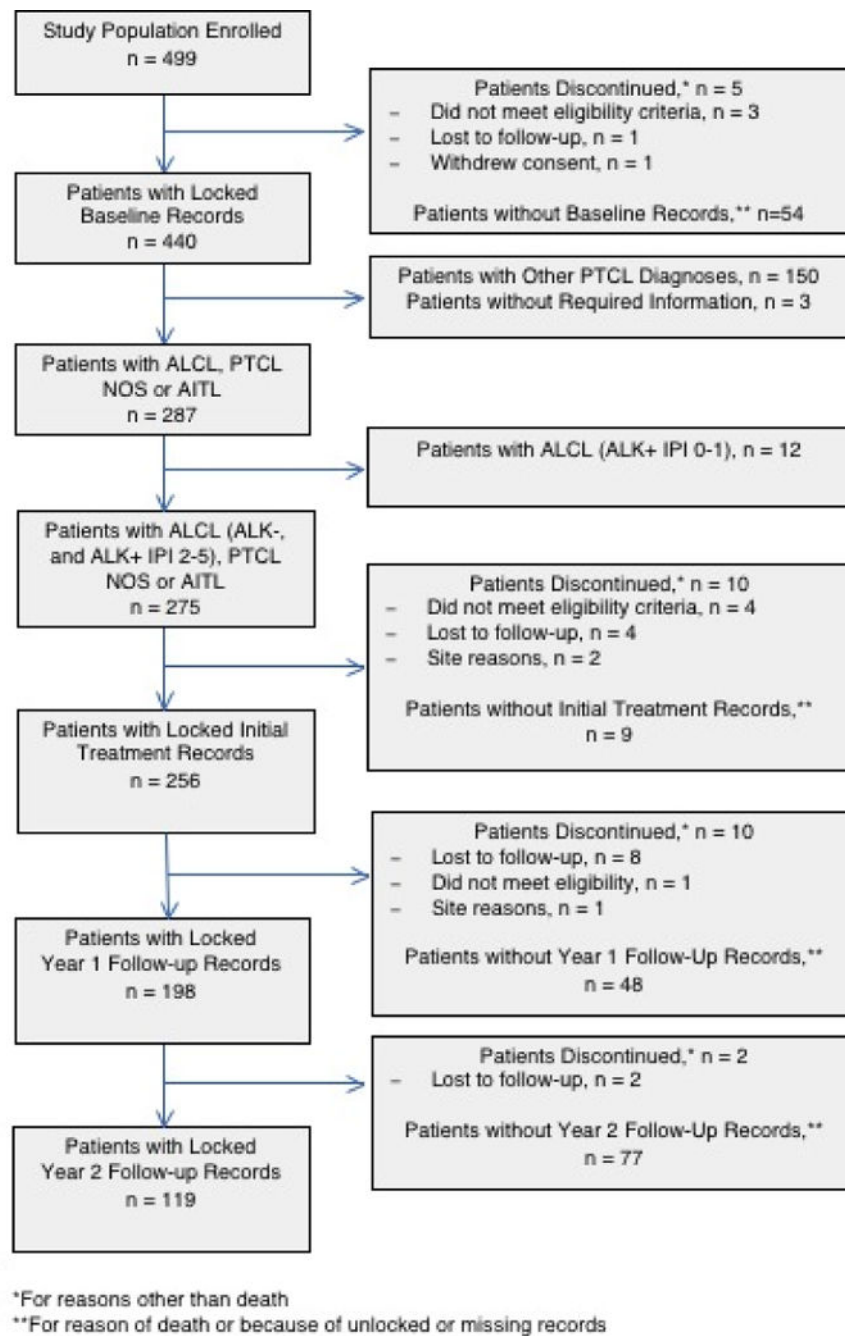
There is no clear standard of care in the treatment of PTCL in the United States. While efforts to improve front-line treatments are necessary, anthracyclines remain an important component of initial therapy of curative intent.

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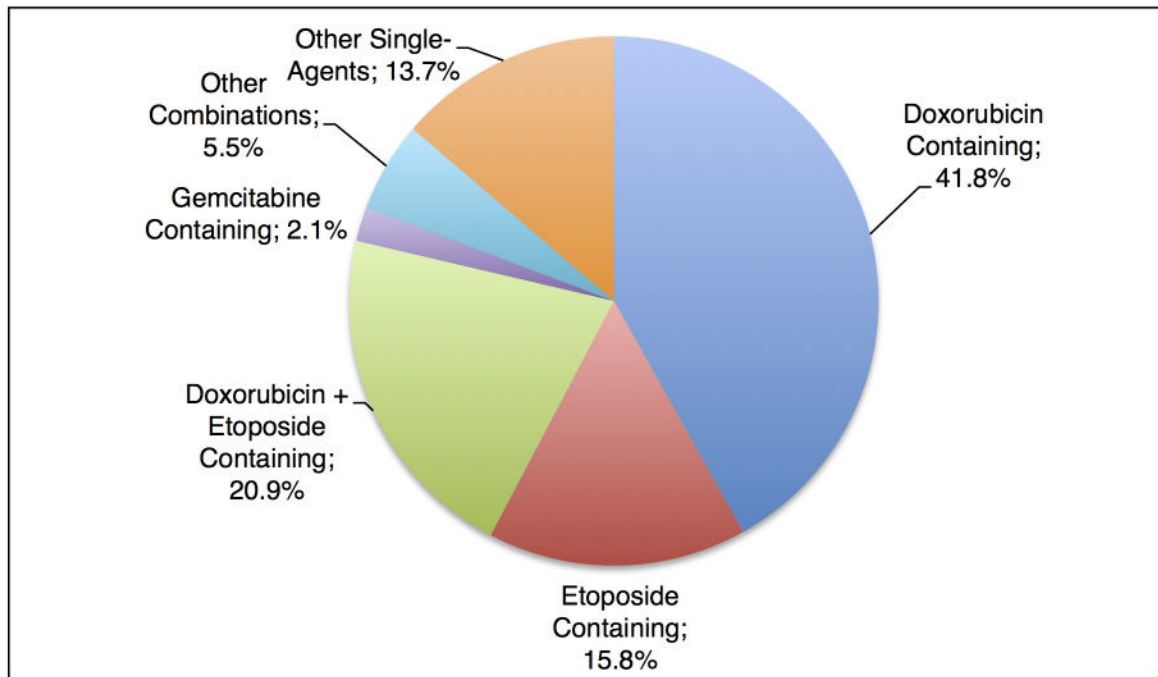
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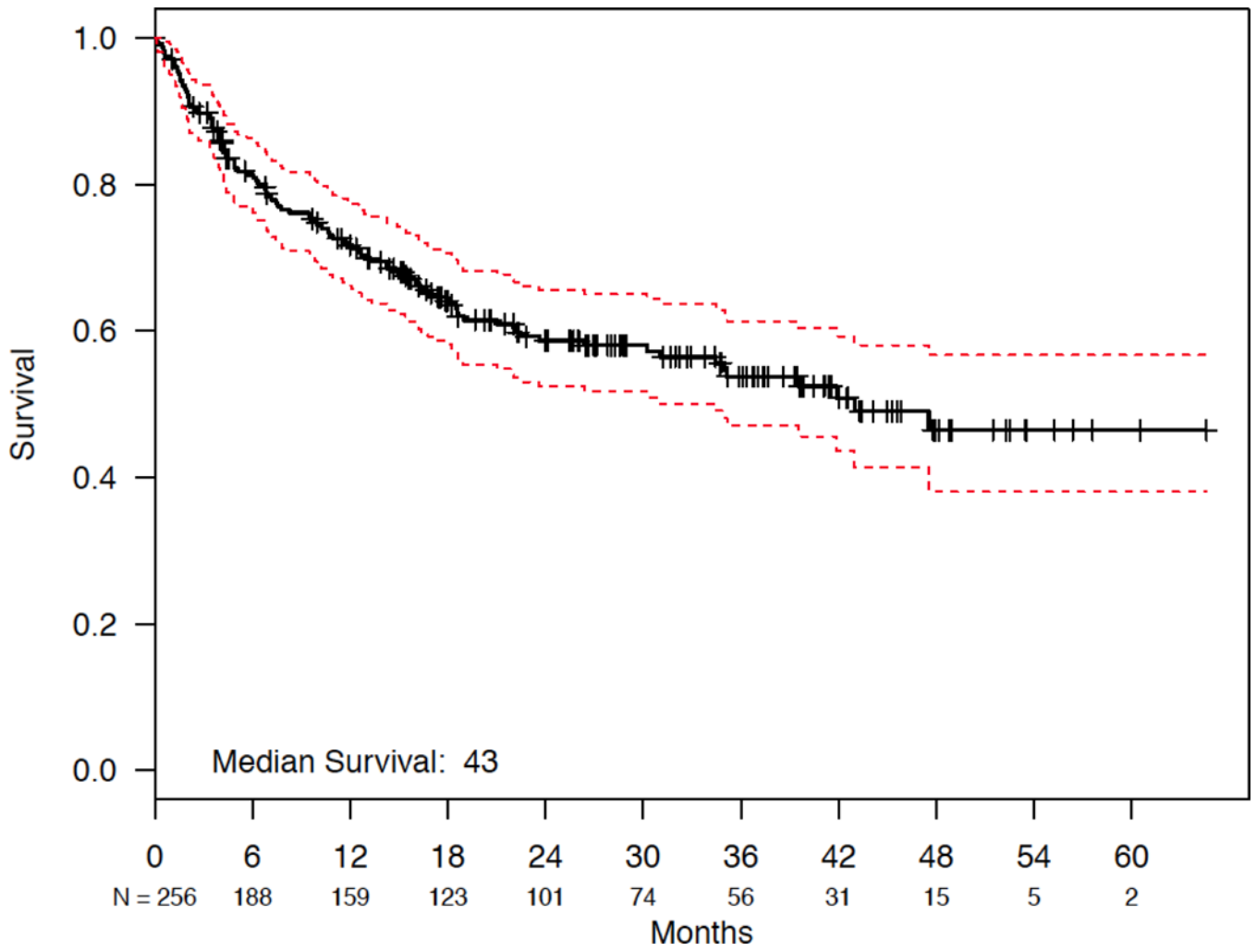
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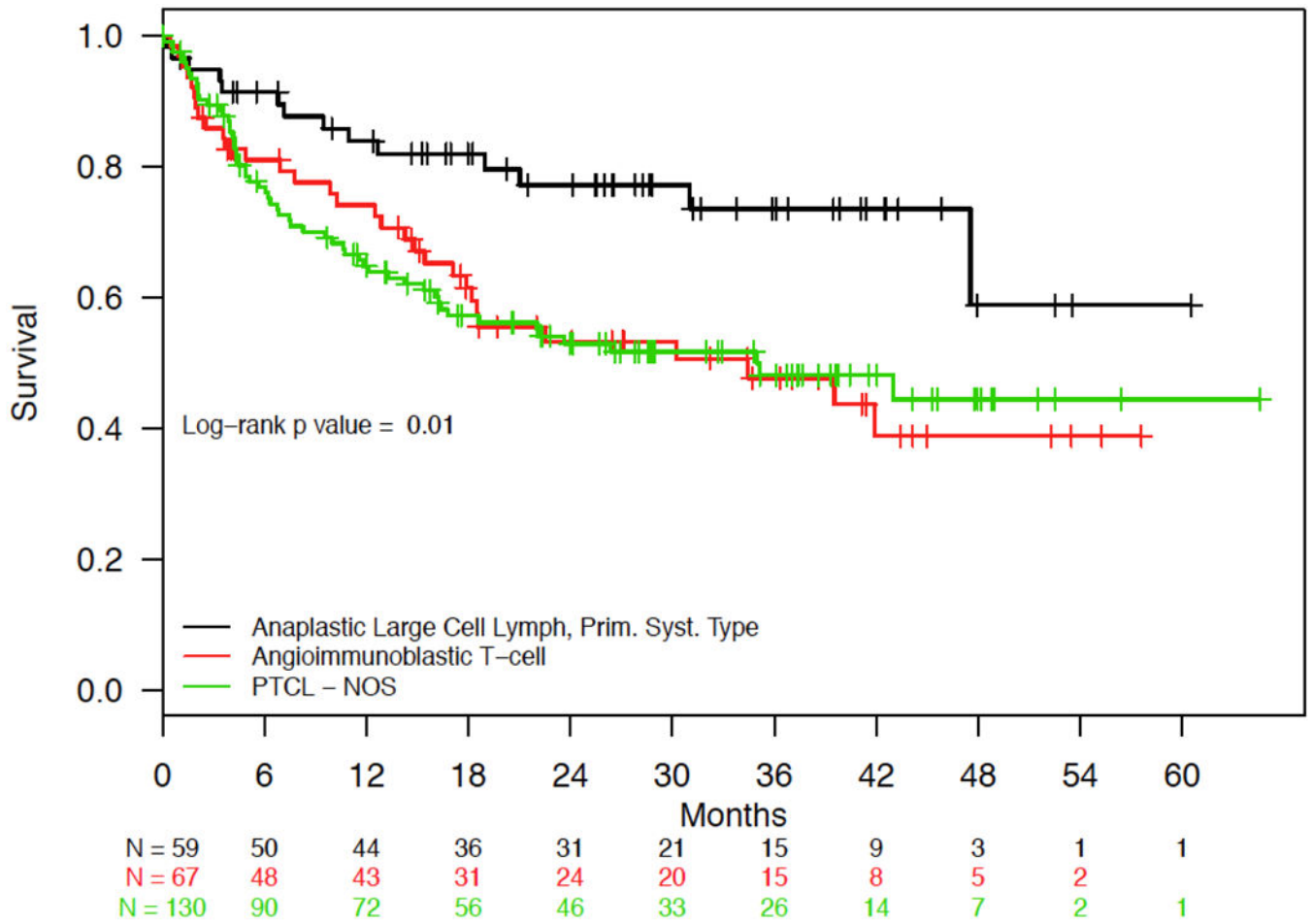
**Fig. 1.**  
STROBE diagram

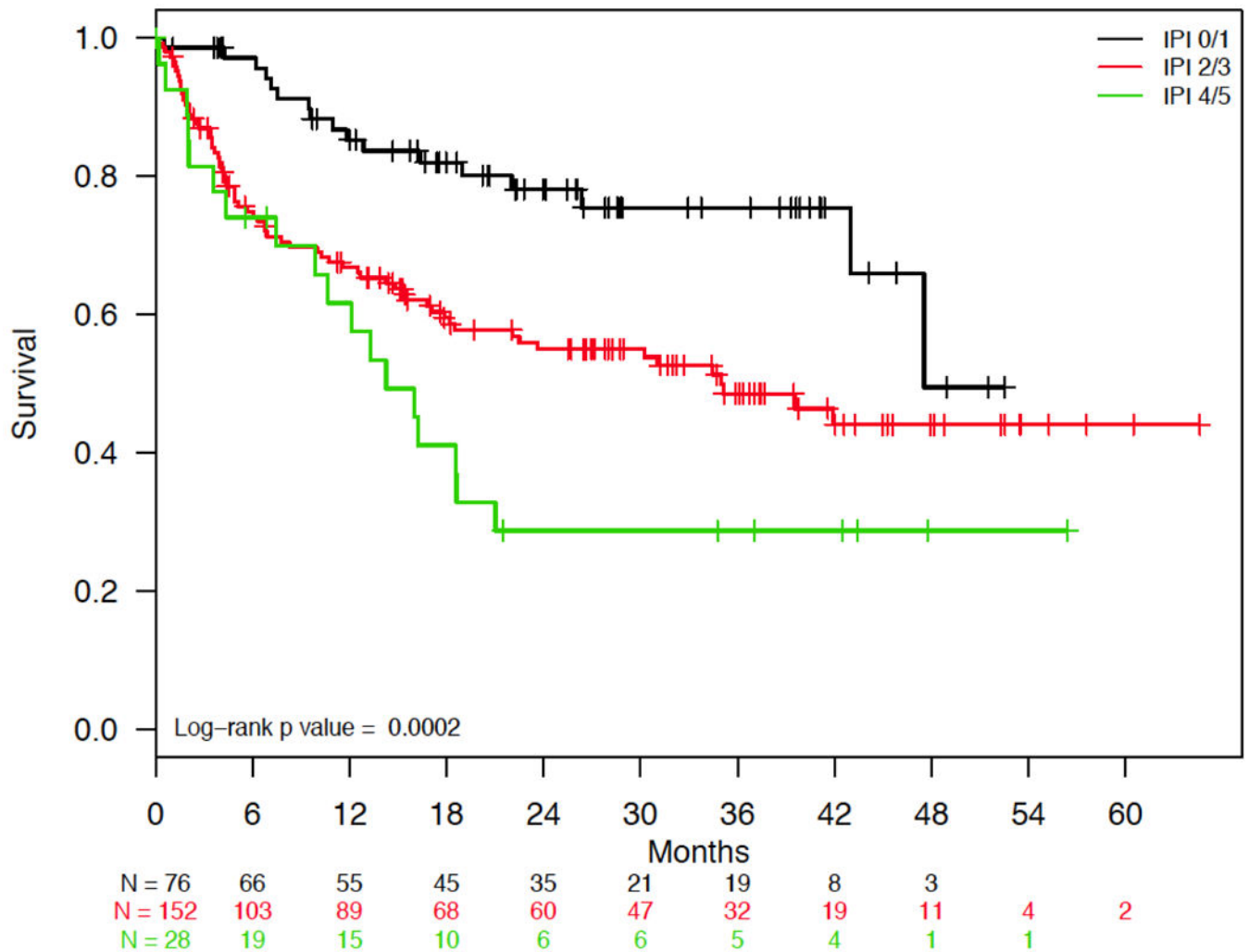


**Fig. 2.** Induction Regimen for Patients with PTCL-NOS, AITL, and ALCL (N = 234). Information on treatment regimen is missing for 4 patients.









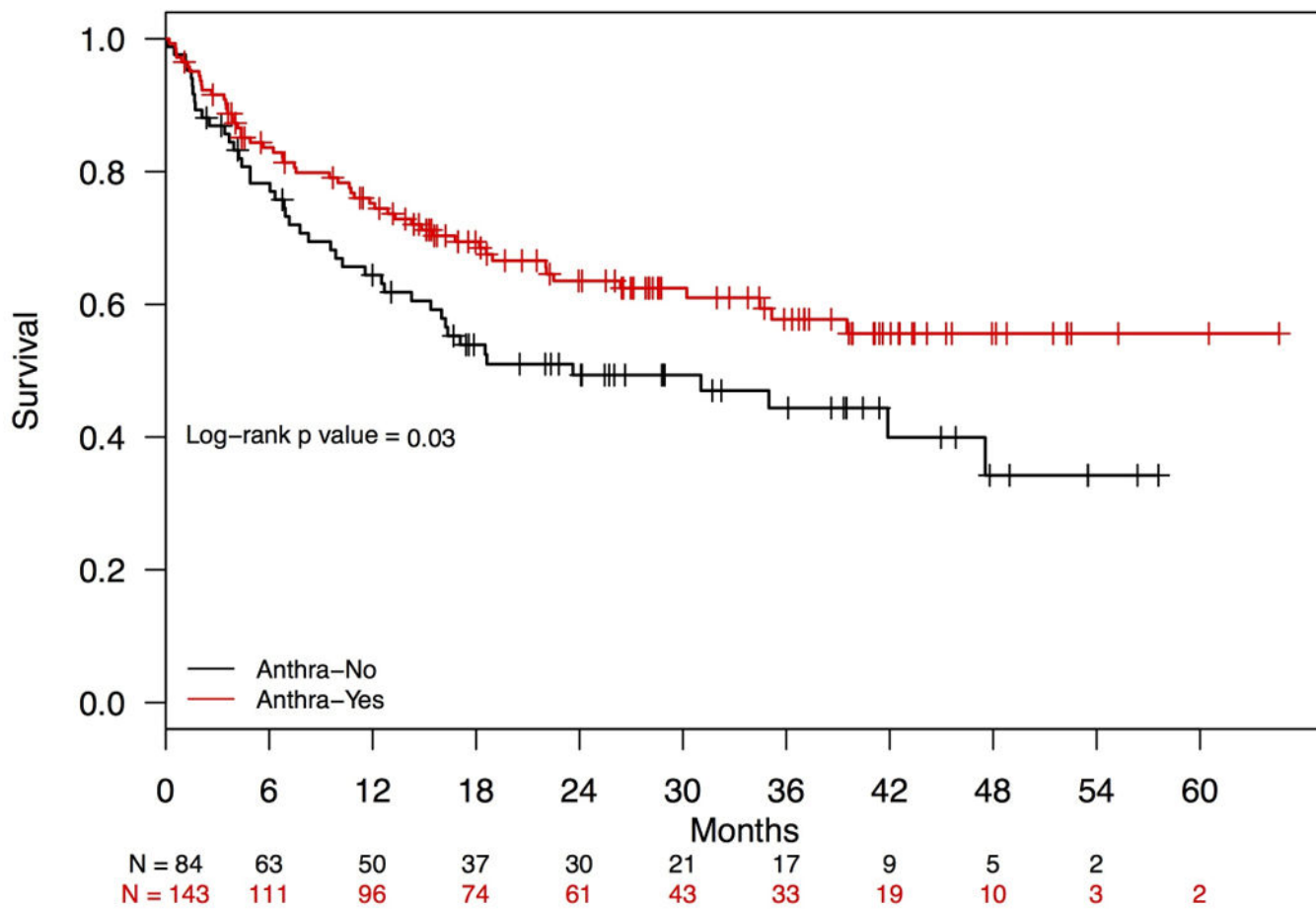
**Fig. 3.**  
 (a) Overall Survival for Patients with PTCL-NOS, AITL, and ALCL. (b) Overall Survival for Patients with PTCL-NOS, AITL, or ALCL, Stratified by PTCL Subtype. (c) Overall Survival for Patients with PTCL-NOS, AITL, and ALCL, Stratified by IPI Score. Abbreviations: ALCL, anaplastic large cell lymphoma; prim syst type, primary systemic type; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; IPI, International Prognostic Index

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**Fig. 4.** Overall Survival for Patients with PTCL-NOS, AITL, and ALCL, Stratified by Anthracycline Use.  
 Abbreviations: Anthra, anthracyclines; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma IPI; ALCL, anaplastic large cell lymphoma

**Table 1**

Baseline Demographics and Clinical Characteristics of Patients with PTCL-NOS, AITL, and ALCL (N = 273)

Characteristic	No. (%)
Age (years)	
Median	63.1
65+	123 (45.1%)
Sex	
Male	181 (66.3)
Female	92 (33.7)
Race	
Black	42 (15.4)
White	211 (77.3)
Other	13 (4.8)
Unknown	7 (2.6)
Ann Arbor Stage	
I	29 (10.6)
II	35 (12.8)
III	82 (30.0)
IV	127 (46.5)
Any B-Symptoms present	126 (46.2)
Serum LDH elevated *	118 (44.4)
Histopathology	
PTCL-NOS	140 (51.3)
AITL	71 (26.0)
ALCL	62 (22.7)
ALK-	49 (79.0)
ALK+ (IPI 2-5)	13 (21.0)
Median IPI	2
ECOG Performance Status	
0-1	248 (90.8)
2	23 (8.4)
3	2 (0.7)
Enrolling institution	
Academic	236 (86.0)
Community	37 (14.0)
Clinical trial participant	57 (20.9)

Baseline information is missing for 2 patients.

Abbreviations: LDH, lactate dehydrogenase; IPI, International Prognostic Index; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; ECOG, Eastern Cooperative Oncology Group

\* Information on LDH is missing for 7 patients.

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**Table 2**

Overall Best Response to Induction Therapy for Patients with PTCL-NOS, AITL, and ALCL, Stratified by Anthracycline Use (N = 227)

<b>Best Response</b>	<b>Did not Receive Anthracycline (%)</b>	<b>Received Anthracycline (%)</b>	<b>P*</b>
Complete Response	46.4	62.9	.05
Partial Response	14.3	11.9	
Stable Disease	6.0	7.0	
Progressive Disease	16.7	11.9	
Not evaluable	16.7	6.3	

\* Chi-square test

Information on response is missing for 29 patients.

Abbreviations: ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified

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**Table 3**

Cox Regression Model for Multivariable Analysis of Overall Survival (N = 250)

Factor	Hazard Ratio	95% CI	P value*
IPI score			
2–3	2.16	1.25–3.72	.006
4–5	3.28	1.67–6.43	<.001
Histopathology			
AITL	0.93	0.59–1.45	.73
ALCL	0.46	0.25–0.84	.01
Anthracycline used <sup>†</sup>			
	0.71	0.48–1.05	.09
Etoposide used <sup>‡</sup>			
	1.00	0.66–1.53	.99

\* Wald chi-square test

<sup>†</sup> Alone or in combination with another agent including etoposide.<sup>‡</sup> Alone or in combination with another agent including an anthracycline.

Abbreviations: IPI, International Prognostic Index; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CI, confidence interval

Reference levels: IPI 0–1, peripheral T-cell lymphoma-not otherwise specified

Number of events = 100