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Patterns of care, outcomes, and prognostics for transformed follicular lymphoma in the rituximab era

Jonathan R. Day[1,2], Melissa C. Larson[3], Carla Casulo[4], Urshila Durani[2], Yucai Wang[2], Dai Chihara[5], Loretta J Nastoupil[6], Umar Farooq[1], Eric Mou[1], Brad S. Kahl[7], Peter Martin[8], Izidore S. Losso[9], Jason Romancik[10], Amy A. Ayers[5], W. Richard Burack[4], Thomas M. Habermann[2], James R. Cerhan[2,3], Christopher R. Flowers[5], *Matthew J. Maurer[2,3], *Brian K. Link[1]

1. Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA;
2. Division of Hematology, Mayo Clinic, Rochester MN;
3. Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN;
4. University of Rochester Medical Center, James P. Wilmot Cancer Center, Rochester, NY;
5. The University of Texas, MD Anderson Cancer Center, Houston TX;
6. Southwest Oncology, CommonSpirit Mercy, Durango, CO
7. Siteman Cancer Center, Washington University School of Medicine in St. Louis, St. Louis, MO;
8. Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY;
9. Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL;
10. Emory University, Winship Cancer Institute, Atlanta, GA

*These authors contributed equally to the manuscript and share senior authorship.

Correspondence:
Matthew J. Maurer, ScD
Professor of Biostatistics
Department of Quantitative Health Sciences
Mayo Clinic
200 1st St SW, Rochester, MN 55905
email: maurer.matthew@mayo.edu

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Drafted the manuscript: JRD, MCL, CC, BKL, MJM

Final approval of the manuscript: JRD, MCL, CC, UD, YW, DC, LJN, UF, EM, BSK, PM, ISL, JR, AAA, WRB, TMH, JRC, CRF, BKL, MJM

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Data Sharing Statement

These data are not publicly available. Data sharing policies and the process to request LEO data that support the findings of this study can be found on the LEO Cohort website (https://leocohort.org/).

Abstract: (249/250 words)

Histologic transformation (HT) is the leading of death in follicular lymphoma (FL), yet outcomes remain poorly defined due to small cohorts and heterogenous definitions. To characterize outcomes and treatment patterns in the rituximab era we analyzed 344 patients with an initial biopsy-confirmed FL diagnosis between 2002 and 2022 who subsequently developed biopsy-confirmed HT in the Lymphoma Epidemiology of Outcomes (LEO) Consortium of Real-World Evidence (CReWE). Median age at HT was 64 (IQR 57-72). Initial treatment for HT (index therapy) included R-CHOP-like (n=154, 45%) and aggressive/salvage (n=85, 25%). The median event free survival (EFS) from HT was 9 months (95% CI, 7-11), and 2-year EFS was 30% (95% CI, 26%-36%). Median OS from HT was 4.9 years (95% CI, 4.0 -7.5) with 2-year and 5-year OS estimates of 66% (95% CI, 61%-71%) and 49% (95% CI, 43%-56%), respectively.

Relapses after HT occurred in 60%. Relapse histology included DLBCL 70%, FL 15%, and HGBCL 12%. Treatment following relapse from index therapy was commonly aggressive/salvage (often incorporating ASCT/CAR-T) in 44%.

FLIPI (3-5), FL3A histology, IPI (4-5), ECOG >1, diagnosis to HT <2 years, HT within 2 years of immunochemotherapy (POD24), LDH, Hgb <10, prior anthracycline, and alkylator exposure were predicted inferior EFS. Age > 70 and HGBCL transformation portended inferior OS. An exploratory multivariable model, older age, HGBCL histology, prior anthracycline exposure, and shorter time to transformation predicted inferior OS. These data define the clinical course and treatment heterogeneity of tFL in a largely pre-CAR-T/bispecific era and provide context for future studies.

Key Points:

Transformation of follicular lymphoma leads to brief remissions following a heterogeneous treatment pattern and high rates of lymphoma-related mortality.

Prior anthracycline, early transformation (in 24 months of diagnosis or chemo), and transformation to high-grade lymphoma predict inferior EFS & OS after HT.

Introduction

Follicular Lymphoma (FL) is the second most common lymphoma in the United States and Western Europe and the most frequently diagnosed indolent lymphoma.[1-3] Histologic transformation (HT) to an aggressive lymphoma histology is a rare complication of FL occurring at a rate of approximately 1-2% per year in the rituximab era.[4,5] Despite the low frequency of HT, it has a disproportionate impact on survival with 50% of lymphoma related deaths in the first decade from diagnosis preceded by a HT event.[6] Pre-rituximab era survival of patients experiencing HT was poor, with median 2 year survival of 22 months, [7,8] while early rituximab era cohorts identified a 48% 5yr OS for patients with HT.[9] Subsequent studies have also reported wide ranges in overall survival (OS),with varying definitions of HT.[4,10,11 12]While there appears to be improvement in OS over time, there is still heterogeneity among reports likely due to cohort selection/composition, limited sample sizes, and duration of follow-up.

Given the differences in published outcomes, defining prognosis for transformation at the individual patient level remains a challenge. Efforts have been made to evaluate some clinical factors influencing outcomes, such as stage, tumor burden and lactate dehydrogenase (LDH).[4,8,11,12] Importantly, there is insufficient data on the histology at relapse, which leaves a gap in understanding of the disease trajectory. Alongside lack of consensus regarding optimal treatment for HT, in addition to the difficulty with assessing prognosis, treatment discussions for patients with HT also present a unique challenge due to a paucity of published treatment specific outcomes. Given the lack of randomized clinical trials targeting treatment of HT, current NCCN guidelines are mostly extrapolated from relapsed/refractory large cell lymphoma, recommending regimens for aggressive B-cell lymphoma, including anti CD19 chimeric antigen receptor T-cell (CAR-T) therapy, clinical trials, or in appropriate patients, proceeding to autologous stem cell transplant.[13]

Given the rarity of HT overall, differences in outcomes between HT and FL, and lack of established treatment guidance, we conducted a study using patients with HT from a large multicenter US cohort of patients diagnosed in the rituximab era (mostly prior to widespread CAR-T/Bispecific use) to evaluate therapeutic choices, outcomes, and factors associated with prognosis for HT from academic practices.[14,15] We hypothesized that outcomes after HT would be heterogeneous and associated with clinical, pathologic, and prior-treatment factors, including prior anthracycline exposure, time to transformation, and transformation histology.

Methods

We utilized the Lymphoma Epidemiology of Outcomes (LEO) Consortium of Real-World Evidence (CReWE) dataset. Briefly, patients with FL who had a HT following a previous diagnosis of were identified from the eight academic centers in the United States participating in the LEO Cohort Study (NCT02736357; https://leocohort.org/): Cornell University, Emory University, Mayo Clinic-Rochester, MD Anderson, University of Iowa, University of Miami, University of Rochester, and Washington University in St. Louis. This was supplemented with patients with HT identified at institutional databases at each LEO Center as part of the LEO CReWE as LEO participants are tracked from initial diagnosis.[15,16] We also reviewed and identified patients who had only received 2 lines of therapy who were not included in the original LEO or CreWE datasets.[15,17] There were 51 patients in this cohort that were also reported by Link et al, *JCO*, 2013.[4] Clinical data, including details at each line of therapy, were abstracted from medical records using a standard protocol into a central database maintained by the LEO Cohort

Biostatistics Core. The study was approved by IRBs at all institutions. All management decisions for those not on a clinical trial protocol were per the practice of the treating physicians.

Patients selected for analysis in the study were initially diagnosed between 2002-2022, had a biopsy proven grade 1-3A FL at diagnosis with a subsequent biopsy (at least 3 months after the first biopsy) showing HT to an aggressive lymphoma (FL 3B, DLBCL, or high-grade B cell lymphoma (HGBCL)). Patients were excluded from the study if there was any pathological-confirmed involvement of FL3B, DLBCL, or HGBCL at the time of initial diagnosis. For patients with HGBCL, where noted in the pathology reports and included patients with double hit confirmed by FISH when available.

The principal endpoints of interest were event-free survival (EFS) and OS. EFS was defined as the time from diagnosis of transformation to the first progression, relapse, initiation of a new line of treatment for lack of efficacy, or death from any cause. OS was defined as the time from HT to death from any cause. Index therapy was defined as the first treatment for the treatment of pathology-confirmed transformation. Aggressive/Salvage therapy was defined as multiagent, dose-dense, highly myelosuppressive regimens with platinum agents or ifosfamide with the exception of rituximab with gemcitabine and oxaliplatin (R-GemOx) which is used at some centers with palliative intent and at others for salvage.[18] Treatments for FL prior to HT were grouped by the most intensive line of therapy received as either non-systemic (observation or radiation), anti-CD20 antibody monotherapy (CD20), alkylator without anthracycline, or prior anthracycline exposure. Histology of relapse after HT was assigned when repeat biopsy and pathology was available. The hemoglobin cut point of less than 10 g/dL was selected to reduce confounding of other mild anemias.

Time-to-event variables were estimated using the Kaplan-Meier method. Differences between subgroups were evaluated using an unadjusted Cox proportional hazards model. Causes of death were modeled using a competing risk approach. Cause of death was determined via a review of death certificate copy and/or medical records using a standard protocol and classified as the result of lymphoma (progression), treatment, unrelated cancer, other causes, or unknown.[19] Treatment-related mortality was broadly defined as previously described.[20] All analyses utilized complete case data on all eligible patients. Numbers of patients in subsets and/or with missing data for analysis variables are provided in results tables. All models and results are presented with 95% confidence intervals (CI). An exploratory multivariable model was generated based on statistical and clinical significance.

All analyses were performed using R (version 4.3.2). This study was approved by a centralized institutional review board coordinated at the Mayo Clinic.

Results

Clinical Characteristics prior to transformation

19% of patients were treatment naïve prior to HT, 81% received FL directed treatment before HT. Two hundred forty eight (72%) patients received immunochemotherapy as their most intensive therapy for FL prior to transformation, 118 received alkylator without anthracycline use (34% of all patients) and 130 had an anthracycline exposure prior to transformation (38% of all patients). Median number of treatments prior at time of transformation was 2. Seventeen patients (5%) had undergone stem cell transplantation prior to transformation (Figure 2). HT within 24 months of diagnosis occurred in 36% of patients (N=123). (Table 1) Patient histology and FLIPI scores at diagnosis are reported in Table 1.

Clinical Characteristics at transformation

Three hundred forty-four patients were identified with biopsy proven HT (170 from the prospective LEO cohort and 174 from institutional databases as part of CReWE) (Figure 1). The median age of patients at HT was 64 years (range 24-93; interquartile range [IQR] 57-72). Most patients were male (59%, n=204), white (89%, n=307) and had Ann Arbor stage of III-IV (90%, n=258) at the time of HT. Among patients with international prognostic index (IPI) scores at HT: low 0-1 (16%, n=35), intermediate 2 (27%, n=59), and high 3-5 (57%, n=125). B-symptoms were reported in 6%, n=21 of patients. Histology at HT was DLBCL in 82% (n=283), FL grade 3B in 4% (n=15), and HGBCL in 13% (n=46, of which 34 patients were confirmed by FISH as having Double or Triple Hit). (Table 1). The median time from FL diagnosis to HT was 41 months (range 3 to 199 months; IQR 14 to 80 months). (Table 1).

Patterns of Treatment for HT and Subsequent Outcomes

344 number of patients received treatment for HT. Treatment for HT was heterogeneous. The most common therapies (e.g. first treatment after HT) were CD20-CHOP (n=154, 45%), aggressive/salvage therapies (n=85, 25%), CD20-EPOCH (n=41, 12%), followed by other combinations (Figure 2). Following first HT-directed/ index treatment, consolidation strategies included autologous stem cell transplant in 18% (n=63). CAR T-cell therapy was delivered to 2% of patients (n=7) (Figure 2).

With a median follow up of 5.4 years (IQR: 4.7-7.2 years), 268 (78%) patients had an event after HT. (Figure 3) The median EFS from HT was 9 months (95% CI, 7.1-11.0). Median EFS for patients with prior alkylator exposure was 9 months (95% CI, 5.3-13.0), and was 6 months (95% CI, 3.0-6.8) with prior anthracycline exposure. Two-year EFS was 30% (95% CI, 26%-36%) and 5-year EFS was 18% (95% CI, 14%-23%) (Figure 3).

205 patients relapsed following treatment for HT, with all undergoing repeat biopsy. The most common histology was DLBCL (N=144, 70%), followed by FL or other indolent lymphoma (N=31, 15%), HGBCL (N= 25, 12%), and FL3B (N=4, 2%) and 1 low grade B-cell lymphoma NOS (0.5%).

In total, 176 (52%) patients died, 151 known causes and 25 were unable to have records obtained. Median OS was 4.69 years (95% CI, 4.0 -7.4). Overall survival was 66% at 2 years (95% CI, 61%-72%) and 49% (95% CI, 44%-56%) at 5 years (Figure 3). The leading cause of death was progressive lymphoma (74%, n=111), followed by therapy related mortality (10%, n=15), secondary malignancies (4%, n=6), and other causes (10%, n=15) in patients with known causes of death. The cumulative incidence of lymphoma related death was 29% (95%CI 25-35%) at 2 years and 40% (95%CI 34-46%) at 5 years (Figure 4).

Two-hundred and five patients (60%) received a subsequent line of therapy for relapses following HT directed treatment. The leading subsequent treatments were aggressive/salvage with or without ASCT or CAR-T (in n=90, 44%); other treatments (including clinical trials n=20, targeted agents, other chemotherapy) in n=57, 28%); and anti-CD-20 + alkylator (with or without ASCT) in n=17, (8%). Other less frequent choices are depicted in Figure 2. Stem cell transplant at next line treatment was utilized in n=45 (22%) (39 Auto-SCT, 6 Allo-SCT) and 31 patients (15%) received CAR T-cell therapy for relapses after index treatment (Figure 2).

The median number of lines therapy throughout the patient's course from diagnosis was 4, (range 2-16, IQR 3-5), 2 (2-10) prior to HT. In total, 14% of patients (N=49) received CAR T-cell therapy and 130 patients (38%) received stem cell transplant as part of their therapeutic journey.

Prognostic Factors and Outcomes after Transformation

Clinical factors associated with shorter EFS following HT included male gender, high risk FLIPI (3-5) vs low risk FLIPI (0-1) at diagnosis, FL grade 3A histology at diagnosis, high risk IPI (4-5) at HT, ECOG PS>1, and diagnosis to transformation time of less than 2 years (Table 2). No difference in EFS was observed based on age, BMI, bulky disease, or number of nodal groups. Clinical factors associated with inferior OS were age at transformation over 70 years, intermediate risk (score 2) or high risk (3-5) FLIPI at diagnosis, higher ECOG PS (2-4), high risk IPI (3-5) at time of transformation, and diagnosis to transformation time of less than 2 years (Table 2). There was no OS difference observed for gender, race/ethnicity, follicular lymphoma grade at diagnosis, BMI, Ann Arbor stage at HT, presence or absence of B symptoms at transformation, bulky vs non-bulky disease at transformation, greater than or equal to 2 vs less than 2 extra nodal groups, and intermediate vs low risk IPI at time of transformation. (Table 2).

Laboratory and pathology factors at HT associated with inferior EFS were elevated LDH and hemoglobin of less than 10mg/dl at transformation. There was no difference in EFS based on pathology at HT. Patients with transformation to DLBCL had a median EFS of 9.2 months, 2-year EFS was 31%. Patients with HGBCL at HT had a median EFS of 6.7 months, 2-year EFS was 27%. Laboratory and pathology findings associated with inferior OS were hemoglobin less than 10 mg/dl at HT, elevated LDH at HT, and transformation to HGBCL. No differences in OS were observed for patients with increased absolute lymphocyte count, absolute monocyte count, absolute neutrophil count at time transformation, or transformation to FL 3B vs DLBCL. (Table 2)

Exposure to alkylator without anthracycline and anthracycline exposure were associated with inferior EFS compared to patients who did not receive immunochemotherapy. Transformation within 24 months of IC was associated with a inferior EFS compared to no prior therapy. There was no difference in EFS for patients who had 1 prior line of therapy or 2+ lines of therapy for FL. Treatment related factors associated with inferior OS included prior treatment, which appeared to mostly be driven by prior anthracycline exposure (Supplemental Figure 1) and HT within 2 years of IC event (Supplemental Figure 2). Exposure to any therapy prior to HT was associated with inferior OS and did not vary with number of lines of prior therapy. Shorter diagnosis to transformation interval was also associated with inferior OS. (Supplemental Figure 3)

Anti-CD20-CHOP for HT was associated with improved OS compared to CD20 alkylator or CD20 Gem-Ox (HR 2.5 ; 95%CI 1.4-4.4), CD20-EPOCH (HR 1.7; 95%CI 1.1-2.8), and other treatments, including single agents and clinical trials (HR 2.6 ; 95%CI 1.6-4.1) who had commonly had prior anthracycline containing regimens. (Table 2).

Fifty-nine patients received autologous stem cell transplant (with 1 patient proceeding to allo transplant) as part of index therapy with 2-year OS of 85% and 5-year OS of 72%. Seven patients had CAR T-cell therapy as part index treatment, none had died by data cut off, and only 2 patients receiving CAR-T had reached the 2-year interval for follow up.

An exploratory multivariable model for OS at the time of transformation was developed with the following variables: increasing age, HGBCL subtype (yes vs no), prior anthracycline exposure (yes vs no), and shorter diagnosis to transformation interval, (Figure 3) the model's (uncorrected) c-statistic was 0.669; OS by the model's risk tertile is provided in Supplemental Figure 4.

Discussion

Histologic transformation of follicular lymphoma to a higher-grade lymphoma represents a significant change in a patient's disease course, characterized by short remissions (median EFS 9 months overall, 9 months for prior alkylator exposure, 6 months for prior anthracycline), recurring with predominantly aggressive histologies (84% DLBCL/HGBCL) and OS remained limited (median 4.7 years) with high lymphoma related mortality. Treatment patterns were heterogeneous and largely reflected a pre-CAR T-cell/bispecific-antibody era. This study confirms known adverse factors such as older age, LDH, prior therapy, and early transformation, while adding detailed treatment sequencing, relapse histology after index HT therapy, and a large biopsy-confirmed multicenter cohort restricted to patients with biopsy proven transformation without composite aggressive disease at initial diagnosis. We propose an exploratory multivariable clinical prediction model to identify highest risk patients. Though validation is needed, these data highlight the heterogeneity of patients with HT. Age, transformation to HGBCL, prior anthracycline, and shorter time to HT remain independently prognostic in our model. Treatment patterns were varied, and we did not find a treatment regimen for HT that was associated with better survival over anti-CD20-CHOP, though we acknowledge the selection bias in regimen choice. These findings support prospective evaluation of consolidation and cellular and immune-based strategies in high-risk patients and reinforce the importance of clinical trial enrollment and further studies will be needed to see how CAR-T and bispecific antibodies change the natural history of the disease. Importantly, we do not identify a low-risk group, and clinicians should set expectations for short remissions and the need for additional therapeutic strategies.

The strengths of this study include the comparatively large sample size of patients with HT in the rituximab era, inclusion of only biopsy proven transformations after an initial (non-composite) diagnosis of FL and capturing transformation at any time in the clinical journey rather than first event. While patients in the LEO cohort were prospectively followed from diagnosis, we also include patients captured in institutional databases at the time of transformation. Limitations include the observational study design, which is subject to selection and confounding biases. The practice patterns of this study may contain some selection bias based on the academic practices of the LEO Cohort from which these patients were drawn. The generalizability of the study also has limitations as the population was mostly white and treated at an academic center. We also acknowledge that not all patients were included from the time of initial enrollment and that the LEO centers often have referrals of relapsed or refractory cases. We also acknowledge the limitation that biopsy-confirmed FL at diagnosis does not exclude concomitant transformation elsewhere and that sampling error may influence very early HT cases. Furthermore, we acknowledge that there may have been lower enrollment numbers early in the reviewed period as the cohort began enrolling. We do report the outcomes of those who did successfully undergo ASCT but note the limitations that this is a biased population for those who were able to receive salvage therapy and proceed to transplant. The number of patients treated with CAR-T was limited due to the timing of CAR-T approvals in relationship to the cohort. We report outcomes for

patients who receive CAR-T as part of treatment at the time of HT but not those who receive CAR-T therapy in later lines.

Given the rarity of HT, large studies are needed but have been limited to date. Definitions of what is included in HT studies have also varied across studies between groups. Given this paucity of data, consensus is lacking on how these patients should be treated and patterns of care generally follow large-cell lymphoma-like treatments, with the majority of patients receiving R-CHOP-like regimens at the time of transformation, while those who had received prior anthracycline tended to receive more aggressive/salvage regimens. CAR-T as part of treatment for index transformation was rare, likely due to timing of FDA approval. Historical data from The National LymphoCare Study (NLCS) included 379 patients with HT, of which 100 cases only had clinically defined transformation. Compared to the NLCS, our cohort more frequently received R-chemotherapy and underwent bone marrow transplantation, and rarely received R-monotherapy or radio-immunotherapy.[9] Compared to clinical trials (PRIMA and GALLIUM) reporting on patients with HT, our cohort was similar with a high use of R-chemotherapy and salvage chemotherapy, but had lower utilization of bone marrow transplantation compared to the 43-57% reported in these trials.[11,21] We additionally report for the first time treatment patterns at first relapse of transformed FL, which are increasingly aggressive with frequent incorporation of salvage/aggressive chemotherapy with ASCT and CAR-T.

At first relapse after index HT, most patients in this cohort have seen an anthracycline containing regimen and are being considered for additional aggressive treatments. For patients receiving ASCT our outcomes were numerically favorable compared with prior reports, but interpretation is limited by selection bias, eligibility for salvage therapy; with 2-year OS 85% (95% CI 76-95%) compared to previously reported outcomes of transplant for HT, 2-year OS of 70-82%, and higher 5-year OS in our cohort 72% (95%CI 60%-86%) than previously reported data which mostly ranged between 50-60%. [22-27] Given recent FDA approvals of cellular therapy and bispecific antibodies in the second line for aggressive lymphoma and third line for follicular lymphoma, the number of patients in our study receiving these therapies at the index line were low. There has been interest in cellular therapy in patients with HT. Other real-world studies report 2 and 3-year OS rate of 57%, and EFS of less than 1 year, though there is significant variation which may reflect differences in treatment timing and selection. [28-30] Additionally many reports have more heavily pretreated populations with >3 lines of therapy with others including patients with a concurrent transformation at diagnosis.[29,30] Recently, cohort studies suggest favorable outcomes with CAR-T, however this is challenging to compare as these patients received CAR-T later in the disease course.[31,32] Our data help to fill the knowledge gap by characterizing treatment patterns and outcomes at specific points after transformation, providing a reference for interpreting outcomes of advancing therapies in this space.

There is significant heterogeneity in OS after HT in the literature with median OS ranging from 3.8 years to over 5 years. Our study is in line with these results with a median OS of 4.9 years.[9] However, some of these studies may have higher OS due to inclusion of composite lymphoma.[10,12] This cohort is notable for inclusion of only patients with pathology confirmed HT following an initial diagnosis of only FL. Our findings should not be extrapolated to patients diagnosed with concurrent elements of FL and aggressive histologies as those patients have a distinctly different clinical course. [10,27,33] EFS is not well reported in the literature but is generally low with reported 5-year EFS of 18%, and median PFS of 1 year in the rituximab era. [9,10] With very short EFS but increasing or variable OS reported in the literature, one may hypothesize that this is due to improvements with additional lines of therapy and the development

of agents, but further data will be needed. Our study also highlights that relapses are far more likely to be with aggressive lymphoma (84%) rather than indolent lymphomas. The most common cause of death following HT was progressive disease in 74% and therapy related mortality in 10%, in cases where cause was known.

In terms of prognostic factors, we confirm prior findings that older age, advanced stage, higher LDH, and previous treatment are predictors of inferior survival.[8,11,12,27,34] Similar to previous findings, we observed that anthracycline exposure prior to HT was associated with an inferior OS compared anthracycline naïve patients.[4,9] However, prior anthracycline exposure may be confounded by indication, more aggressive FL biology requiring early intensive therapy, treatment-related selection pressure, and the inability to reuse anthracycline-containing regimens at HT. We demonstrate that exposure to alkylator or anthracycline exposure are associated with decreased EFS. Our study is not able to identify a group in which prognosis is comparable to de novo large cell lymphoma, where 5 year OS is expected to be above 70%.[16] We do however identify some higher risk groups such as those with transformation within 24 months of diagnosis or 24 months of immunochemotherapy with median OS of 21 months. Though other efforts have been made to evaluate higher risk groups such as early versus late transformation in the SEER dataset analysis, which showed a post transformation survival of 46.9% at 5 years and median OS of 41 months, this may be due to limitations in identification of cases from coding for SEER data.[34] The highest risk groups we identified being patients with prior anthracycline exposure perhaps reflecting a treatment refractory disease, transformation as a event within 24 months of immunochemotherapy, time from diagnosis to transformation, or HGBCL all with a median OS of 25 months or less representing an aggressive biology, being not dissimilar from the 22 month survival for transformation patients reported in 1995.[7] These patients are most in need of novel treatment strategies. With these high-risk groups identified, we utilized the largest data set to date to build an exploratory multivariable model including increasing age (between 65-80), transformation to HGBCL, prior exposure to anthracycline, and timing to transformation. This model is a steppingstone for future evaluation and further validation will be necessary.

Summary

HT of FL represents a clinically unstable event, and patients will have treatment courses that vary significantly based on prior therapy exposure. Regimens used at HT tend to the more intensive chemotherapeutic approaches followed by increasing use of cellular therapy or transplant. The data presented fills an important knowledge gap regarding practice patterns and subsequent outcomes in patients with transformed FL. We present an exploratory multivariable model that will need further clinical validation before use but identifies highest risk patients. The data underscore the need for prospective studies, clinical trial enrollment, and evaluation of cellular and immune-based therapies in patients with HT, particularly those with early transformation, prior anthracycline exposure, or HGBCL histology. The data will also help provide critical context for future study results as cellular therapy and bispecific antibodies move forward in therapy. Patients with HT continue to remain at high risk of death, especially those who have transformation within 2 years of diagnosis or immunochemotherapy. As we were unable to identify a low-risk group, novel therapeutic interventions and further research will continue to be needed for all patients with HT.

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Table 1 - Patient Characteristics		
	At Diagnosis (N=344)	**At Histologic Transformation (N=344)**
Age, Median (IQR)	60 (52,67)	64 (57,72)
Sex, male	204 (59.3%)	204 (59.3%)
Race		
Asian	3 (0.9%)	3 (0.9%)
Black	5 (1.5%)	5 (1.5%)
Other/Unknown	29 (8.4%)	29 (8.4%)
White	307 (89.2%)	307 (89.2%)
Year of diagnosis		
(2001,2009)	161 (46.8%)	49 (14.2%)
(2009,2014)	110 (32.0%)	112 (32.6%)
(2014,2019)	69 (20.1%)	125 (36.3%)
(2019,2023)	4 (1.2%)	58 (16.9%)
Histology		
FL 1-2	281 (81.7%)	NA
FL 3A	48 (14.0%)	NA
FL, grade unknown	15 (4.4%)	NA
DLBCL	NA	283 (82.3%)
FL3B	NA	15 (4.4%)
HGBCL	NA	46 (13.4%)
ECOG PS 2-4	15 (6.1%)	31 (11.4%)
Ann Arbor Stage III/IV	251 (82.3%)	258 (89.6%)
B-symptoms Reported	27 (7.8%)	21 (6.1%)
Bone Marrow Involvement	132 (48.7%)	48 (22.5%)
Elevated LDH	NA	126 (54.3%)
Hgb >=10	NA	167 (64.5%)
Prior lines of systemic therapy, Median (IQR)		1 (1,2)
Prior Treatment Group		
Non-Systemic	NA	68 (19.8%)
CD20-Mononotherapy	NA	28 (8.1%)
Alkylator w/o Anthracycline	NA	118 (34.3%)
Anthracycline	NA	130 (37.8%)
POD24 Status		
No prior systemic	NA	64 (18.7%)
Not IC treated at 1L	NA	66 (19.3%)
IC treated, not POD24	NA	74 (21.6%)
IC treated, POD24	NA	138 (40.4%)
Time from Diagnosis to Transformation		
0-23 months	NA	123 (35.8%)
24+ months	NA	221 (64.2%)

Table 2 - Outcomes by Prognostic factors					
	N (%)	**2-Year EFS (95% CI)**	**EFS HR (95% CI)**	**5-Year OS (95% CI)**	**OS HR (95% CI)**
Clinical					
Age at Transformation					
18-59	117 (34.0%)	29.4% (22.0%,39.4%)	ref	58.7% (49.4%,69.8%)	ref
60-69	123 (35.8%)	30.7% (23.1%,40.7%)	0.81 (0.60, 1.08)	53.6% (44.3%,64.8%)	0.88 (0.60, 1.30)
70+	104 (30.2%)	30.3% (22.3%,41.2%)	0.93 (0.69, 1.25)	34.1% (25.0%,46.5%)	1.80 (1.25, 2.59)
ECOG PS at Transformation					
0-1	240 (88.6%)	34.6% (28.8%,41.5%)	ref	51.9% (45.0%,59.9%)	ref
2-4	31 (11.4%)	16.0% (6.9%,37.1%)	1.71 (1.14, 2.58)	33.2% (19.2%,57.3%)	2.51 (1.58, 4.00)
Pathology and Labs					
Histology at Transformation					
DLBCL	283 (82.3%)	31.3% (26.2%,37.5%)	ref	51.8% (45.6%,58.9%)	ref
FL3B	15 (4.4%)	21.4% (7.9%,58.4%)	0.96 (0.53, 1.77)	48.5% (27.8%,84.5%)	0.86 (0.40, 1.84)
HGB	46 (13.4%)	26.5% (15.6%,45.0%)	1.20 (0.84, 1.72)	25.4% (11.7%,55.1%)	1.87 (1.21, 2.88)
LDH at Transformation					
Not elevated	106 (45.7%)	39.4% (30.7%,50.6%)	ref	49.6% (39.0%,62.9%)	ref
Elevated	126 (54.3%)	19.1% (13.0%,28.0%)	1.82 (1.34, 2.46)	40.9% (32.1%,52.2%)	1.67 (1.15, 2.43)
Treatment					
Prior Systemic Treatment, Yes	278 (81.3%)	24.5% (19.7%,30.4%)	1.89 (1.37, 2.62)	44.6% (38.2%,52.1%)	1.61 (1.09, 2.40)
Prior Number of Systemic lines					
0	65 (18.9%)	52.7% (41.5%,67.0%)	ref	66.2% (55.1%,79.6%)	ref
1	151 (43.9%)	24.0% (18.0%,32.2%)	1.80 (1.28, 2.53)	44.3% (36.1%,54.3%)	1.57 (1.03, 2.37)
2+	128 (37.2%)	26.4% (19.4%,36.0%)	1.90 (1.33, 2.70)	44.7% (35.0%,57.0%)	1.58 (1.03, 2.44)
POD24					
No prior systemic	64 (18.7%)	53.5% (42.2%,67.9%)	ref	67.4% (56.2%,80.8%)	ref
Not IC treated at 1L	66 (19.3%)	35.0% (24.8%,49.5%)	1.44 (0.96, 2.16)	51.3% (38.7%,67.9%)	1.37 (0.84, 2.23)
IC treated, Not POD24	74 (21.6%)	37.5% (27.5%,51.2%)	1.16 (0.77, 1.75)	57.7% (45.2%,73.7%)	0.95 (0.56, 1.62)
IC Treated, POD24	138 (40.4%)	12.8% (8.1%,20.1%)	3.31 (2.33, 4.71)	35.1% (27.1%,45.5%)	2.29 (1.50, 3.49)
Time from Diagnosis to Transformation					
0-23 months	123 (35.8%)	17.9% (12.0%,26.6%)	ref	33.3% (25.4%,43.7%)	ref
24+ months	221 (64.2%)	37.2% (31.1%,44.6%)	0.52 (0.40, 0.66)	58.4% (51.0%,66.8%)	0.47 (0.35, 0.63)

Table 3 - Exploratory OS Multivariate Model				
	Univariate HR	**P value (univariable)**	**Multivariate HR**	**P value (multivariable)**
Age as continuous variable between 65 - 80	1.07 (1.04, 1.10)	< 0.001	1.07 (1.04, 1.10)	< 0.001
Non-HGBCL	0.52 (0.35, 0.82)	0.004	0.49 (0.32, 0.77)	0.002
Anthracycline exposed	1.45 (1.07, 1.97)	0.017	1.80 (1.32, 2.47)	< 0.001
Diagnosis to transformation as continuous interval between 0-48 months	0.98 (0.97, 0.99)	< 0.001	0.98 (0.97, 0.99)	< 0.001

Figure 1: Consort diagram of patient population

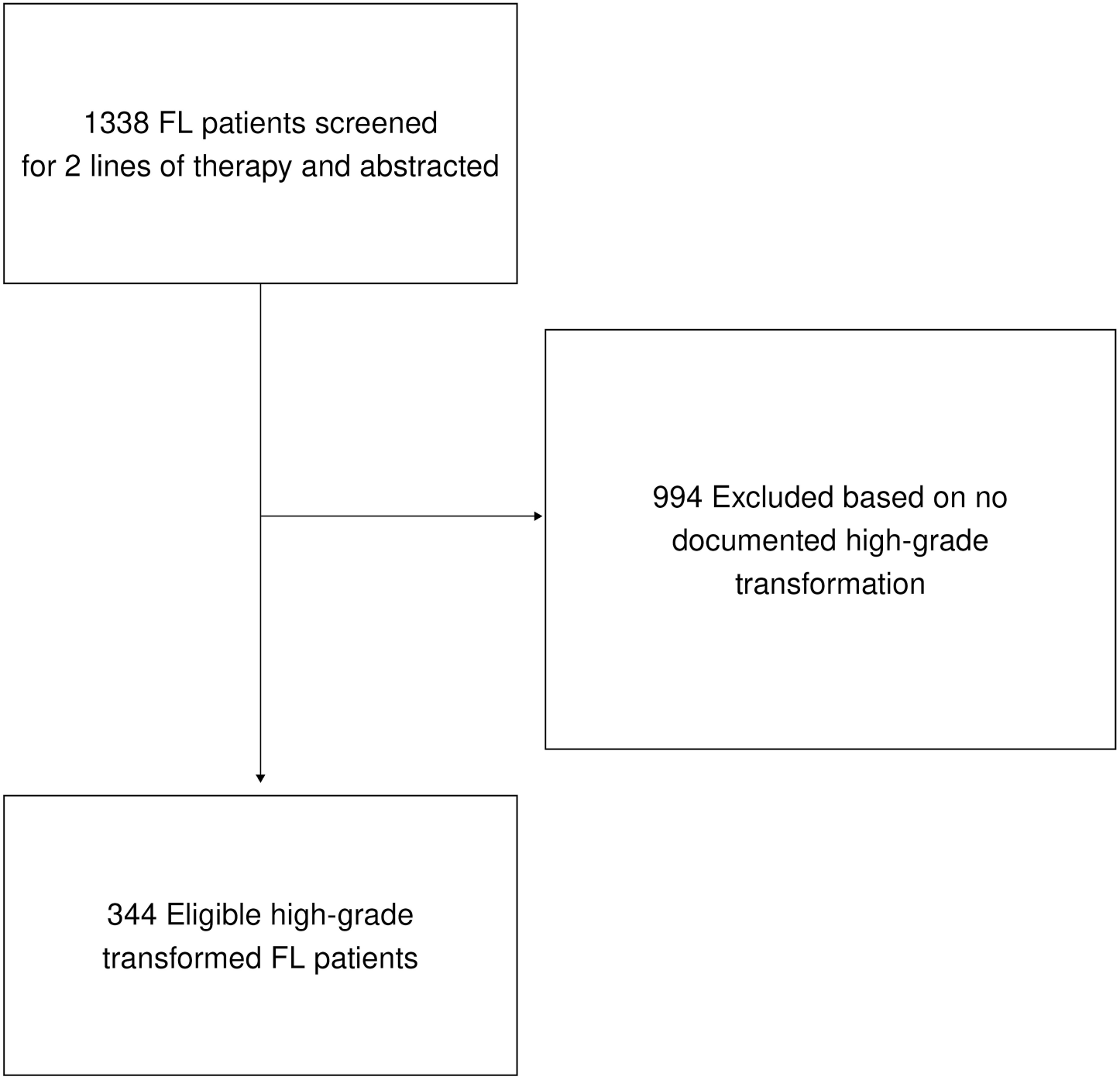
Figure 2:Patterns of care for patients with Transformed FL

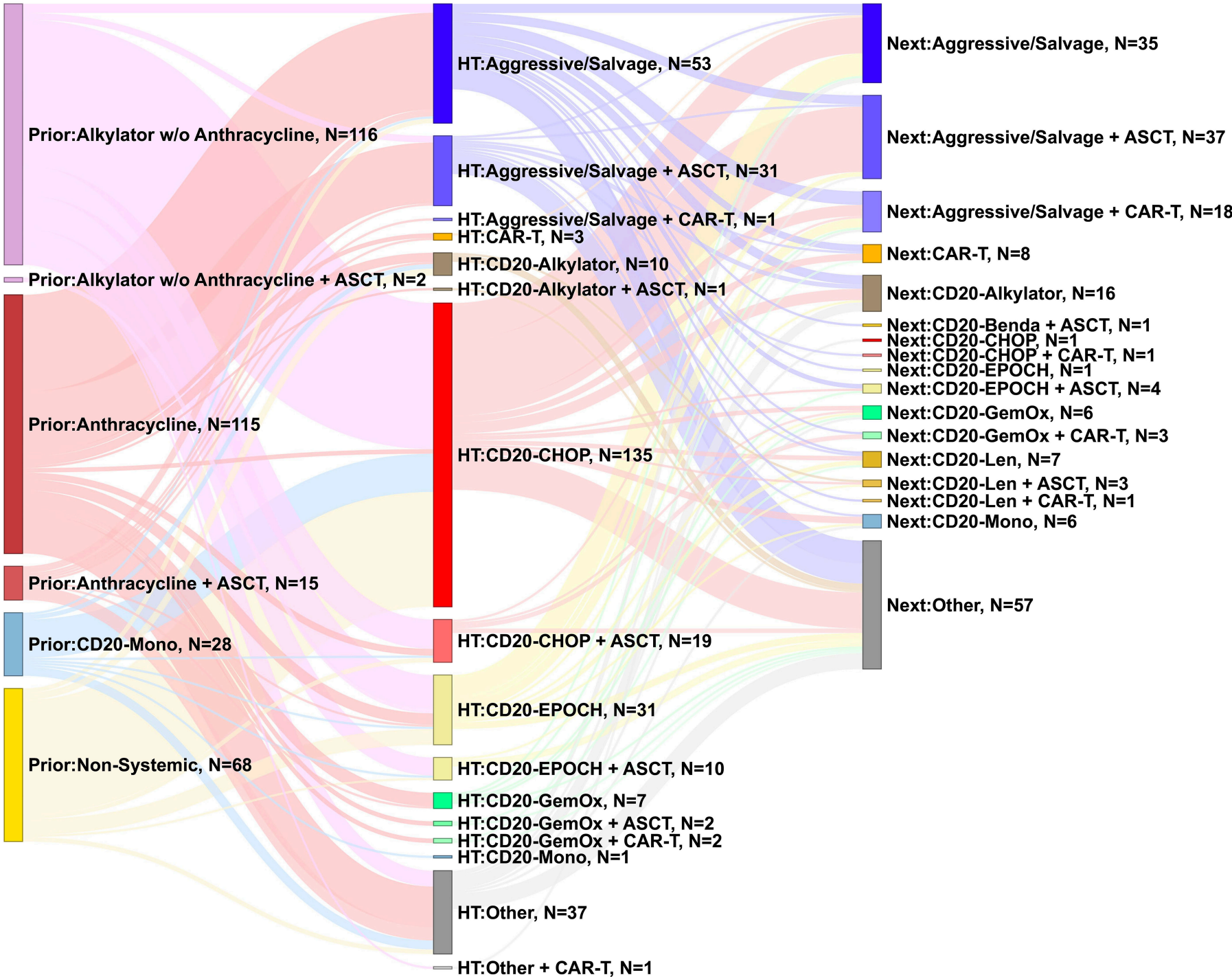
Figure 3: EFS and OS of patients with HT

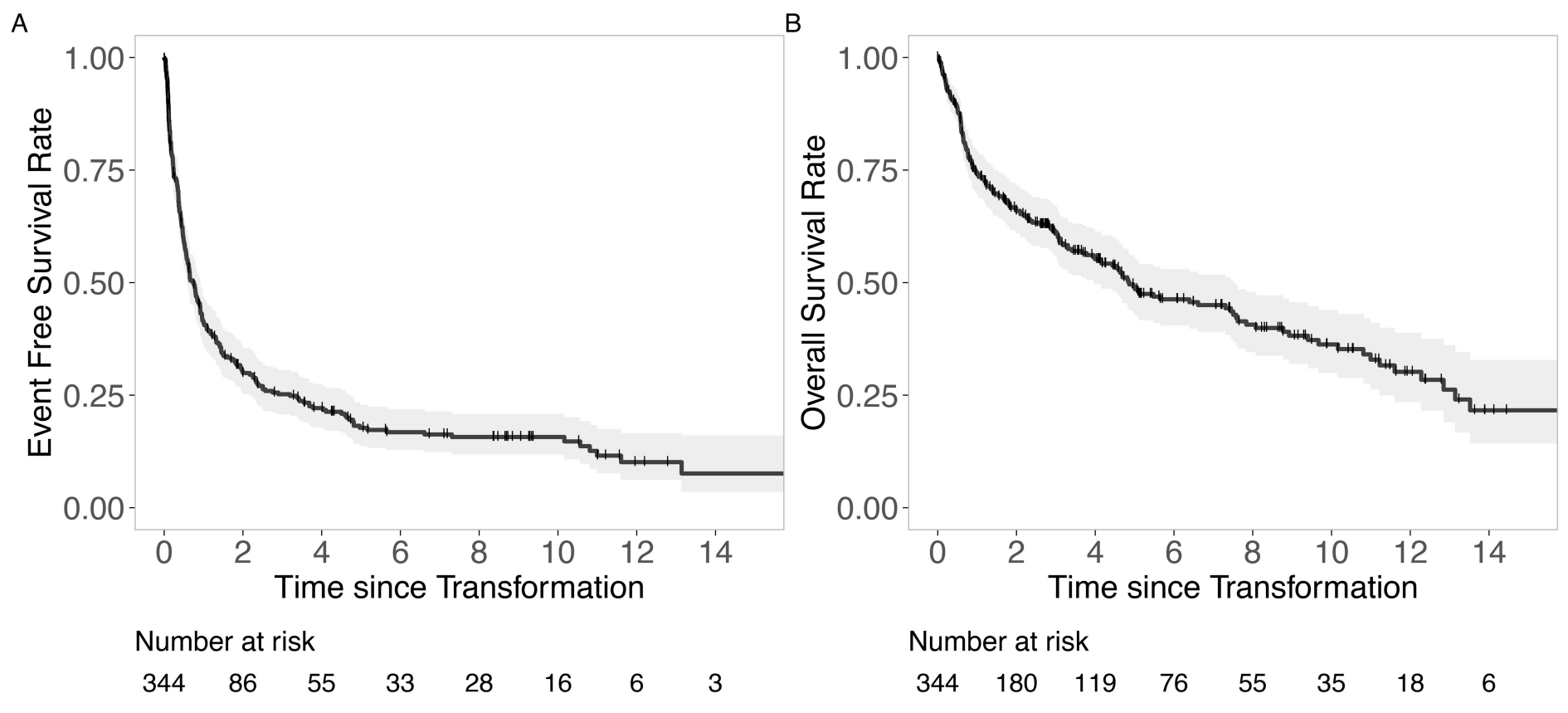
Panel A: Event free survival rate by time since transformation in years. Panel B: Overall survival rate from time of transformation in years.

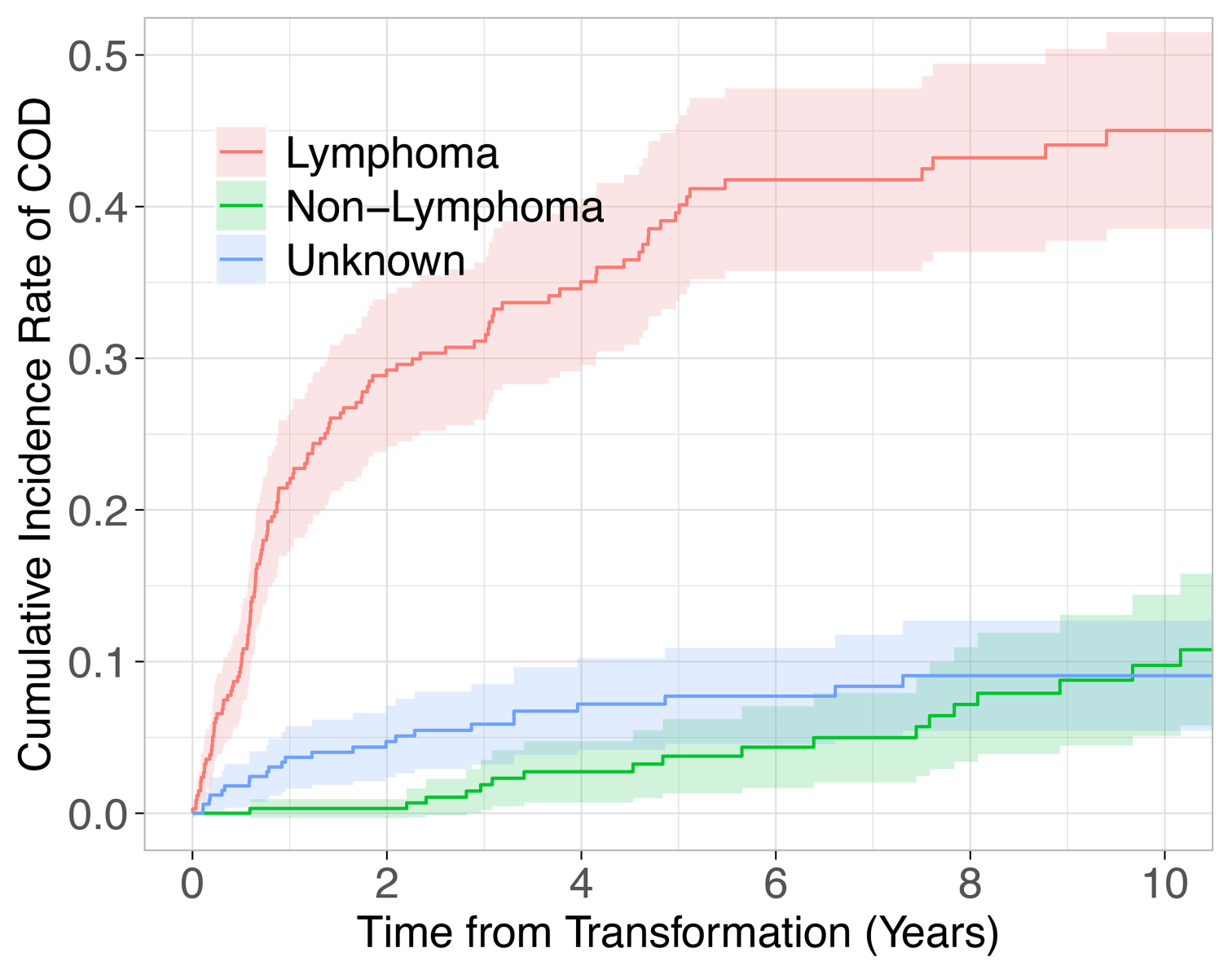
Figure 4: Cause of Death (COD) for patients with transformed FL

Cumulative incidence for cause of death with lymphoma causes and competing non-lymphoma and other causes.


1338 FL patients screened
for 2 lines of therapy and abstracted
994 Excluded based on no
documented high-grade
transformation
344 Eligible high-grade
transformed FL patients


Prior:Alkylator w/o Anthracycline, N=116
Prior:Alkylator w/o Anthracycline + ASCT, N=2
Prior:Anthracycline, N=115
Prior:Anthracycline + ASCT, N=15
Prior:CD20-Mono, N=28
Prior:Non-Systemic, N=68
HT:Aggressive/Salvage, N=53
HT:Aggressive/Salvage + ASCT, N=31
HT:Aggressive/Salvage + CAR-T, N=1
HT:CAR-T, N=3
HT:CD20-Alkylator, N=10
HT:CD20-Alkylator + ASCT, N=1
HT:CD20-CHOP, N=135
HT:CD20-CHOP + ASCT, N=19
HT:CD20-EPOCH, N=31
HT:CD20-EPOCH + ASCT, N=10
HT:CD20-GemOx, N=7
HT:CD20-GemOx + ASCT, N=2
HT:CD20-GemOx + CAR-T, N=2
HT:CD20-Mono, N=1
HT:Other, N=37
HT:Other + CAR-T, N=1
Next:Aggressive/Salvage, N=35
Next:Aggressive/Salvage + ASCT, N=37
Next:Aggressive/Salvage + CAR-T, N=18
Next:CAR-T, N=8
Next:CD20-Alkylator, N=16
Next:CD20-Benda + ASCT, N=1
Next:CD20-CHOP, N=1
Next:CD20-CHOP + CAR-T, N=1
Next:CD20-EPOCH, N=1
Next:CD20-EPOCH + ASCT, N=4
Next:CD20-GemOx, N=6
Next:CD20-GemOx + CAR-T, N=3
Next:CD20-Len, N=7
Next:CD20-Len + ASCT, N=3
Next:CD20-Len + CAR-T, N=1
Next:CD20-Mono, N=6
Next:Other, N=57


A
Event Free Survival Rate
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
14
Time since Transformation
Number at risk
344
86
55
33
28
16
6
3
B
Overall Survival Rate
1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
12
14
Time since Transformation
Number at risk
344
180
119
76
55
35
18
6



Number at risk

344	180	119	76	55	35

Supplementary

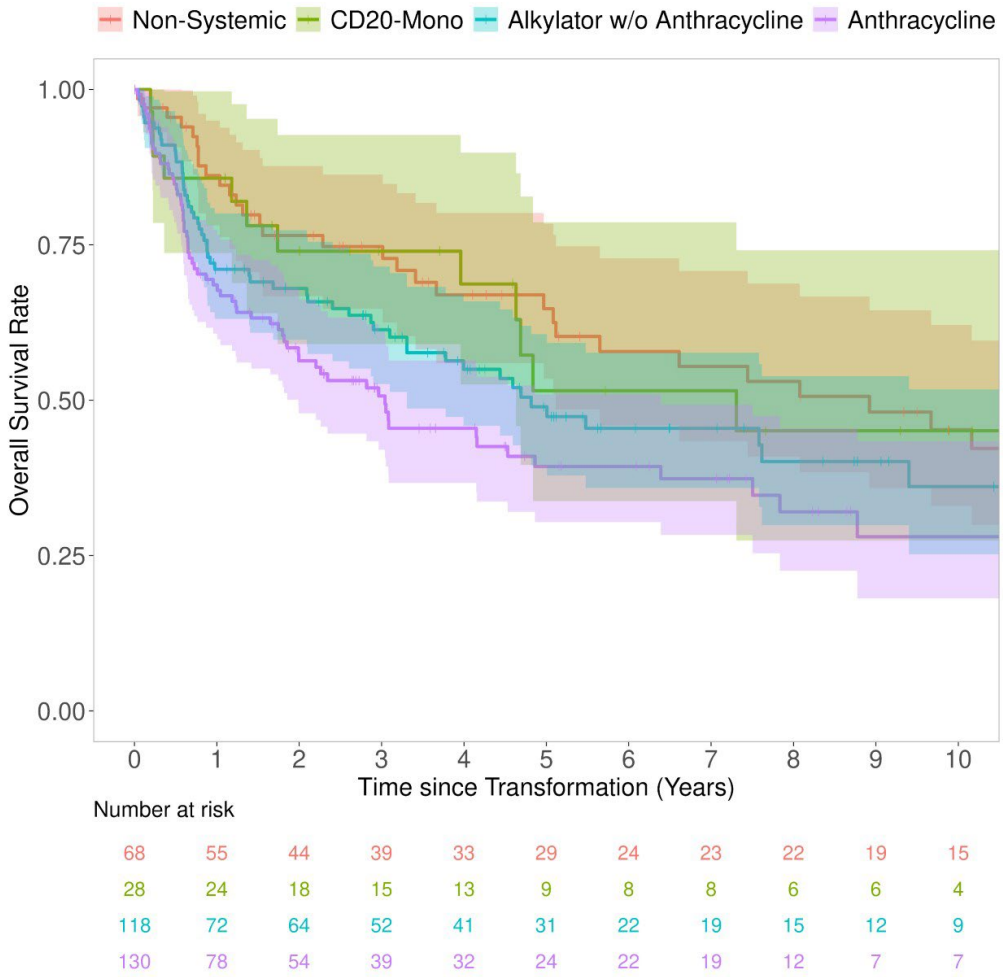
Supplemental Table 1 - Outcomes by Prognostic factors					
	N (%)	**2-Year EFS (95% CI)**	**EFS HR (95% CI)**	**5-Year OS (95% CI)**	**OS HR (95% CI)**
Clinical					
Age at Transformation					
18-59	117 (34.0%)	29.4% (22.0%,39.4%)	ref	58.7% (49.4%,69.8%)	ref
60-69	123 (35.8%)	30.7% (23.1%,40.7%)	0.81 (0.60, 1.08)	53.6% (44.3%,64.8%)	0.88 (0.60, 1.30)
70+	104 (30.2%)	30.3% (22.3%,41.2%)	0.93 (0.69, 1.25)	34.1% (25.0%,46.5%)	**1.80 (1.25, 2.59)**
Sex					
F	140 (40.7%)	35.7% (28.4%,45.0%)	ref	50.9% (42.2%,61.4%)	ref
M	204 (59.3%)	26.3% (20.6%,33.6%)	1.30 (1.02, 1.66)	47.8% (40.5%,56.4%)	1.10 (0.81, 1.49)
Histology at Diagnosis					
FL 1-2	281 (85.4%)	34.5% (29.1%,40.8%)	ref	51.6% (45.4%,58.8%)	ref
FL 3A	48 (14.6%)	10.3% (4.1%,26.0%)	1.93 (1.38, 2.70)	32.8% (20.2%,53.3%)	1.48 (0.98, 2.22)
FLIPI at Diagnosis					
0-1	48 (26.1%)	39.9% (27.4%,58.1%)	ref	69.7% (57.1%,85.2%)	ref
2	56 (30.4%)	40.6% (29.1%,56.6%)	1.30 (0.80, 2.12)	49.8% (37.0%,66.9%)	**2.10 (1.11, 3.94)**
3-5	80 (43.5%)	22.5% (14.6%,34.8%)	1.85 (1.19, 2.88)	37.1% (26.8%,51.3%)	**2.39 (1.32, 4.32)**
Ann Arbor Stage at Transformation					
I/II	30 (10.4%)	43.7% (28.6%,66.5%)	ref	50.3% (34.1%,74.1%)	ref
III/IV	258 (89.6%)	30.8% (25.5%,37.3%)	1.26 (0.81, 1.97)	48.4% (41.8%,56.1%)	1.19 (0.71, 2.00)
ECOG PS at Transformation					
0-1	240 (88.6%)	34.6% (28.8%,41.5%)	ref	51.9% (45.0%,59.9%)	ref

2-4	31 (11.4%)	16.0% (6.9%,37.1%)	1.71 (1.14, 2.58)	33.2% (19.2%,57.3%)	**2.51 (1.58, 4.00)**
Bone Marrow Involvement at Transformation					
No	165 (77.5%)	32.1% (25.5%,40.4%)	ref	46.9% (39.0%,56.5%)	ref
Yes	48 (22.5%)	28.8% (18.1%,45.9%)	1.02 (0.71, 1.47)	55.5% (42.6%,72.4%)	1.01 (0.65, 1.58)
IPI at Transformation					
0-1	35 (16.0%)	41.9% (27.8%,63.1%)	ref	55.9% (38.0%,82.1%)	ref
2	59 (26.9%)	33.7% (23.4%,48.5%)	1.16 (0.70, 1.90)	51.8% (39.4%,68.0%)	1.12 (0.58, 2.17)
3-5	125 (57.1%)	19.6% (13.5%,28.6%)	1.57 (1.00, 2.46)	39.2% (30.5%,50.4%)	**1.88 (1.04, 3.40)**
Pathology and Labs					
Histology at Transformation					
DLBCL	283 (82.3%)	31.3% (26.2%,37.5%)	ref	51.8% (45.6%,58.9%)	ref
FL3B	15 (4.4%)	21.4% (7.9%,58.4%)	0.96 (0.53, 1.77)	48.5% (27.8%,84.5%)	0.86 (0.40, 1.84)
HGB	46 (13.4%)	26.5% (15.6%,45.0%)	1.20 (0.84, 1.72)	25.4% (11.7%,55.1%)	**1.87 (1.21, 2.88)**
LDH at Transformation					
Not elevated	106 (45.7%)	39.4% (30.7%,50.6%)	ref	49.6% (39.0%,62.9%)	ref
Elevated	126 (54.3%)	19.1% (13.0%,28.0%)	1.82 (1.34, 2.46)	40.9% (32.1%,52.2%)	**1.67 (1.15, 2.43)**
Hemoglobin at Transformation					
<10	38 (14.7%)	9.3% (3.2%,27.2%)	ref	19.7% (9.8%,39.6%)	ref
>=10	221 (85.3%)	32.0% (26.2%,39.2%)	0.49 (0.33, 0.71)	48.2% (40.9%,56.9%)	**0.35 (0.23, 0.53)**
Treatment					
Prior Systemic					
No	64 (18.7%)	53.5% (42.2%,67.9%)	ref	67.4% (56.2%,80.8%)	ref

Yes	278 (81.3%)	24.5% (19.7%,30.4%)	1.89 (1.37, 2.62)	44.6% (38.2%,52.1%)	**1.61 (1.09, 2.40)**
Prior Treatment(s)					
Non-Systemic	68 (19.8%)	52.4% (41.4%,66.5%)	ref	64.7% (53.4%,78.4%)	ref
CD20-Mono	28 (8.1%)	38.1% (23.6%,61.6%)	1.28 (0.78, 2.11)	51.5% (33.8%,78.6%)	1.19 (0.64, 2.24)
Alkylator w/o Anthracycline	118 (34.3%)	28.4% (21.0%,38.3%)	1.67 (1.17, 2.37)	48.9% (39.5%,60.6%)	1.46 (0.95, 2.25)
Anthracycline	130 (37.8%)	18.1% (12.3%,26.7%)	2.41 (1.70, 3.41)	39.3% (30.4%,50.9%)	**1.81 (1.19, 2.76)**
Prior Number of Systemic lines					
0	65 (18.9%)	52.7% (41.5%,67.0%)	ref	66.2% (55.1%,79.6%)	ref
1	151 (43.9%)	24.0% (18.0%,32.2%)	1.80 (1.28, 2.53)	44.3% (36.1%,54.3%)	**1.57 (1.03, 2.37)**
2+	128 (37.2%)	26.4% (19.4%,36.0%)	1.90 (1.33, 2.70)	44.7% (35.0%,57.0%)	**1.58 (1.03, 2.44)**
POD24					
No prior systemic	64 (18.7%)	53.5% (42.2%,67.9%)	ref	67.4% (56.2%,80.8%)	ref
Not IC treated at 1L	66 (19.3%)	35.0% (24.8%,49.5%)	1.44 (0.96, 2.16)	51.3% (38.7%,67.9%)	1.37 (0.84, 2.23)
Not POD24	74 (21.6%)	37.5% (27.5%,51.2%)	1.16 (0.77, 1.75)	57.7% (45.2%,73.7%)	0.95 (0.56, 1.62)
POD24	138 (40.4%)	12.8% (8.1%,20.1%)	3.31 (2.33, 4.71)	35.1% (27.1%,45.5%)	**2.29 (1.50, 3.49)**
Diagnosis Transformation Interval					
0-23 months	123 (35.8%)	17.9% (12.0%,26.6%)	ref	33.3% (25.4%,43.7%)	ref
24+ months	221 (64.2%)	37.2% (31.1%,44.6%)	0.52 (0.40, 0.66)	58.4% (51.0%,66.8%)	**0.47 (0.35, 0.63)**
Transformation Treatment					
CD20-CHOP	154 (44.8%)	42.8% (35.4%,51.7%)	ref	62.1% (54.0%,71.4%)	ref
Aggressive/Salvage	85 (24.7%)	18.2% (11.2%,29.5%)	2.02 (1.49, 2.74)	42.3% (31.9%,55.9%)	1.48 (1.02, 2.15)
CD20-Alk/GemOx	22 (6.4%)	13.6% (4.8%,39.0%)	2.36 (1.49, 3.75)	38.7% (19.0%,78.6%)	2.48 (1.39, 4.44)

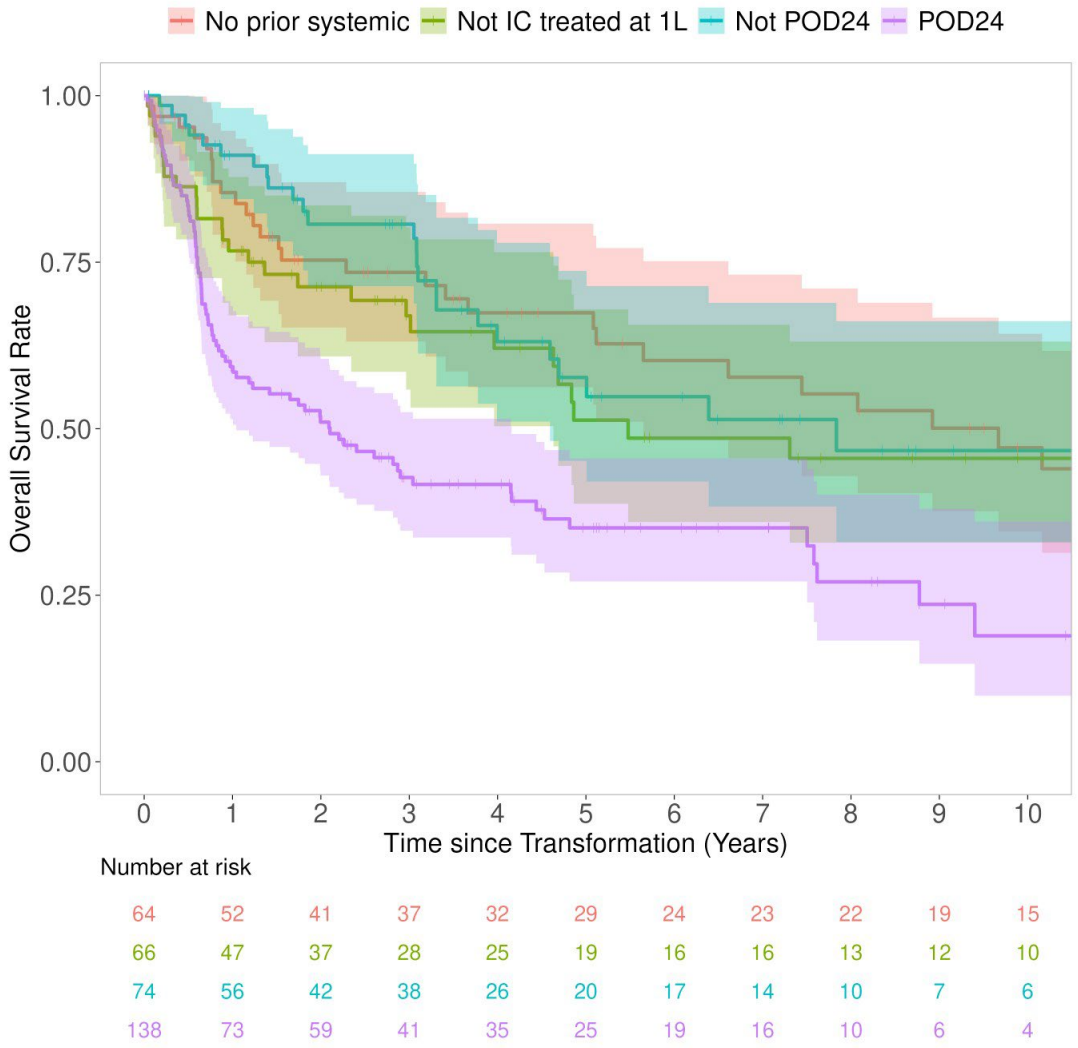
CD20-EPOCH	41 (11.9%)	22.6% (12.5%,40.9%)	1.47 (1.00, 2.18)	41.5% (27.2%,63.1%)	1.71 (1.04, 2.81)
Other	42 (12.2%)	24.6% (13.8%,44.0%)	1.86 (1.23, 2.79)	22.5% (10.4%,48.9%)	2.56 (1.61, 4.08)

Supplemental figure 1: Overall survival by prior therapy exposure.



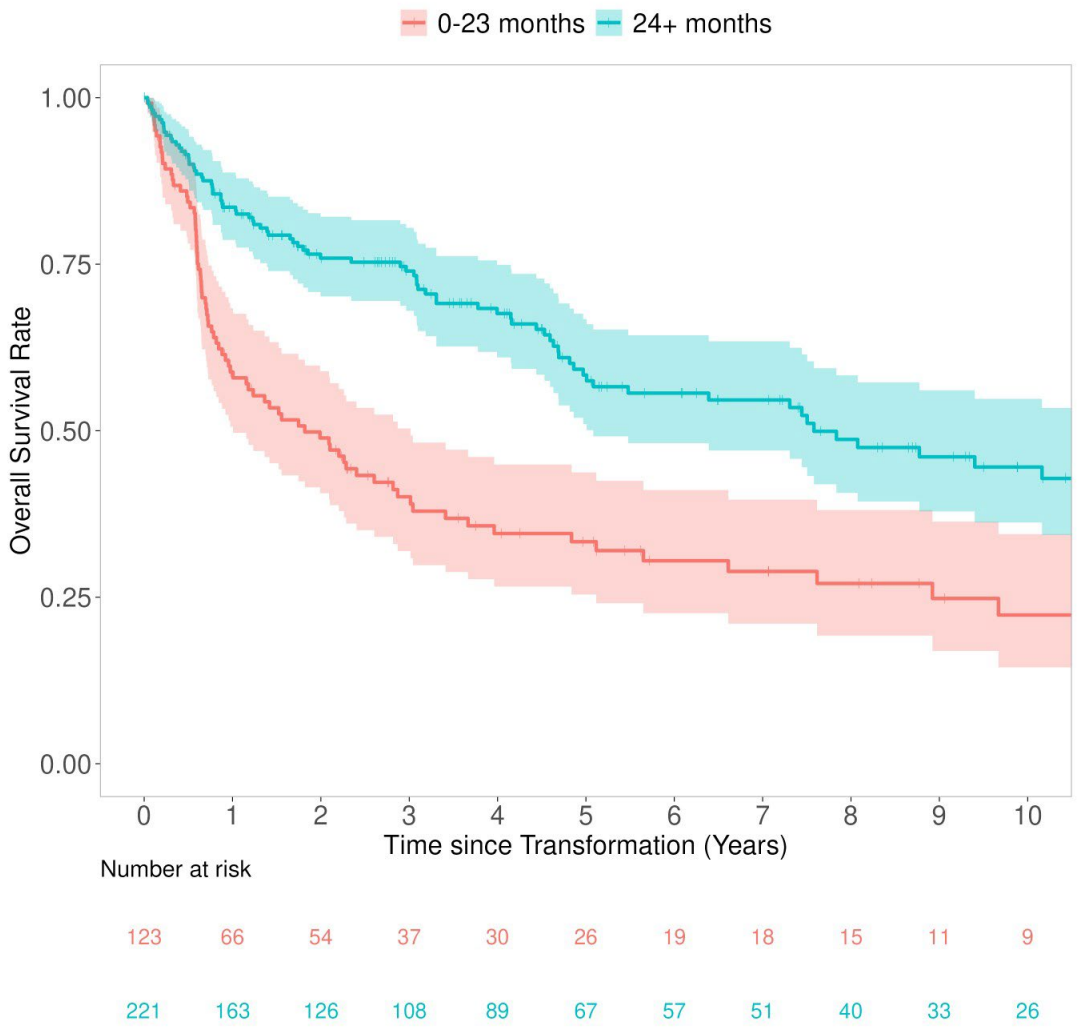
Supplemental figure 2: Overall survival by POD24 (progression of disease within 24 months of immunochemotherapy) status.

POD24 patients had transformation within 24 months of IC, with transformation as the progression event.



Supplemental figure 3: Overall survival by diagnosis to transformation interval

Transformation within 24 months of diagnosis or after 24 months from diagnosis.



Supplemental figure 4: Overall survival by multivariate model in tertiles