blood advances

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Evaluating Lab-Based Eligibility Criteria by Race/Ethnicity in Clinical Trials of Diffuse Large B-Cell Lymphoma

Tracking no: ADV-2024-012838R2

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Abstract:
Underrepresentation of racial and ethnic subgroups in cancer clinical trials remains a persistent challenge. Restrictive clinical trial eligibility criteria have been shown to exacerbate this problem. We previously identified that up to 24% of patients treated with standard immunochemotherapy (IC) would have been excluded from recent first-line trials in diffuse large B-cell lymphoma (DLBCL) based on 5 lab-based criteria. These ineligible patients had worse clinical outcomes and increased deaths related to lymphoma progression suggesting the potential exclusion of patients who could have benefited most from the novel therapies being evaluated. Utilizing data from the prospectively enrolled Lymphoma Epidemiology Outcomes (LEO) Cohort study, with demographics broadly similar to the U.S. patients diagnosed with lymphoma, we evaluated the impact of laboratory eligibility criteria from recent first-line DLBCL trials across various racial and ethnic backgrounds. There were significant differences in the baseline lab values by race/ethnicity with Black/African American (AA) patients having the lowest mean hemoglobin and highest creatinine clearance. Based on recent clinical trial eligibility criteria, AA and Hispanic patients had higher rates of lab-based ineligibility compared to Non-Hispanic Whites. The largest gap in the clinical outcomes between eligible (ref) and non-eligible patients was noted within AA patients with an overall survival hazard ratio based on POLARIX clinical trial criteria of 4.09, 95% CI: 1.83-9.14. A thoughtful approach to the utility of each criterion and cut offs for eligibility needs to be evaluated in the context of its differential impact across various racial/ethnic groups.

Conflict of interest: COI declared - see note

COI notes: LJN has received honorarium for participation in advisory boards/consulting from Abbvie, ADC Therapeutics, Atara Biotherapeutics, BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Janssen, Incyte, Morphosys, Novartis, and Takeda; research support from BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Gilead/Kite, IGM Biosciences, Janssen, Novartis, and Takeda Unrelated to this analysis JRC has received research funding to Mayo from BMS, Genmab, and NanoString; compensation to Mayo for participation on a scientific advisory board from BMS; and personal compensation for participation in a SMC for Protagonist Therapeutics. MJM: research funding: BMS, Genetech/Roche, GenMab; Advisory Board/Consulting: BMS, AstraZeneca, Adaptive Biotechnologies

Preprint server: No;

Author contributions and disclosures: Study conception and design: AK, TEW, GSN, MJM Collection and/or assembly of the data: AK, RM, LJN, TMR, UF, JTR, TJM, SMR, ISL, BSK, PM, JRC, CRF, GSN, MJM Statistical analysis: AK, RM, SMR, MJM Manuscript writing and review: all authors

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and 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/).

Clinical trial registration information (if any):

Evaluating the Impact of Lab-Based Eligibility Criteria by Race/Ethnicity in First-line Clinical Trials of Diffuse Large B-Cell Lymphoma

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Presented in abstract form at the 64th annual meeting of the American Society of Hematology, New Orleans, LA, 12 December 2022

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Word count: 2846

Abstract

Underrepresentation of racial and ethnic subgroups in cancer clinical trials remains a persistent challenge. Restrictive clinical trial eligibility criteria have been shown to exacerbate this problem. We previously identified that up to 24% of patients treated with standard immunochemotherapy (IC) would have been excluded from recent first-line trials in diffuse large B-cell lymphoma (DLBCL) based on 5 lab-based criteria. These ineligible patients had worse clinical outcomes and increased deaths related to lymphoma progression suggesting the potential exclusion of patients who could have benefited most from the novel therapies being evaluated. Utilizing data from the prospectively enrolled Lymphoma Epidemiology Outcomes (LEO) Cohort study, with demographics broadly similar to the U.S. patients diagnosed with lymphoma, we evaluated the impact of laboratory eligibility criteria from recent first-line DLBCL trials across various racial and ethnic backgrounds. There were significant differences in the baseline lab values by race/ethnicity with Black/African American (AA) patients having the lowest mean hemoglobin and highest creatinine clearance. Based on recent clinical trial eligibility criteria, AA and Hispanic patients had higher rates of lab-based ineligibility compared to Non-Hispanic Whites. The largest gap in the clinical outcomes between eligible (ref) and non-eligible patients was noted within AA patients with an overall survival hazard ratio based on POLARIX clinical trial criteria of 4.09, 95% CI: 1.83-9.14. A thoughtful approach to the utility of each criterion and cut offs for eligibility needs to be evaluated in the context of its differential impact across various racial/ethnic groups.

Key Point 1: Patients excluded from clinical trials of DLBCL are at a higher risk of dying from lymphoma when treated with standard of care therapy.

Key Point 2: Minorities, in particular Black patients, are at a greater risk of being left behind on clinical trials of DLBCL.

Introduction

Therapeutic clinical trials are an essential component of providing care to cancer patients by enhancing discovery of new agents and providing access to precision medicine approaches. Representation in clinical trials is particularly important in the context of changing U.S. demographics. Additionally, differences exist in disease biology, clinical presentations, and treatment tolerability based on race and ethnicity.[1-3] Eligibility criteria are essential gatekeepers to prevent excessive toxicity from experimental treatments and to increase internal validity by creating a more homogeneous population to test the trial hypothesis.[4] However, restrictive eligibility criteria can limit the generalizability of the trial data when the drugs are approved and used in populations underrepresented or not represented in the trials. Clinical trial eligibility criteria account for the reason for non-participation in cancer clinical trials in up to a quarter of patients.[5-8] Furthermore, clinical trials have become more complex and may require a central review of pathology, molecular subtyping prior to enrollment, and an exhaustive trial enrollment process requiring special diagnostics that may delay enrollment to the point where patients and physicians decide to proceed with standard therapy.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma in the US. [9] It is a clinically heterogenous disease with variable clinical presentations such as bulky disease, rapid tumor growth, or symptomatic disease. These high-risk patients in particular can have lab-based derangements as a manifestation of the disease itself. We previously identified that up to 24% of patients treated with standard immunochemotherapy (IC) would have been trial ineligible based on 5 lab-based criteria alone.[10] Additionally, ineligible patients had worse clinical outcomes and increased deaths related to lymphoma progression suggesting the potential exclusion of patients who could have benefited most from novel therapies. According the to FDA's 2018 Drug Trials Snapshots a total of 5157 patients participated in oncology clinical trials that led to 17 new drug approvals. Of these 68% were whites, 5% were Asian, 4% were African American and 4% were Hispanic. These proportions sharply contrasted with the racial distribution of the general US population and US cancer population.[11] This leads to significant limitations in applying data from the clinical trials pertaining to drug efficacy and safety/toxicity to the real-world population. The stakeholders from ASCO, FDA, Friends of Cancer Research and the Association of Community Cancer Centers have all published recommendations and commitment to increasing diversity, equity and inclusion in clinical trials.[12-16]. Our prior study on the impact of trial eligibility in DLBCL was in a cohort of patients predominantly from the upper midwest US with limited racial and ethnic diversity.[17] Therefore, we sought to confirm our findings in a larger, more diverse Lymphoma Epidemiology Outcomes (LEO) cohort and examine the differential impact of these lab-based criteria on trial exclusion based on race/ethnicity.

Methods

Study population

Patients were enrolled within 6 months of diagnosis in the LEO Cohort Study (ClinicalTrials.gov Identifier: NCT02736357) at one of 8 institutions: Mayo Clinic, Rochester MN, MD Anderson, Houston TX, University of Miami, Miami FL, Emory University, Atlanta GA, University of Iowa, Iowa City IA, Washington University, St. Louis MO, Weill Cornell Medicine, New York NY, University of Rochester, Rochester NY and prospectively followed.[18] Baseline clinical data was abstracted using a standard protocol. Central pathology review was performed by an expert hematopathologist at each LEO center. Patients were managed by the treating physician (either at one of the 8 academic centers or locally) and contacted prospectively and systematically every 6 months for the first 3 years and then annually thereafter. Events (new treatments, progression, and death) were validated by medical record review. Patients included in this analysis were enrolled in LEO from 7/1/2015-5/31/2020. All patients provided informed consent to enroll in the LEO Cohort study. Utilization of the LEO data for this study was approved by the Mayo Clinic IRB.

This analysis included adult patients 18 years or older with a diagnosis of DLBCL who initiated first-line treatment with anthracycline plus CD20 antibody-based IC. The exclusion criteria were: Burkitt lymphoma, Burkitt-like intensive therapy (e.g. CODOX-M, HyperCVAD), lack of information regarding race/ethnicity, missing values for 3 or more of the 5 lab-based criteria. Creatinine clearance was calculated per Cockcroft-Gault w/o race adjustment as per the protocol from the POLARIX clinical trial.[19] Race and ethnicity were self-reported by the patients at the time of LEO enrollment and were categorized as follows: Hispanic (any race), non-Hispanic Black or African American (AA), non-Hispanic white (NHW), and all other race/ethnicities (i.e, non-white race and non-Hispanic).

Organ-function lab values at the time of diagnosis were abstracted from the medical record as part of standard LEO data collection. Baseline lab-based eligibility criteria parameters were identified from recent phase 3 first-line DLBCL clinical trials as previously described. These included hemoglobin, absolute neutrophil count (ANC), platelet count, creatinine clearance and bilirubin. The cutoff values for different lab parameters reported in the respective clinical trial's protocol (POLARIX, ENGINE, PHOENIX, ROBUST, ECOG 1412, REMoDL-B, GOYA, CALGB 50303) were identified (supplement table 1).[19-26]

Statistical methods

The percentage of patients excluded based on clinical trial criteria was determined for each lab value individually as well as across all lab parameters. The percentage exclusion across trial was then compared between various race/ethnicity groups. Event-free survival (EFS) was defined as the time from diagnosis to relapse, progression, retreatment (second-line therapy), or death because of any cause. Overall survival (OS) was defined as the time from diagnosis until death because of any cause. EFS was reported at 24 months (EFS24), as previously described.[27] Kaplan-Meier curves and Cox models were used to compare EFS and OS outcomes between eligible and ineligible patients. Logistic regression was used to compare EFS24 between eligible and ineligible patients. Causes of death were evaluated using a competing risk approach.[28] An interactive tool was developed in R-Shiny to allow users to estimate the percentage of patients who would be excluded by changing organ function cutoffs and race/ethnicity. All analyses were performed using R version 3.6.2, R-Shiny, and SAS version 9.4M5.1

Data Sharing

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

Results

Baseline characteristics

A total of 7746 patients enrolled in the LEO cohort between July 2015 and December 2020; 2748 had DLBCL or other aggressive B-cell lymphoma and 2353 patients initiated first-line IC. Of these, 2185 patients had ≥3 of 5 lab values available at the time of diagnosis (Figure 1). Approximately 79% of the cohort was treated at one of the 8 US academic centers and rest at referring sites. The baseline characteristics of the total cohort (2185 patients) and race/ethnicities are shown in Table 1. The median age at diagnosis for the entire cohort was 63 years (IQR 52-72) with males accounting for 57% of the patients. The median time from diagnosis to treatment was 21 days (IQR 12-33). A total of 9% of the patients were treated on various first-line clinical trials available at the time of presentation. The median follow-up of the cohort was 37 months; 420 patients (19%) died during the follow-up period and 73% achieved 24 months of EFS.

There were significant differences in clinical presentation and management by race and ethnicity within the LEO cohort. In comparison to NHW patients, AA patients and Hispanic patients who enrolled in the LEO were much younger with a median age of 51 years (IQR 39-62) for AA patients and 56 years (IQR 41-65) for Hispanic patients compared to 65 years (IQR 55-73) in NHW. AA (44%) and Hispanic (37%) patients with DLBCL presented with significantly higher rates of B-symptoms compared to NHW (30%). NHW (10%) were also more likely to receive first-line therapy on a clinical trial compared to the AA (7%) and Hispanic (5%) patients.

Impact of lab-based criteria on trial exclusion based on race/ethnicity

We observed significant differences in the distributions of lab-based criteria by race/ethnicity (Table 2). NHW and Hispanic patients with DLBCL had the highest median levels of hemoglobin in the LEO cohort, with significantly lower hemoglobin levels observed in AA and other non-white minority patients; a 10 gm/dL cutoff for hemoglobin as utilized in the ENGINE trial, would exclude 28% of AA LEO patients with DLBCL compared to only 13% of NHW (Figure 2A). There was also a significant difference in neutrophil counts by race/ethnicity, with AA patients having the lowest neutrophil counts. However, a cutoff of 1.0 x 10^9/L as utilized in the POLARIX trial would have excluded very few patients across all race and ethnicity groups (Figure 2B). The race/ethnicities with the highest distributions of creatinine clearance were AA and Hispanic patients (Figure S1), which were also the race/ethnicities with the youngest age distributions.

When the lab-based cut offs were applied, between 9 and 26% of the LEO Cohort patients were considered ineligible across the different trials (Table 3) with the ReMODL-B trial being the least restrictive and the ENGINE trial being the most restrictive. Notably, as the trials got more restrictive, the impact was greater on minorities compared to NHW (table 3). There was a significantly higher ineligibility of the AA (37%), Hispanic (29%), and other non-Hispanic minority (30%) patients when compared to the NHW (24%) in the LEO cohort based on the ENGINE trial's lab-based criteria. Similar findings were noted for the GOYA and POLARIX trials. An interactive tool to further evaluate the impact of potential cutoffs on eligibility using study data from the LEO Cohort is publically available at rtools.mayo.edu/leo_dlbcl_left_behind/

Impact of trial exclusion on outcomes based on race/ethnicity

To confirm our prior results, we next compared clinical outcomes and cause of death in the LEO cohort based on eligibility and race/ethnicity. DLBCL patients enrolled in LEO who did not meet trial eligibility based on the 5 lab criteria had significantly inferior EFS and OS. When applying lab-based cutoffs from the recent POLARIX trial, EFS24 was 79% (95% CI, 77-81) in trial eligible patients compared to 62% (95%CI, 57-68) in trial ineligible patients ($p<0.001$) (Figure S4). Additionally, patients that were trial ineligible had a significantly increased risk of dying from progressive lymphoma, with no increase in therapy-related deaths. Five-year OS was 80% (95% CI, 78-83) versus 55% (95% CI, 48-62) with a risk of death from progressive disease at 5 years was 20% (95% CI, 16-25) versus 8% (95% CI, 7-9) Figure S5). This observation was consistent across the various trial eligibility criteria examined (data not shown).

The discrepancy in outcomes in the LEO Cohort was most notable in AA patients. When eligibility cutoffs from the POLARIX trial were applied, AA patients had the most disparate outcomes between eligible and ineligible patients (Figure 3). This effect remained significant after adjusting for IPI, with AA trial ineligible patients have significantly inferior EFS (HR=2.56, 95% CI: 1.35-4.85) and OS (HR=4.09, 95% CI: 1.83-9.14) compared to AA trial eligible patients.

Discussion

This study confirms our previous findings of the impact of lab-based eligibility criteria in newly diagnosed DLBCL patients and extends these results to a much more diverse population. Patients ineligible for trials due to 5 lab-based criteria had worse clinical outcomes as well as increased risk of dying from progressive lymphoma. Furthermore, these lab-based eligibility criteria led to a disproportionately higher exclusion of Hispanic, AA and other minority patients as compared

to NHW. To our knowledge these data have not been previously reported in first-line DLBCL and will help in future clinical trial design. We also confirmed the previously reported findings of AA patients presenting with DLBCL at a much younger age and with more adverse/high-risk disease as compared to NHW, which may be responsible for worse lab-based criteria.[29] This suggests an even greater unmet need for such patients who could potentially benefit from novel treatments in clinical trials than standard of care IC.

In the last few decades clinical trials have become increasingly more restrictive. Loh et al. analyzed 42 phase III clinical trials in first-line DLBCL patients and reported that the total number of criteria per study increased from 14.5 between 1993-2005 to 23 in 2014-2020.[8] Furthermore, in the same study when these criteria were applied to a cohort of newly diagnosed DLBCL patients from an institutional database, the percent of patients ineligible also increased from 32% to 53% between these time periods. While these ineligibility numbers are higher than our current report, the ineligibility in our study is only based on 5 lab-based criteria. The percentage of DLBCL patients ineligible from the LEO cohort is similar to our previous report as well as recently reported Danish nationwide cohort study (18-29% exclusion).[30]

Many efforts are currently underway to modernize clinical trial eligibility criteria.[12,15,31-34] Lab-based criteria are easily modifiable in trial design. However, the progress remains slow due to a paucity of data regarding toxicities related to investigational drugs in the early phase trials for patients with organ dysfunction as they are typically excluded causing further regulatory issues. Determination of lab-based eligibility criteria can be subjective and may not necessarily be related to the mechanism of action of the investigational agent. The differential impact of various lab-based criteria on DLBCL patients based on race/ethnicity has not been reported previously. While it can be hypothesized that some differences in labs exist due to race/ethnicity, such as AA

having higher proportion of benign ethnic neutropenia, the ANC threshold used in current trial eligibility did not show a substantial impact on eligibility. In contrast, HGB eligibility cutoffs were >10 g/dL in the ENGINE trial and >9 in the POLARIX trial while not present in half of the trials examined. This high threshold for HGB contributed to a 37% exclusion of AA patients in the LEO Cohort based on the ENGINE criteria compared to 24% in the NHW. This is notable as AA patients were the youngest age and highest kidney function distributions across the race/ethnicity groups. In addition, the largest gap in the clinical outcomes was noted for the AA trial eligible and trial ineligible patients. This suggests a true unmet need in a population that could benefit the most from trial participation and novel therapeutics. Similar findings have been reported in a recent report from the FDA in multiple myeloma trials.[35] Sixteen myeloma trials over a 14 year (2006-2019) period were evaluated for specific trial eligibility criteria as a potential barrier to enrollment of underrepresented racial and ethnic subgroups. Ineligibility rates were highest among AA (24%) than White patients (17%).

Several barriers such as lack of access, financial disadvantage, mistrust in the health system, low health literacy, limited access to transportation, increased comorbidity burden and others have been reported as reasons for low minority accrual on clinical trials. Unger *et al*. reported that more than half of patients if offered clinical trial were willing to participate with no differences in the participation rates for Black versus White patients.[36] The minority patients in the LEO cohort represent a patient population that has access to large academic center and is willing to participate in research, as evidenced by providing informed consent for the LEO Cohort study. Exclusion of such high-risk population despite a younger at presentation based on eligibility criteria requires a thorough re-evaluation of these criteria in the context of race/ethnicity.

The strengths of the study include a large well studied prospective patient cohort enrolled at 8 U.S. academic medical centers that is representative of patients considered for clinical trials. Limitations include lack of standardized timing of lab evaluations prior to initiation of treatment across centers and potential changes in these parameters between diagnosis and treatment initiation. This study specifically focused on 5 lab-based criteria for newly diagnosed DLBCL only, so the impact of other criteria and in other disease settings is limited. However, the study was specifically designed to evaluate these criteria as they are objective and are easily modifiable once their impact is identified. The patients in LEO cohort self-report their racial/ethnicity status and those with overlaps were first identified based on Hispanic ethnicity and then segregated based on race. Lastly, data regarding chemotherapy dosing and modifications was unavailable for this study and hence the effect of differences in the chemotherapy dose intensity on outcomes between the groups cannot be identified.

In conclusion, lab-based eligibility criteria have a substantial impact on clinical trial enrollment, study design, and generalizability of its findings. The trial exclusion based on these lab criteria also disproportionately impacts AA, Hispanics and other non-White minority groups compared to the NHW. Exclusion of patients especially belonging to minority groups that are willing participants in research and have access to trials, due to eligibility criteria requires a strategic approach and close evaluation of relevance of each criterion for improvement of trial designs. Future studies focused on modification of early phase studies to include patients with organ dysfunction in separate arms or with provisions for additional support and monitoring are required to bypass some regulatory barriers for large phase 3 trials and broadening of eligibility criteria. Optimization strategies aimed at reversing organ dysfunction prior to trial enrollment

need further evaluation to identify a cohort of these high-risk DLBCL that can be safely brought back in clinical trials without additional toxicity burden.

Acknowledgements: This work was supported by grants from the National Cancer Institute: Lymphoma Epidemiology of Outcomes (U01 CA195568), University of Iowa/Mayo Clinic Lymphoma SPORE (P50 CA97274).

Authorship Contributions:

Study conception and design: AK, TEW, GSN, MJM

Collection and/or assembly of the data: AK, RM, LJN, TMR, UF, JTR, TJM, SMR, ISL, BSK, PM, JRC, CRF, GSN, MJM

Statistical analysis: AK, RM, SMR, MJM

Manuscript writing and review: all authors

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LJN has received honorarium for participation in advisory boards/consulting from Abbvie, ADC Therapeutics, Atara Biotherapeutics, BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Janssen, Incyte, Morphosys, Novartis, and Takeda; research support from BMS/Celgene, Caribou Biosciences, Daiichi Sankyo, Epizyme, Genentech/Roche, Genmab, Gilead/Kite, IGM Biosciences, Janssen, Novartis, and Takeda

Unrelated to this analysis JRC has received research funding to Mayo from BMS, Genmab, and NanoString; compensation to Mayo for participation on a scientific advisory board from BMS; and personal compensation for participation in a SMC for Protagonist Therapeutics.

MJM: research funding: BMS, Genetech/Roche, GenMab; Advisory Board/Consulting: BMS, AstraZeneca, Adaptive Biotechnologies

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Figures and Tables

Table 1) Patient characteristics by Race/Ethnicity

Characteristic	Total N =2185	White (non-Hispanic) N = 1666	Black/African American (non-Hispanic) N = 155	Hispanic (any) N = 288	Other minority N = 76	P value
Age at diagnosis, median (years, IQR)	63 (42-72.5)	65 (55-73)	51 (39-62)	56 (41-65.5)	63 (42-72.5)	**<0.0001**
Male, (%)	1237 (56.6%)	959 (57.6%)	80 (51.6%)	160 (55.6%)	38 (50.0%)	0.30
ECOG PS ≥2 (%)	333 (16.2%)	269 (17.1%)	19 (13.1%)	34 (12.5%)	11 (16.9%)	0.19
Ann Arbor stage, III-IV (%)	1331 (63.9%)	1008 (63.4%)	108 (73.5%)	171 (62.6%)	44 (60.3%)	0.085
Extranodal sites > 1 (%)	568 (26.6%)	414 (25.4%)	48 (31.8%)	88 (31.0%)	18 (24.3%)	0.1099
Elevated LDH (%)	1143 (56.4%)	849 (54.8%)	87 (61.7%)	161 (59.9%)	46 (66.7%)	0.059
IPI						**0.020**
0-2	1353 (62%)	1020 (61%)	101 (65%)	183 (64%)	49 (64%)	
3-5	832 (38%)	646 (39%)	54 (35%)	105 (36%)	27 (36%)	
DTI in days, median (IQR)	21 (12-33)	21 (12-32)	24 (13-39)	21 (13-33)	17 (9-33)	**0.027**
B-symptoms (%)	699 (32.0%)	508 (30.5%)	68 (43.9%)	107 (37.2%)	16 (21.1%)	**0.0007**
Bone marrow involvement (%)	276 (15.9%)	217 (16.5%)	26 (20.8%)	26 (10.9%)	7 (11.7%)	0.14
1L Treatment received						**<0.0001**
R-CHOP	1402 (64.2%)	1111 (66.7%)	86 (55.5%)	162 (56.3%)	43 (56.6%)	
R-EPOCH	576 (26.4%)	385 (23.1%)	56 (36.1%)	107 (37.2%)	28 (36.8%)	
Clinical trial	189 (8.6%)	159 (9.5%)	11 (7.1%)	14 (4.9%)	5 (6.6%)	
Other IC	18 (0.8%)	11 (0.7%)	2 (1.3%)	5 (1.7%)	0 (0.0%)	
Abbreviations: LDH – lactate dehydrogenase, IPI – international prognostic index, IC – immunochemotherapy, DTI – diagnosis to treatment interval						

Table 2) Trial Eligibility Lab values by Race/Ethnicity

Lab Values (Mean, SD)	Total N =2185	White (non-Hispanic) N = 1666	Black/African American (non-Hispanic) N = 155	Hispanic (any) N = 288	Other minority N = 76	P value
ANC ($x10^9$/L)	5.2 (2.3)	5.3 (2.3)	4.7 (2.6)	5.5 (2.4)	5.4 (1.9)	0.0005
PLT ($x10^9$/L)	267 (104)	261.4 (101)	283 (115)	285 (111)	278 (104)	0.0037
HGB (g/dL)	12.4 (2.2)	12.5 (2.2)	11.5 (2.3)	12.2 (2.2)	11.9 (2.3)	<0.0001
Bilirubin (mg/dL)	0.6 (0.6)	0.6 (0.6)	0.6 (0.4)	0.6 (0.7)	0.6 (0.6)	0.0023
Creatinine Clearance (mL/min)	100 (45)	98 (44)	111 (49)	109 (45)	97 (50)	<0.0001
Abbreviations: ANC – absolute neutrophil count, PLT – platelet count, HGB - hemoglobin						

Table 3) Lab based trial Eligibility by Race/Ethnicity

Trial	Total (N=2185)	White (Non-Hispanic) (N=1666)	Black/AA (Non-Hispanic) (N=155)	Hispanic (Any) (N=288)	Other Minority (Non-Hispanic) (N=76)	P-Value
REMoDL-B, n (%)						0.51
Ineligible	194 (8.9%)	144 (8.6%)	16 (10.3%)	24 (8.3%)	10 (13.2%)	
Eligible	1991 (91.1%)	1522 (91.4%)	139 (89.7%)	264 (91.7%)	66 (86.8%)	

ROBUST, n (%) Ineligible Eligible	218 (10.0%) 1967 (90.0%)	161 (9.7%) 1505 (90.3%)	22 (14.2%) 133 (85.8%)	25 (8.7%) 263 (91.3%)	10 (13.2%) 66 (86.8%)	0.20
ECOG 1412, n (%) Ineligible Eligible	237 (10.8%) 1948 (89.2%)	177 (10.6%) 1489 (89.4%)	23 (14.8%) 132 (85.2%)	27 (9.4%) 261 (90.6%)	10 (13.2%) 66 (86.8%)	0.30
PHOENIX, n (%) Ineligible Eligible	261 (11.9%) 1924 (88.1%)	199 (11.9%) 1467 (88.1%)	17 (11.0%) 138 (89.0%)	32 (11.1%) 256 (88.9%)	13 (17.1%) 63 (82.9%)	0.52
CALGB 50303, n (%) Ineligible Eligible	361 (16.5%) 1824 (83.5%)	280 (16.8%) 1386 (83.2%)	22 (14.2%) 133 (85.8%)	43 (14.9%) 245 (85.1%)	16 (21.1%) 60 (78.9%)	0.50
POLARIX, n (%) Ineligible Eligible	362 (16.6%) 1823 (83.4%)	263 (15.8%) 1403 (84.2%)	34 (21.9%) 121 (78.1%)	48 (16.7%) 240 (83.3%)	17 (22.4%) 59 (77.6%)	0.12
GOYA, n (%) Ineligible Eligible	374 (17.1%) 1811 (82.9%)	270 (16.2%) 1396 (83.8%)	39 (25.2%) 116 (74.8%)	48 (16.7%) 240 (83.3%)	17 (22.4%) 59 (77.6%)	0.022
ENGINE, n (%) Ineligible Eligible	573 (26.2%) 1612 (73.8%)	409 (24.5%) 1257 (75.5%)	58 (37.4%) 97 (62.6%)	83 (28.8%) 205 (71.2%)	23 (30.3%) 53 (69.7%)	0.0028

Figure 1) Consort diagram showing the study cohort selection from LEO cohort

Figure 2) Violin plots showing distribution of baseline hemoglobin (2A) and absolute neutrophil count (2B) in the LEO Cohort among various racial/ethnic subgroups. Cut off values (red solid line) show differential impact among the subgroups for HGB (10 g/dL) and ANC ($1.0x10^9$) cutoffs.

Figure 3) Kaplan Meier curves for event free survival and overall survival in the LEO cohort based on trial eligibility (POLARIX) among various racial/ethnic subgroups.

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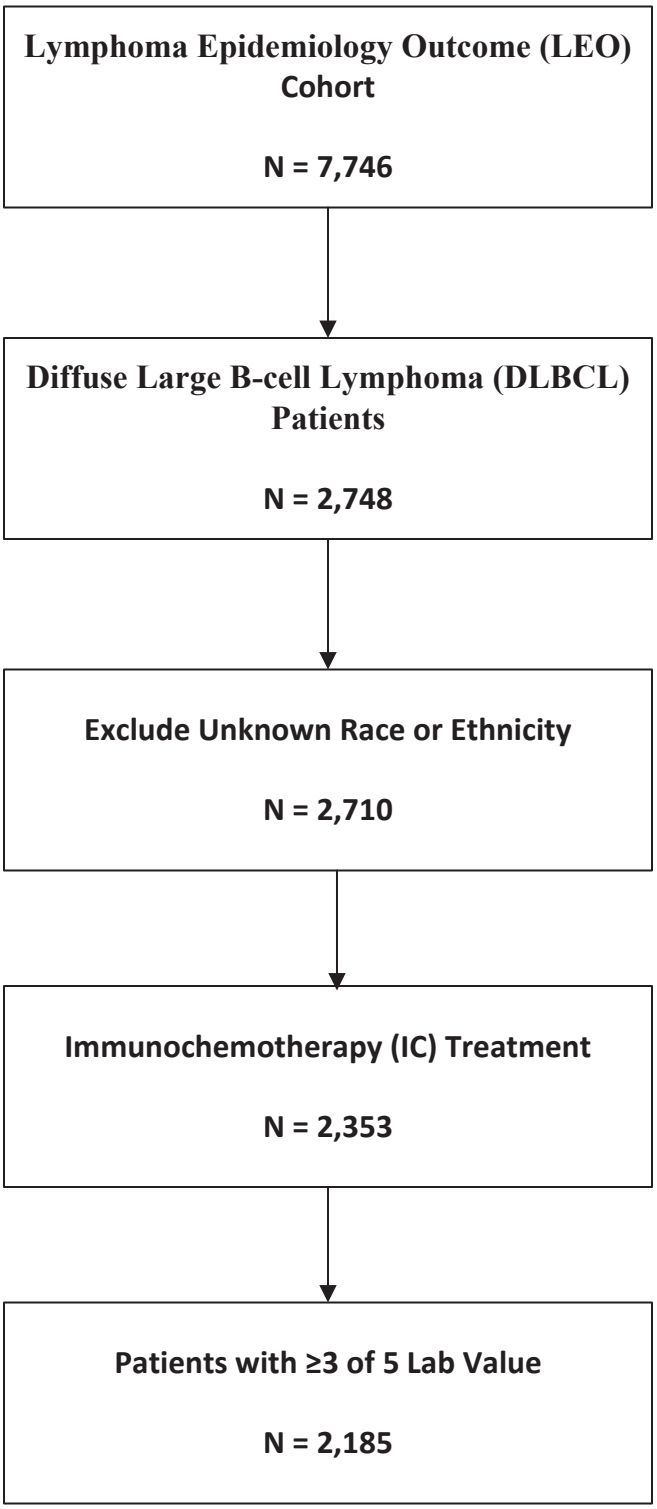
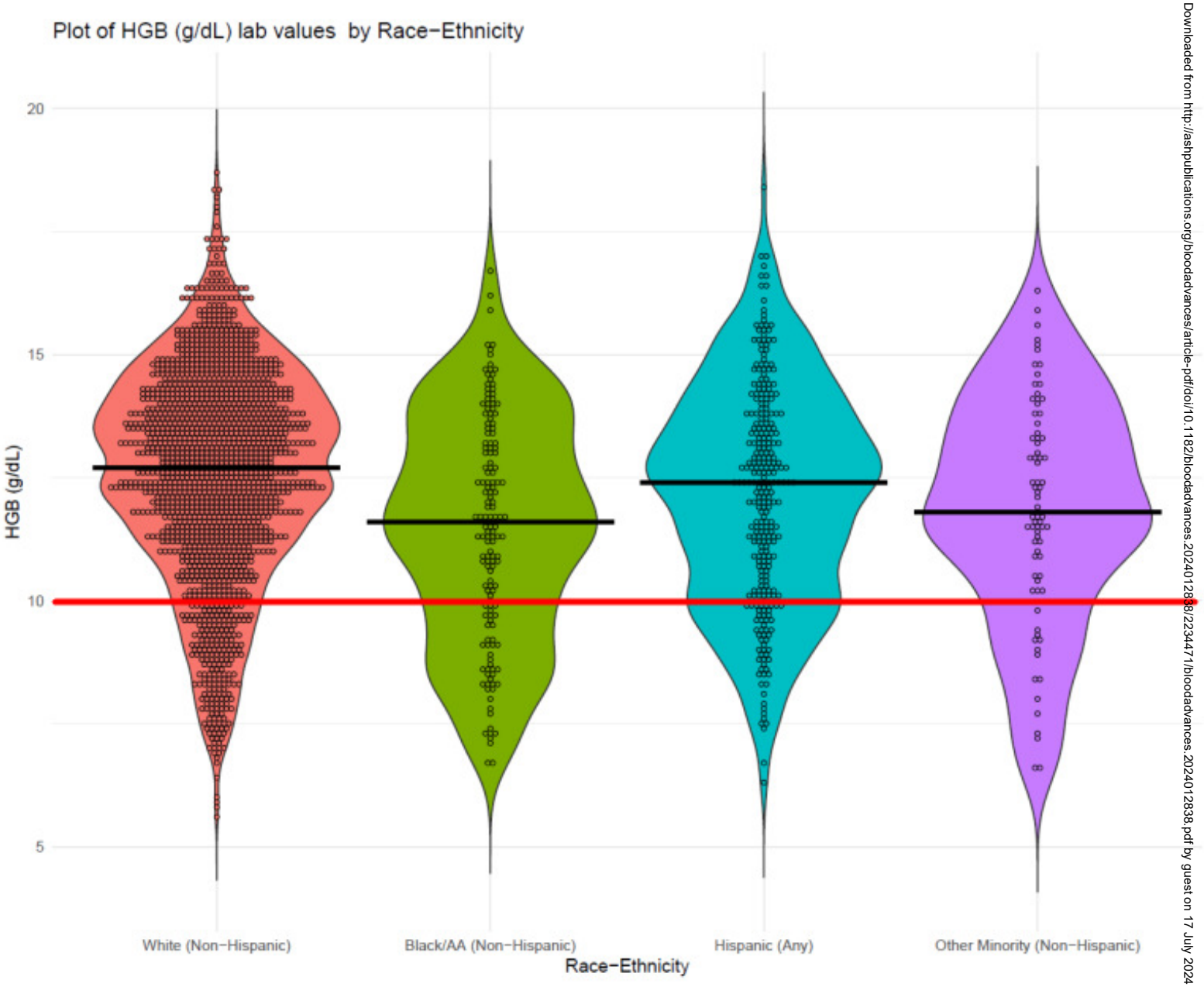
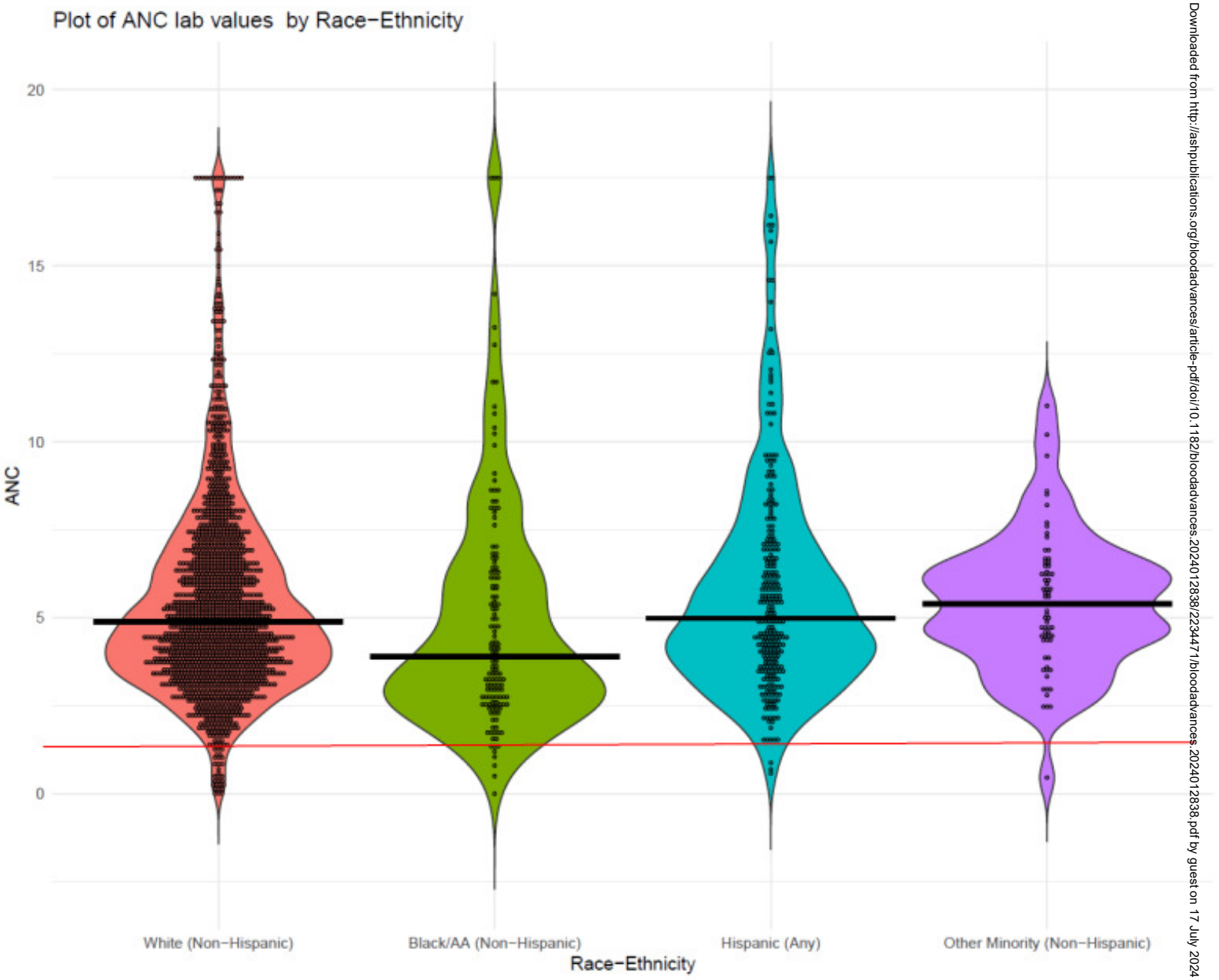
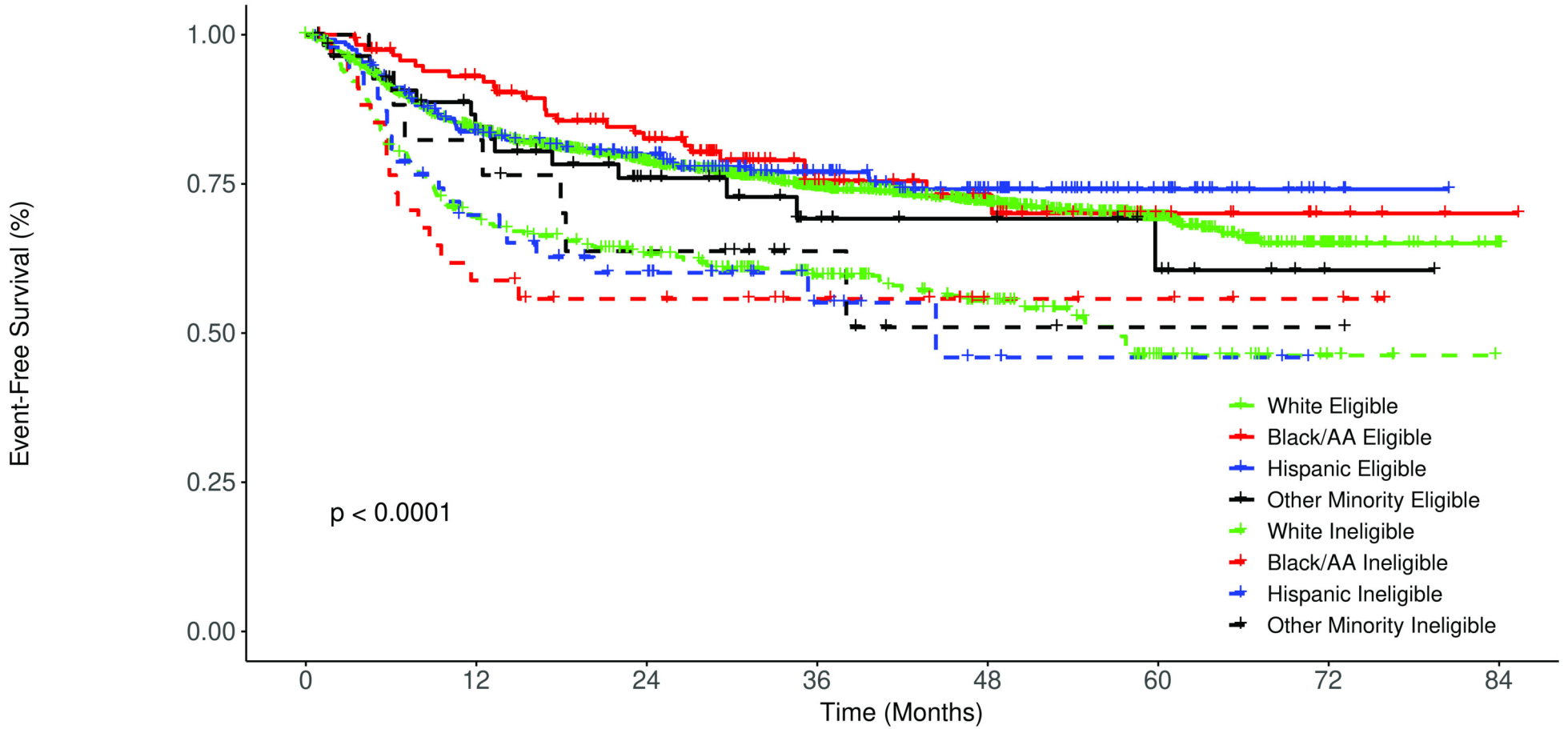
Figure 1: LEO Left Behind Consort Diagram







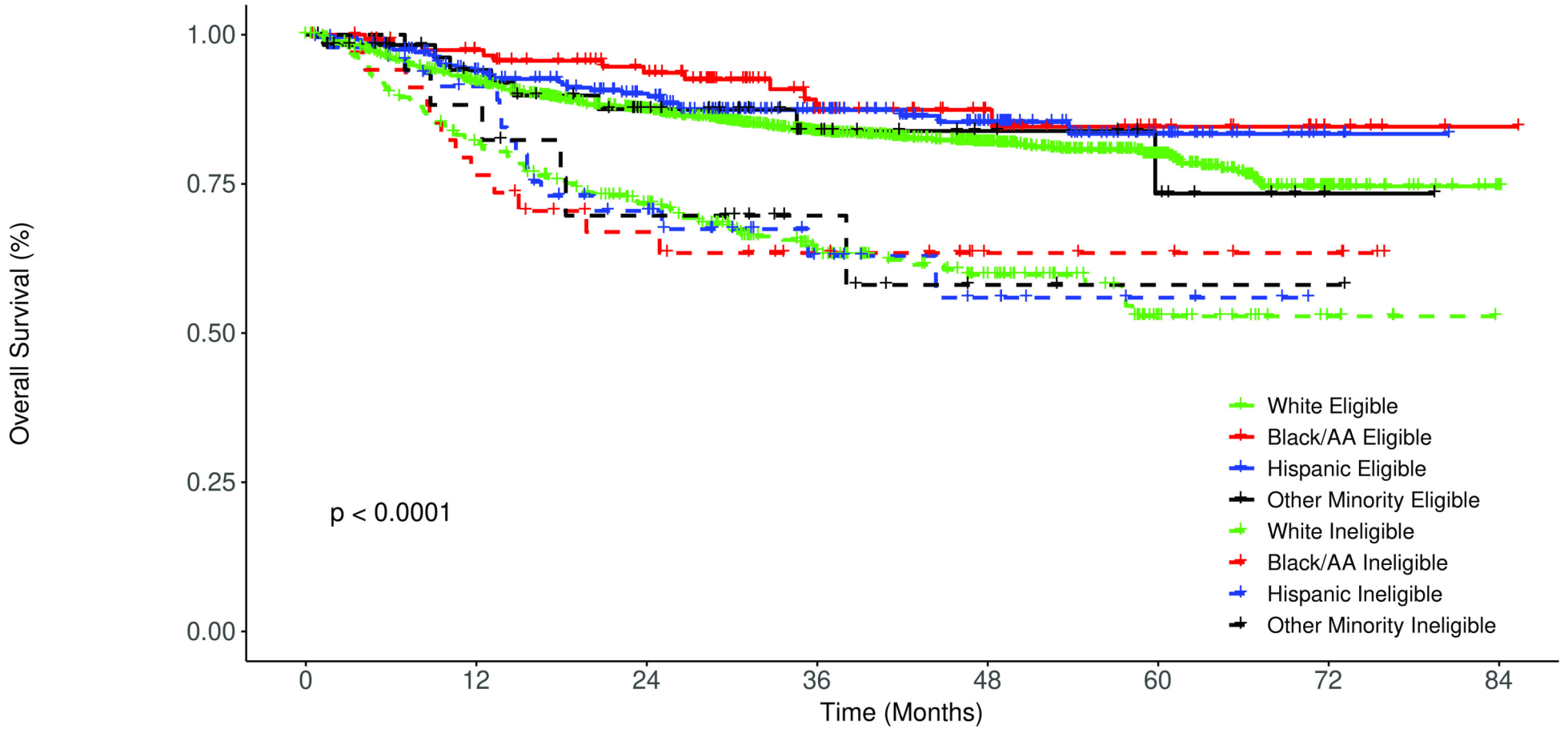


Number at risk

White Eligible	1404	1133	931	610	420	219	48	3
Black/AA Eligible	121	103	81	41	24	10	4	1
Hispanic Eligible	241	186	150	94	58	23	3	0
Other Minority Eligible	59	41	29	15	11	7	1	0
White Ineligible	262	173	136	90	52	19	5	0
Black/AA Ineligible	34	20	16	12	6	5	3	0
Hispanic Ineligible	47	30	22	10	4	2	0	0
Other Minority Ineligible	17	14	10	5	2	1	1	0

Cumulative number of events

White Eligible	0	220	289	333	350	362	372	372
Black/AA Eligible	0	8	19	24	25	26	26	26
Hispanic Eligible	0	38	46	51	54	54	54	54
Other Minority Eligible	0	8	12	14	14	15	15	15
White Ineligible	0	78	93	100	105	111	111	111
Black/AA Ineligible	0	14	15	15	15	15	15	15
Hispanic Ineligible	0	14	18	19	20	20	20	20
Other Minority Ineligible	0	3	6	6	7	7	7	7



Number at risk

White Eligible	1404	1245	1045	689	461	244	52	3
Black/AA Eligible	121	109	92	49	31	14	5	1
Hispanic Eligible	241	208	170	108	67	24	3	0
Other Minority Eligible	59	44	33	19	11	7	1	0
White Ineligible	262	205	156	97	56	19	5	0
Black/AA Ineligible	34	26	19	14	7	6	4	0
Hispanic Ineligible	47	40	27	13	7	3	0	0
Other Minority Ineligible	17	15	11	6	2	1	1	0

Cumulative number of events

White Eligible	0	109	170	209	221	230	241	241
Black/AA Eligible	0	3	7	11	11	12	12	12
Hispanic Eligible	0	14	22	27	29	30	30	30
Other Minority Eligible	0	3	6	7	7	8	8	8
White Ineligible	0	46	71	86	91	95	95	95
Black/AA Ineligible	0	8	11	12	12	12	12	12
Hispanic Ineligible	0	4	13	15	16	16	16	16
Other Minority Ineligible	0	2	5	5	6	6	6	6