

DR. ZOE LOH (Orcid ID : 0000-0002-9215-1441)

DR. ALLISON BARRACLOUGH (Orcid ID : 0000-0003-1615-0540)

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Evolution of eligibility criteria for Diffuse Large B-cell Lymphoma randomised controlled trials over 30 years

Authors: Z. Loh¹, R. Salvaris^{1,4}, G. Chong^{1,3}, L. Churilov³, K. Manos¹, A. Barraclough¹, E. A. Hawkes^{1,2,3}

1. Department of Medical Oncology and Clinical Haematology, Olivia Newton John Cancer Research and Wellness Centre at Austin Health, Heidelberg, Australia
2. Department of Haematology, Eastern Health, Melbourne, Australia
3. Melbourne Medical School, University of Melbourne, Melbourne, Australia
4. Department of Haematology, Monash Health, Clayton, Australia

Corresponding author:

A/Prof Eliza A. Hawkes

Department of Medical Oncology

Olivia Newton-John Cancer, Wellness & Research Centre, Austin Health

145 Studley Road, Heidelberg, Victoria, Australia 3084

Tel: +61 3 9496 9937

E-mail: Eliza.Hawkes@onjcri.org.au

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Summary

Eligibility criteria for randomised control trials (RCT) in diffuse large B-cell lymphoma (DLBCL) may be becoming increasingly strict. In this analysis, 42 first-line phase III RCTs enrolling DLBCL patients since 1990 were identified from PubMed and clinicaltrials.gov. Changes in 31 individual eligibility criteria were assessed using 3 pre-defined eras (1:1993-2005, 2:2006-2013, 3:2014-2020). The presence of 15/31 criteria increased significantly over time, and the total number of criteria per study also increased over time (median Era 1: 14.5; IQR12.6-16.4, Era 2: 21; 18.8-23.3, Era 3: 23; 21-25; $p<0.001$). When each trial's eligibility criteria were applied to 215 consecutive patients from an institutional database treated between 2010-2020, a median of 57%(IQR 47-70) of patients were hypothetically eligible for trial enrolment. The median percentage of patients eligible was 68%(56-91), 54%(37-81) and 47%(38-82) for Era 1, 2 and 3 respectively ($p=0.004$). Phase III frontline DLBCL trial criteria have become increasingly restrictive over the last 3 decades, resulting in a diminishing proportion of trial-eligible patients, with less than 50% of our patients eligible for modern-era studies. This potentially impacts generalisability of recent trial results and will likely limit recruitment to ongoing studies.

KEYWORDS:

diffuse large B-cell lymphoma, randomised controlled trials, eligibility criteria, recruitment

INTRODUCTION

Randomised clinical trials (RCTs) are the key method of advancing cancer outcomes, yet clinical trial participation has consistently been estimated to be less than 10% [1, 2]. While safety is paramount, for phase III clinical trial results to be relevant, trial populations must, to a degree, reflect patients treated in routine care. Strict enrolment criteria are intended to reduce cohort heterogeneity and minimise treatment toxicities, thus increasing effect size. However, excessive restrictions limit patient accrual and applicability of results to broader clinical populations, curtail advancements in disease biology and behaviour and reduce patient access to novel agents. Eligibility criteria for clinical trials are reportedly becoming stricter over time [3], but data in haematological malignancies are lacking.

Over the last three decades, treatment-naïve diffuse large B-cell lymphoma (DLBCL) has been subject to evaluation in large numbers of randomised phase III trials in an attempt to improve the 70-80% long-term survival rate associated with R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy. Strategies such as autologous stem cell transplant consolidation [4], maintenance therapy [5, 6], alternate chemotherapeutic regimens [7] and addition of targeted agents [8–10] have predominantly failed to improve upon CHOP-based chemotherapy as the standard of care in 30 years of phase III RCTs [11]. Reasons for failure to translate benefit of novel agents in relapsed DLBCL studies to the frontline setting are unclear. While molecular advances suggest DLBCL is a heterogeneous disease and studies still recruit ‘all-comer’ populations, data also support clear differences in DLBCL trial cohorts compared to routine care populations. For example, shorter time-to-treatment is a robust adverse predictor of outcomes in treatment-naïve DLBCL and is uniformly longer in clinical trials compared to population databases [12]. Increasingly strict eligibility criteria in the modern era may contribute to the repeatedly negative studies by selecting for a relatively good prognosis group, however this has never been analysed objectively.

Eligibility criteria such as prognostic group, stage and age group are justifiable, as they have implications for treatment options, such as autologous stem cell transplantation, intensified chemotherapy and radiotherapy. Criteria selecting for subtypes of DLBCL based on molecular markers are also increasingly being used to explore whether certain subgroups may benefit from targeted therapies. However other criteria, particularly those relating to comorbidities and patient fitness, may result in only the fittest of patients being enrolled into trials. This means that the effects

of new drugs on the true population likely to receive the treatment in clinical practice will not be detected prior to regulatory approval[13].

Here, we investigate changes in eligibility criteria relating to organ function and baseline clinical disease factors used in phase III clinical trials in DLBCL over the last three decades, and the association with changes to eligibility on hypothetical enrolment for a real-world population of DLBCL patients treated with combination rituximab-chemotherapy at a tertiary care centre. We hypothesize that eligibility criteria became more restrictive over time as demonstrated by: a) the total number of eligibility criteria per trial and b) the probability of a given eligibility criteria being used in a trial. We also hypothesize that percentage of a real-world population of DLBCL patients eligible for hypothetical enrolment into clinical trials decreases with time.

METHODS

The endpoints for the first hypothesis were the total number of eligibility criteria per trial as well as the probability of a given eligibility criteria being used in a trial. The endpoint for the second hypothesis was the change in percentage of patients eligible for enrolment into a trial, from an R-CHOP treated, institutional DLBCL population.

To address the first aim, we identified phase III RCTs enrolling treatment-naïve adult DLBCL patients receiving CHOP, or CHOP-like chemotherapy +/- rituximab over a 30 year period via a systematic literature search of the PubMed online database using the search terms (diffuse large B-cell lymphoma) AND (clinical trial) AND (phase III), and ClinicalTrials.gov for all phase III RCTs for DLBCL which commenced after 1990. Active and unpublished trials were included if full eligibility criteria was published online. Studies commencing after 2016, which enrolled high-grade B cell lymphoma NOS and high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, were also eligible if R-CHOP was a treatment arm. Studies which included other subtypes of lymphoma, or published in a language other than English, were excluded.

For each phase III RCT, inclusion/exclusion criteria were extracted from the published reports, study protocols, and from ClinicalTrials.gov, where available. To allow for comparison, only eligibility criteria that were common to at least 5 individual studies were included for analysis. The presence of these criteria, as well as the specific laboratory value thresholds and use of restrictive language (e.g. on timeframes for prior malignancy or life expectancy) were collected from each protocol.

Biomarker-related eligibility that identified disease subsets according to specific molecular markers (for example cell-of-origin), were not recorded as they do not relate to patient fitness, and were not known prior to 2000. In addition to eligibility criteria, data were collected from published trials

regarding baseline characteristics (age, performance status, disease stage) and compared to that of our population.

For the purpose of comparison, included studies were divided into three equal groups: Era 1(1993-2005), Era 2 (2006-2013) and Era 3 (2014-2020), according to year of recruitment commencement.

To address the second aim, a population of consecutive patients with histologically-confirmed DLBCL from our institutional database treated with R-CHOP between January 2010 and March 2020 were assessed against the eligibility criteria from each phase III RCT to assess the percentage of patients that would be eligible for each trial.

All data from our patient population were obtained from electronic medical records, and included age, disease stage, ECOG performance status, International Prognostic Index, tumour size, comorbidities, prior treatments and organ function laboratory values.

In the calculation of proportion of eligible patients from our real-world population for trials, where studies had a specific enriched target population based on age (young defined as ≤ 60 or elderly ≥ 60), stage (limited versus advanced) or prognostic group (low versus high-risk International Prognostic Score), only those patients from our population that met this delineating criterion were used as the denominator with which to apply the eligibility criteria of the trial. The percentage of our population that was eligible was then calculated by applying the individual inclusion and exclusion criteria to this corresponding subgroup, including specific laboratory value thresholds for adequate organ function. Descriptive statistics were used to summarise the characteristics of the evaluated studies and our population. Changes in number of criteria used per study was assessed using negative binomial regression analysis. Incidence rate ratios (IRRs) per 5 years of time were reported with respective 95% confidence intervals. Logistic regression analysis was used to determine the effect of time on presence of each eligibility criterion. Odds ratios (OR) per 5 years of time were reported with respective 95% confidence intervals. IRRs and ORs should be interpreted as a factor increase in the expected count or odds of a given criteria used in a study. Differences in percentage of potentially eligible patients between eras was compared using Friedman test. Two-sided p-values of <0.05 were regarded as indicative of statistical significance. No explicit correction for multiple testing was performed unless stated otherwise. Statistical analysis was performed using SPSS statistical software version 25 (IBM corp, 2017).

This study was approved by the local institutional review board (LNR/17/Austin/186).

RESULTS

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Characteristics of included studies

The literature search identified 46 studies that met our pre-specified inclusion criteria, from 1993 – 2020 (based on year of study commencement). Four studies were excluded due to unavailable protocols. As of June 2020, 27/42 studies had been published, 3/42 were active trials which had completed recruitment, and 12/42 studies were still recruiting participants. Characteristics of the 42 studies and their target population are detailed in Table 1. Studies are listed in full in Supplementary Table 1. There were 14 studies in each Era.

The number of studies per decade was 6 from 1990-2000, 18 from 2001-2010, and 18 from 2011-2020. The total number (or expected number) of patients recruited per decade was 4477 from 1990-2000, 9410 from 2001-2010, and 7818 from 2011-2020.

Eligibility criteria

Thirty-one eligibility criteria were present in at least 5/42 studies and thus included in this analysis. The number of eligibility criteria listed per study varied from 7-27, with a median (IQR) of 19.5(15.5-23.5). The median number of criteria per study was 14.5(12.6-16.4) in Era 1, 21(18.8-23.3) in Era 2, and 23(21-25) in Era 3. The total number of eligibility criteria per study increased over time (Figure 1). The IRR per 5-year increase was 1.142 (95% CI, 1.077-1.211), $p < 0.001$.

Table 2 displays the 31 analysed eligibility criteria and the proportion of trials that included them in each cohort, and Table 3 shows the change in presence of each criteria over time. There were statistically significant increases over time in the presence of 15/31 (48%) of these criteria in trial protocols. These increases were predominantly for organ function criteria (cardiovascular, haematological, hepatic), and the largest absolute increases were seen in unstable arrhythmia (Era 1: 13%, Era 3: 86%), active infection (Era 1: 33%, Era 3: 86%) and unstable angina (Era 1: 20%, Era 3: 71%), with ORs of 2.44, 2.06 and 1.89 respectively for change over time.

Changes to the thresholds used to define certain criteria also occurred over time. In the trials that specified a minimum life expectancy ($n=25/46$), only 3 months was required for all studies in Era 1, while in Era 3 the majority of studies (60%) required at least 6 or 12 months for inclusion. Similarly, for ECOG performance status, 43% of studies in Era 1 allowed patients beyond ECOG 2, compared to only 7% in Era 3. Of the trials that excluded patients with a previous cancer diagnosis, the majority (71%) specified a minimum remission of 3-5 years, however 'any prior malignancy' was increasingly used over time (13%, 17% and 36% of studies in Era 1, 2 and 3 respectively). In contrast, platelet count requirements reduced over time; all protocols specified a platelet count of $>100 \times 10^9/L$ in Era 1, while most protocols (83%) specified a lower platelet count threshold ($50-80 \times 10^9/L$) in Era 3.

Real-world DLBCL Population

In the second part of this analysis, 215 treatment-naïve DLBCL patients identified from the institutional database were individually assessed for eligibility for all 42 studies based on data obtained from medical records. The estimated percentage of patients from the database that fulfilled eligibility criteria for each trial are displayed in Table 4, with a median of 57% (range 37-91%, IQR 47-70%). The most restrictive was a 2007 industry-sponsored trial of RCHOP plus bevacizumab or placebo, and the least restrictive was a collaborative group trial of autologous stem cell transplant in high-risk young patients, commencing in 1999. The most common reason for exclusion in our population was haemoglobin <100g/L (16.3%) or <90g/L (8.4%), lack of radiologically measurable disease (8.4%), ECOG performance status >2 (7.0%) and transformation from indolent lymphoma (6.5%). There was a statistically significant difference in the proportion of hypothetically eligible patients between the 3 Eras, $p = 0.004$. Median eligible proportions for Era 1, 2, and 3 were 68% (IQR 56-91), 54% (37-81) and 47% (38-82), respectively. There was a statistically significant difference between Era 1 and 3 ($p=0.002$), and Era 1 and 2 ($p=0.012$), but not between Era 2 and 3 ($p= 0.701$).

Trial eligibility was further analysed based on the type of intervention; trials involving a novel targeted agent ($n=14$) had the strictest requirements, with a median of only 48% patients (range 37-61%) eligible from our hospital population. This subgroup of trials had a median of 22.5/31 criteria present per study and were all in Era 2 and 3. Of note, 11/14 of the targeted-agent trials were industry sponsored. In contrast, trials of intensified chemotherapy regimens had higher eligibility rates (median 67%) and lower number of eligibility criteria per protocol (median 15/31). The majority (80%) of these trials were in Era 1. Industry-sponsored trials had a significantly lower proportion of eligible patients than non-industry sponsored trials (median 54% vs 58%, $p=0.046$).

Five trials, all after 2003, were further restricted based on cell-of-origin (2 non-germinal centre B cell-like, 2 double expressor, 1 activated B cell-like). A median of 48% (45-74%) of our population was eligible for these trials based on non-biomarker eligibility criteria.

A Spearman's rank-order correlation was run to determine the relationship between number of criteria and percentage of patients hypothetically eligible for each trial. There was a strong negative correlation between number of eligibility criteria and percentage of eligible patients, which was statistically significant ($r_s=0.641$, $p<0.001$).

Taking in account each patient's age, stage, prognostic group and the 31 criteria previously mentioned, the number of patients eligible to be enrolled into at least one trial was 202/215 (94%) for Era 1, 166/215 (77%) for Era 2, and 169/215 (78%) for Era 3 respectively. The median number of trials each patient was eligible to enrol into was 5 (IQR 2-7), 5 (1-8) and 3 (1-7) per Era respectively.

There was a statistically significant difference between Era 1 and 3 ($p=0.004$), but not between Era 1 and 2 ($p=0.988$) or Era 2 and 3 ($p=0.056$).

Trial versus Routine Care Populations

Baseline characteristics including median age, performance status, stage of our own DLBCL database population were compared with those of the 30 trials already published to assess the impact of restricted eligibility on patient cohorts (Table 5). Overall, published trial cohorts were younger with a better performance status and earlier stage disease than our institutional routine care population.

DISCUSSION

This comprehensive analysis of trial eligibility in frontline DLBCL phase III randomised control studies is the first to confirm and quantify the increasing restrictiveness of eligibility criteria, over a 30 year period, despite international calls to broaden cancer clinical trial eligibility criteria[14, 15]. We also demonstrate objective evidence of the impact on patients with a direct correlation between this increased restrictive eligibility and a declining number of trial-eligible patients identified from a real-world treatment-naïve DLBCL population treated in the modern era. This is despite excluding molecular-based eligibility (which reflect knowledge gains in DLBCL subtypes over the time period) from the analysis and focusing on organ-based parameters and clinical disease characteristics. When the eligibility criteria from these RCTs using CHOP-like treatment were applied to DLBCL patients receiving R-CHOP in routine care, only 57% on average were hypothetically eligible for enrolment to these RCTs, with a clear downward trend across the 3 pre-specified Eras in our analysis. Industry-sponsored trials involving novel targeted agents had the highest rates of ineligibility, despite the established safety profile from earlier phase studies.

The DLBCL trial population has evolved; our analysis demonstrates not only that trial populations are fitter and younger than real-world cohorts, but that modern-day trial participants are likely to have better performance status and fewer comorbidities compared to cohorts from trials conducted in prior decades. The influence of this trend on outcomes of current era studies is likely to be significant. As trials select for increasingly fitter populations, results from these restrictive studies, including overall survival estimates, are less translatable to the clinical management of DLBCL overall. In addition, enrolment of only good-prognosis patients may exclude the patients most likely to benefit from new treatments and fail to identify an improvement over the control. Focus is shifting towards molecular-based treatments in DLBCL and the addition of biomarker selection to already restrictive eligibility criteria will likely result in even lower trial accrual and unrealistic outcomes. Even without accounting for molecular subgroups in our analysis, our results suggest that the number of trials available to an individual patient is declining with time. These challenges are reflected to a degree in

the comparison of time-to-treatment and negative prognostic associations in real-world, trial, and biomarker-driven DLBCL trial populations reported to date [12, 16]. However, newer trials continue to fail to address these issues.

Selection criteria are an important component of clinical trial design, in particular due to concerns for excessive treatment toxicity, particularly from newer agents combined with standard R-CHOP. However, evidence of disconnect between study criteria and expected toxicities has been previously described [17], and were apparent in our analysis. We demonstrated almost universal stringent thresholds for renal and hepatic function, even in studies where renal and hepatic toxicity are not a concern, including studies evaluating consolidative radiotherapy, differing rituximab schedules or duration, and new rituximab formulations. A pattern of increasing exclusion of corticosteroid use and various cardiac conditions was also observed. However, none of the studies preventing steroids included drugs which contraindicate this, such as checkpoint inhibitors, and only 17% involved a drug with known cardiovascular side effects (in addition to the anthracycline in R-CHOP). The stringent definitions of radiologically measurable disease, another common reason for screen-failure in our cohort, do not relate to safety, nor to the primary endpoint of phase III studies, and instead reflects limitations in formalised response assessment methods. Stratification would be a more practical way to address these. Other trends observed may be reflective of widely accepted eligibility criteria for other conditions and therapeutic agents, such as immunotherapy in solid malignancies or vascular endothelial growth factor (VEGF-) and Bruton tyrosine kinase (BTK) inhibitors; eligibility criteria are known to be replicated from previous trials, often in the absence of sound clinical rationale. In addition, exclusion criteria such as HIV positivity are increasingly outdated given that excellent disease control may be achieved in the modern era.

We propose that future phase III trials should only include criteria that are well justified, and are relevant to the study objectives and the trial drug's safety considerations. In particular, thresholds for anaemia, renal or hepatic function, or age and performance status should be lowered if this does not affect the safety of delivering treatment. Patients with well-controlled HIV or with transformed disease have comparable prognosis to those without, and should not be routinely excluded. Steroid use and certain cardiac conditions should only be included if they relate to the expected toxicities or mechanism of action of the drug.

In the current era where DLBCL trials are defined by molecular subgroups, it is even more important that all criteria are carefully justified and if possible, supported by evidence. Many criteria currently in widespread use cannot be regarded as DLBCL-based enrichment strategies that would serve to amplify the treatment effect. Broadening of entry criteria is essential so that each Phase III

randomised trial is conducted in a truly representative cohort, and so that all trials continue to become more accessible for patients around the world.

The main limitation of this analysis is that we applied eligibility criteria to a retrospective, single-institution patient population, potentially reducing generalisability. However, our population included all patients in a 10-year period treated at a tertiary centre with a recognised global standard of care (R-CHOP) and we deliberately included only trials that used CHOP-like treatment as the control arm. The estimated proportions of eligible patients are likely to be an overestimate, as they do not account for other trial-specific reasons for screen failure, such as disease trajectory or biomarker-based selection criteria. We also acknowledge that we arbitrarily divide the analysis into 3 eras according to number of trials in each, thus the duration of each period varies, and that novel therapies are a feature of more recent trials. Furthermore, for the purposes of our analysis the haemoglobin level at diagnosis was used to determine eligibility, however we acknowledge that some protocols may have permitted a supported haemoglobin for entry. The majority of protocols (38/42) did not specify whether the blood transfusions were permitted prior to enrolment. The other potential limitation to this longitudinal analysis is that the diagnosis of DLBCL has been refined over time. However, we deliberately omitted studies with mixed non-Hodgkin lymphoma populations, included only those trials using CHOP-based chemotherapy and did not analyse any change in biomarker-driven criteria to minimise bias. Despite these potential limitations, this is the most comprehensive review of eligibility criteria of phase III DLBCL trial protocols using CHOP-like therapy to date, and the first to our knowledge to quantify differences over time, then benchmark against real-world data to assess the impact of a large number of common eligibility criteria on recruitment of a standard clinical DLBCL population.

CONCLUSION

Both the number and stringency of eligibility criteria relating to patient fitness and clinical disease characteristics for frontline phase III DLBCL trials has increased over time, resulting in fitter, younger populations being enrolled to current trials and less than 50% of a real-world patient cohort being eligible for modern-era studies. This is likely to impact on the ability to generalise results of modern clinical trials, extrapolate biological knowledge from trial cohorts to routine populations and complete timely recruitment to ongoing trials. Future investigators should carefully consider the suitability and consequences of the eligibility criteria included in every protocol.

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REFERENCES

1. Murthy VH, Krumholz HM, Gross CP. Participation in Cancer Clinical Trials Race-, Sex-, and Age-Based Disparities. *JAMA* 2004; 291(22):2720–2726.
2. Unger JM, Hershman DL, Albain KS et al. Patient Income Level and Cancer Clinical Trial Participation. *JCO* 2013; 31(5):536–542.
3. Srikanthan A, Vera-Badillo F, Ethier J et al. Evolution in the eligibility criteria of randomized controlled trials for systemic cancer therapies. *Cancer Treatment Reviews* 2016; 43:67–73.
4. Cortelazzo S, Tarella C, Gianni AM et al. Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas. *JCO* 2016; 34(33):4015–4022.
5. Jaeger U, Trnėný M, Melzer H et al. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. *Haematologica* 2015; 100(7):955.
6. Habermann TM, Weller EA, Morrison VA et al. Rituximab-CHOP Versus CHOP Alone or With Maintenance Rituximab in Older Patients With Diffuse Large B-Cell Lymphoma. *JCO* 2006; 24(19):3121–3127.
7. Bartlett NL, Wilson WH, Jung S-H et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *JCO* 2019; 37(21):1790–1799.
8. Vitolo U, Trnėný M, Belada D et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *JCO* 2017; 35(31):3529–3537.
9. Younes A, Sehn LH, Johnson P et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. *JCO* 2019; 37(15):1285–1295.
10. Seymour JF, Pfreundschuh M, Trnėný M et al. R-CHOP with or without bevacizumab in patients with previously untreated diffuse large B-cell lymphoma: final MAIN study outcomes. *Haematologica* 2014; 99(8):1343.

11. Cunningham D, Hawkes EA, Jack A et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *The Lancet* 2013; 381(9880):1817–1826.
12. Maurer MJ, Ghesquières H, Link BK et al. Diagnosis-to-Treatment Interval Is an Important Clinical Factor in Newly Diagnosed Diffuse Large B-Cell Lymphoma and Has Implication for Bias in Clinical Trials. *JCO* 2018; 36(16):1603–1610.
13. Bird ST, Tian F, Flowers N et al. Idelalisib for Treatment of Relapsed Follicular Lymphoma and Chronic Lymphocytic Leukemia: A Comparison of Treatment Outcomes in Clinical Trial Participants vs Medicare Beneficiaries. *JAMA Oncology* 2020; 6(2):248–254.
14. Kim ES, Bruinooge SS, Roberts S et al. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. *JCO* 2017; 35(33):3737–3744.
15. FDA/CDER/Fox S. Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs. 2019:18.
16. Vitolo U, Witzig TE, Gascoyne RD et al. ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematological Oncology* 2019; 37(S2):36–37.
17. Statler A, Radivoyevitch T, Siebenaller C et al. The relationship between eligibility criteria and adverse events in randomized controlled trials of hematologic malignancies. *Leukemia* 2017; 31(8):1808–1815.

FIGURES AND TABLES

Figure and table legend

Figure 1: Changes to total number of trial criteria over time

Table 1: Characteristics of included studies and target population

Table 2: Presence of eligibility criteria as proportion of studies in each era

ECOG = Eastern Cooperative Oncology Group, AST= aspartate aminotransferase, ALT = alanine aminotransferase, LVEF = left ventricular ejection fraction, CNS = central nervous system, HBsAg = hepatitis B surface antigen, NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease, INR = international normalised ratio, APTT = activated partial thromboplastin time

Table 3: Univariable logistic regression for the change in presence of eligibility criteria over time

* 95% confidence interval not crossing 1 is indicative of statistically significant difference at p=0.05 level
ECOG = Eastern Cooperative Oncology Group, AST= aspartate aminotransferase, ALT = alanine aminotransferase, LVEF = left ventricular ejection fraction, CNS = central nervous system, HBsAg = hepatitis B surface antigen, NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease, INR = international normalised ratio, APTT = activated partial thromboplastin time

Table 4: Proportion of eligible patients per trial, based on hospital population of DLBCL patients

IPI=international prognostic index, aaIPI=age-adjusted IPI, a=autologous stem cell transplant, b=biomimetic, c=intensified chemotherapy, m=maintenance, n= novel agent

Table 5: Comparison of baseline characteristics of hospital population and published phase III trial cohorts

* in trials of all prognostic groups; **in trials of all stages & prognostic groups
ECOG = Eastern Cooperative Oncology Group

Supplementary Table 1: Randomised controlled trials in DLBCL from 1993-2020 (online only)

Figure 1. Changes to total number of trial criteria over time

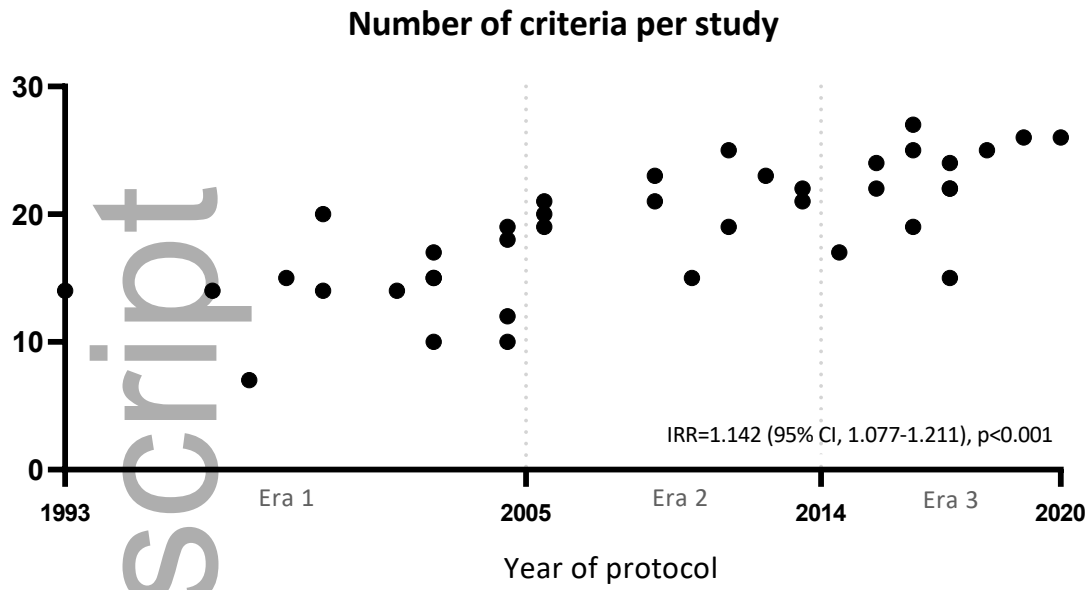


Table 1. Characteristics of included studies and target population

Characteristic	No of trials	Proportion
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(n=42)		
Type of intervention:		
Novel agent	14	33%
Intensified chemotherapy	10	24%
Maintenance therapy	6	14%
Autologous stem cell transplant	3	7%
Biosimilar	3	7%
Radiotherapy	2	5%
Other	10	24%
Sponsorship or Funding		
Industry	18	43%
Non-industry	24	57%
Pre-specified Age group		
All ages	21	50%
Elderly (≥ 60 years)	10	24%
Young (≤ 60 years)	11	26%
Pre-specified Risk group		
All	21	50%
High risk	13	31%
Low risk	8	19%
Pre-Specified Stage:		
All	25	60%
Stage II-IV	12	29%
Limited stage	5	12%

Table 2. Presence of eligibility criteria as proportion of studies in each era

	Criteria	Proportions of studies with each criteria			
		All studies (n=42)	Era 1	Era 2	Era 3
Overall fitness	1 Upper age limit	26 62%	67%	46%	71%
	2 ECOG performance status	37 88%	73%	100%	93%
	3 Life Expectancy	25 60%	27%	85%	71%
Cardiovascular function	4 LVEF	22 52%	47%	31%	79%
	5 NYHA Cardiac disease >II	31 76%	53%	77%	100%
	6 Recent myocardial infarction	23 55%	33%	62%	71%

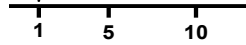
	7	Unstable angina	22	52%	20%	69%	71%
	8	Unstable arrhythmia	21	50%	13%	54%	86%
	9	Uncontrolled hypertension	11	26%	13%	31%	36%
Haematological function	10	Haemoglobin	16	38%	7%	51%	57%
	11	Platelets	34	81%	60%	85%	100%
	12	Neutrophils	33	79%	53%	85%	100%
Hepatic & Renal function	13	Bilirubin	39	93%	80%	100%	100%
	14	AST/ALT	35	83%	53%	100%	100%
	15	Abnormal INR/APTT	7	17%	0%	15%	36%
	16	Creatinine	37	88%	80%	92%	93%
Infections	17	HIV	41	98%	100%	100%	93%
	18	Positive HBsAg	33	79%	67%	77%	93%
	19	Positive Hep C RNA	32	76%	67%	69%	93%
	20	Active infection	28	67%	33%	85%	86%
Previous treatment	21	Prior chemo for lymphoma	38	91%	87%	92%	93%
	22	Prior anti CD20	24	57%	67%	39%	64%
	23	Ongoing steroid use	8	19%	0%	23%	36%
Other comorbidities	24	Previous malignancy	31	74%	64%	85%	86%
	25	Pregnant or breast feeding	27	64%	40%	77%	79%
	26	Severe COPD	14	33%	40%	46%	14%
	27	Uncontrolled diabetes	14	33%	27%	62%	14%
	28	Previous solid organ transplant	9	21%	27%	15%	21%
Disease-specific criteria	29	CNS involvement	34	81%	73%	85%	86%
	30	Transformed disease	33	79%	53%	92%	93%
	31	Minimum lesion size	12	29%	7%	31%	50%

ECOG = Eastern Cooperative Oncology Group, AST= aspartate aminotransferase, ALT = alanine aminotransferase, LVEF = left ventricular ejection fraction, CNS = central nervous system, HBsAg = hepatitis B surface antigen, NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease, INR = international normalised ratio, APTT = activated partial thromboplastin time

Table 3. Univariable analysis for change in presence of criteria over time

Criteria	Odds Ratio	Confidence interval*
Upper age limit	1.17	0.69-1.96
ECOG performance status	1.40	0.65-3.03
Life Expectancy	2.12	1.15-3.92*
LVEF	1.38	0.82-2.33
NYHA Cardiac disease >II	2.00	1.02-3.94*
Recent myocardial infarction	1.42	0.84-2.40
Unstable angina	1.89	1.06-3.36*
Unstable arrhythmia	2.44	1.28-4.68*
Uncontrolled hypertension	1.18	0.66-2.11
Haemoglobin	2.46	1.25-4.85*
Platelets	2.66	1.18-6.00*
Neutrophils	3.16	1.33-7.51*
Bilirubin	4.43	1.05-18.7*
AST/ALT	12.84	1.97-83.6*
Abnormal INR/APTT	2.68	1.04-6.93*
Creatinine	1.64	0.74-3.64
HIV	0.23	0.01-4.13
Positive HBsAg	1.60	0.85-3.02
Positive Hep C RNA	1.82	0.96-3.47
Active infection	2.06	1.12-3.85*
Prior chemo for lymphoma	1.34	0.58-3.11
Prior anti CD20	1.27	0.76-2.12
Ongoing steroid use	3.08	1.18-8.06*
Previous malignancy	1.45	0.79-2.70
Pregnant or breast feeding	1.40	0.82-2.39*
Severe COPD	0.64	0.36-1.12
Uncontrolled diabetes	0.75	0.43-1.28

Previous solid organ transplant	0.84	0.46-1.55
CNS involvement	1.02	0.54-1.92
Transformed disease	2.28	1.10-4.73*
Minimum lesion size	1.94	1.01-3.77*



* 95%CI not crossing 1 is indicative of statistically significant difference at p=0.05 level

ECOG = Eastern Cooperative Oncology Group, AST= aspartate aminotransferase, ALT = alanine aminotransferase, LVEF = left ventricular ejection fraction, CNS = central nervous system, HBsAg = hepatitis B surface antigen, NYHA = New York Heart Association, COPD = chronic obstructive pulmonary disease, INR = international normalised ratio, APTT = activated partial thromboplastin time

Table 4. Proportion of eligible patients per trial, based on hospital population of DLBCL patients

Study Number	Prognostic category	Stage	Age group (young≤60, elderly≥60)	Number potentially eligible based on IPI, stage and/or age	Final number eligible after exclusion criteria	Proportion eligible	Era
1 ^c	aaIPI: 0	-	young	21	15	71%	1993- 2005 Median eligible: 68%
2	-	-	elderly	147	83	56%	
3	-	II-IV	elderly	129	89	69%	
4 ^a	aaIPI: 2-3	II-IV	young	32	29	91%	
5	aaIPI: 0-1	-	young	39	31	79%	
6 ^c	-	-	elderly	143	83	58%	
7 ^m	-	-	-	215	165	77%	
8	-	II-IV	elderly	125	77	62%	

9 ^c	aaIPI: 0-1	-	young	39	26	67%	
10 ^c	aaIPI: 1-3	-	elderly	143	81	57%	
11 ^c	aaIPI: 0-1	I-II	young	28	21	75%	
12 ^c	-	-	-	215	124	58%	
13 ^c	aaIPI: 2-3	II-IV	young	66	37	56%	
14 ^c	-	II-IV	-	184	130	71%	
15	-	I-II	-	71	37	52%	
16 ^a	aaIPI: 2-3	-	young	32	26	81%	
17 ^m	-	-	-	215	145	67%	
18 ^{mn}	-	II-IV	elderly	129	49	38%	
19 ^{mn}	IPI: 3-5	II-IV	-	104	60	58%	2006-
20 ⁿ	-	-	-	215	80	37%	2013:
21 ^{mn}	aaIPI: 1-3	II-IV	elderly	115	49	43%	Median
22 ^{mn}	IPI: 3-5	II-IV	-	105	59	56%	eligible:
23	-	I-II	-	63	51	81%	54%
24	aaIPI: 0	I-II	-	42	22	52%	
25 ⁿ	-	-	-	215	119	56%	
26 ⁿ	IPI: 2-5	-	-	161	72	45%	
27	IPI: 1-5	-	-	191	90	47%	
28 ^b	aaIPI: 0-1	-	young	48	31	65%	
29 ⁿ	IPI: 1-5	II-IV	-	173	91	53%	
30 ⁿ	-	II-IV	elderly ≥ 80	24	13	54%	
31 ⁿ	IPI: 2-5	II-IV	-	151	72	48%	
32	-	-	elderly	147	56	38%	
33	-	-	elderly ≥ 70	92	43	47%	
34 ^b	IPI: 0-2	-	-	110	51	46%	2014-
35 ^c	aaIPI: 2-3	-	young	34	20	59%	2020:
36 ^a	IPI: 2-4	-	young	39	32	82%	Median
37 ^c	aaIPI: 2-3	-	young	39	29	74%	eligible:
38 ⁿ	-	-	-	215	100	47%	47%
39 ⁿ	IPI: 2-5	-	-	161	98	61%	
40 ⁿ	IPI: 3-5	-	-	105	42	40%	
41 ^b	IPI: 0-2	-	-	110	51	46%	
42 ⁿ	IPI: 2-4	-	-	143	65	45%	
<p><i>IPI=international prognostic index, aaIPI=age-adjusted IPI</i></p> <p><i>a=autologous stem cell transplant, b=biosimilar, c=intensified chemotherapy, m=maintenance, n= novel agent</i></p>							

Table 5: Comparison of baseline characteristics of hospital population and published phase III trial cohorts

	Hospital Population	Published trial cohorts (n=30; range of reported results)
Median Age (years)		
All-ages	67 >60yrs: 66%	56-66 >60yrs: 36-61%
Elderly	72	68-72
Young	50	47-51
Performance status		
ECOG 0-1	78%	78-94%*
Stage		
advanced	67%	48-74%**

* in trials of all prognostic groups; **in trials of all stages & prognostic groups

ECOG = Eastern Cooperative Oncology Group

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