REVIEW ARTICLE

Older patients with lymphoma: navigating a landscape of clinical controversies and barriers to innovation

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Abstract

Older patients with lymphoma represent a growing, heterogeneous population whose care is challenged by diverse outcomes, limited evidence, and one-dimensional age definitions. Historically, arbitrary age thresholds such as ≥60 or ≥80 years have guided treatment decisions, yet they fail to capture the biological and functional diversity of aging and can limit opportunities for cure and progress. Current practice relies on arbitrary dose reductions in old age, such as R-miniCHOP, despite limited data on optimal intensity and benefit–risk trade-offs. Likewise, novel agents and combination therapies frequently demonstrate discrepant efficacy and safety across age groups, but systematic attempts to optimize dose for older patients are rarely prioritized. When it comes to clinical trials, documenting benefit of new therapies is more challenging in older patients due to high background mortality, which complicates interpretation of overall and progression-free survival and may lead to underpowered trials. Moreover, prognostic models developed in younger populations have limited applicability in older patients, as they overlook the broader range of clinically relevant outcomes in older patients, including treatment-related mortality, functional decline, and quality of life. Pre-therapeutic geriatric assessments are prognostic, but their predictive capability remains to be demonstrated in prospective trials before use as treatment decision support tools. Addressing these challenges requires reframing of “old age” to a multidimensional construct, incorporating geriatric assessment, patients’ preferences, and biological age. More inclusive trial designs, dedicated dose-finding in older patients, and development of holistic, predictive models are critical to advance care. Without this, progress risks stalling for a growing group of our patients.

Background

Historically, older patients with lymphoma were defined solely by chronological age based on chemotherapy-era toxicity concerns and, thus, had limited treatment options. However, managing lymphoma in older patients has evolved beyond this niche scenario with outdated, low survival expectations. Older patients should receive individualized care that addresses personal beliefs, goals and acceptance of toxicities that potentially cause functional decline in the context of a naturally limited life expectancy. Quality-of-life aspects such as independent living and treatment convenience may be prioritized over crude survival duration, in contrast to the situation in younger patients.[1] The breadth of clinically relevant and possible outcomes in older patients are much more diverse and include cure with or without decline in independent living ability as well as death from progressive lymphoma *versus* treatment toxicity in the setting of substantial competing risk of death from other causes. Traditionally used endpoints such as overall survival (OS) and progression-free survival (PFS) fail to disentangle these important events, which are nevertheless critical for making treatment decisions that align with patients’ preferences. The complex balance of treatment-related benefit and risks in older patients requires careful clinical judgement and respectful, open evidence-informed conversations with greater level of nuance than those held with younger patients. The science of aging is advancing,

enabling improved understanding of age as a highly individual biological and functional measure rather than a purely chronological one. This progress is critical with a projected 115% increase of ≥85-year-olds from 2020 to 2040 in the USA which means that managing lymphoma in octogenarians and above will become a substantial proportion of future clinical practice.[2] The drastic changes in age distributions are already tangible. A Nordic population-based study of patients with newly-diagnosed diffuse large B-cell lymphoma (DLBCL) showed that the median age increased from 67-70 years in 2007 to 72-74 years in 2021.[3] Other recent database/registry studies from Germany, UK, and USA observed similar median ages at DLBCL diagnosis of 70-75 years.[4–6] Paradoxically, while ~50% of DLBCL patients are now >70 years old, high-quality evidence is limited for even the most common treatment decisions in the populations of oldest patients, causing considerable clinical challenges. This review addresses controversies in the management of older lymphoma patients, focusing mostly on DLBCL, but also relevant to hematology in general.

Age-related prognostic implications should not automatically define 'old' patients

Definitions of old age require consideration of the clinical rationale for any age threshold in lymphoma, which is meaningful if clear age-related differences in treatment outcomes and tolerability exist. The World Health Organization[7] (WHO) definition of 'old' is persons ≥60 years of age, but using this definition, most patients with lymphoma are 'old'. Correlations between age and outcome are also highly dynamic and change with treatment landscape, supportive care improvements, and societal risk tolerance. Notably, with the observed increase in life-expectancy over the past three decades, age-matched fitness has also improved.[8] While the WHO definition is not meaningful today, it may have been historically appropriate. Pivotal DLBCL studies conducted two decades ago enrolled "elderly" patients. The landmark study showing superiority of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) over CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) enrolled 60- to 80-year-olds with no significant co-morbidities and Eastern Cooperative Oncology Group (ECOG) performance status ≤2.[9,10] The prior 60-year age-cut was supported by strong correlation between survival and age in lymphoma prognostic models and associated perceived higher unmet needs.[11,12] Later real-world studies identified 70 years as a better OS discriminator in the R-CHOP era, suggesting that these associations are dynamic and heavily influenced by the population of patients studied.[13]

However, categorical age thresholds for prognostic association with OS generally translate poorly into operational definitions of old age (Table 1). Limitations of binary age cut-offs are demonstrated by improved performance of models using age as a continuous variable which do not erroneously assume constant hazards for deaths on each side of a binary cut off.[14] Defining old age based on associations with worse PFS and OS is also generally problematic because both measures include all-cause mortality. In DLBCL, in which cure is a realistic goal for approximately 50% of older patients (≥80 years old), the high background mortality adds events to PFS and OS that are not directly modifiable by treatment adjustments and, therefore, less relevant for treatment decisions *per se*.[15,16] In a Swedish multistate modeling study[17] of 2,941 DLBCL patients in remission, transitions to death from first remission (no relapse) accounted for a substantial proportion of total mortality in older patients, especially those >80 years old. While it is difficult, if not impossible, to truly delineate causes of death in this population, in which treatment-related toxicities contribute directly or indirectly to deaths in remission, the results highlight two important aspects. First, there is likely a substantial number of events that are not directly influenced by treatment decisions but nevertheless contribute to outcomes measures such as OS and PFS used in prognostic models. If dichotomized age thresholds are relevant for treatment decisions at all, they should optimally be identified in studies that can separate deaths from lymphoma progression from other causes (including background and treatment-related mortality). Clinical decisions based on identified high risk of deaths from lymphoma progression differ from those made in response to high risk of treatment-related deaths or deaths from competing causes. Second, the high mortality of patients in first remission underscores the continued need for effective treatments that induce durable remissions in older patients, while minimizing toxicity to reduce the number of deaths in remission, both those occurring as a direct consequence of treatment toxicity as well as indirect causes through worsening of pre-existing comorbidities and/or events that lead to functional decline.

Age may define treatment regimen but not treatment eligibility

Treatment-specific elderly designations are often employed to define the age at which the benefit/risk ratio of therapy changes to become unfavorable due to poor tolerability. However, these are only meaningful in clinical-decision making if rooted in clinically reliable measures of treatment tolerability and not just crude survival. Age-related dose reductions, premature treatment cessation, and treatment-related mortality are important metrics for these assessments. While age correlates strongly with poor treatment tolerability and treatment-related mortality,

more granular data on these metrics could characterize age-related risks. Improved understanding of the biological/clinical reasons for poor tolerability may alleviate potential concerns regarding serious treatment complications in some cases in which more tolerable treatments are needed, but also avoid undertreatment of fit older patients due to an unfounded perceived high risk of complications. Supporting the notion of perceived tolerability related to age, a Danish population-based study showed that 35% of patients with DLBCL between 80-84 years old received substandard therapies, including palliation.[15] Consistently, a USA database study found that less than 50% of all patients with DLBCL ≥80 years received R-CHOP (including R-miniCHOP) and a large proportion received no treatments at all.[18] These numbers emphasize the need for more tolerable treatment options for older patients, but also raise concern that poor outcomes may be in part due to a risk-averse approach leading to substandard treatment in older DLBCL patients.

Table 1. Key topics that are considered barriers to development of novel, safe therapies for older patients with lymphoma, with suggested short- and long-term solutions.

Problem	Consequence	Short-term solution	Long-term solution
Dichotomized old age definition	Arbitrary age cut-offs (e.g., ≥60 or ≥70 years) exclude older adults who are fit and do not capture the biological heterogeneity of old age.	Move away from chronological age-threshold to measures that use age more indirectly through relevant measures such as biological age, comorbidity, and fitness.	Develop models that successfully integrate age, comorbidity, fitness, and functional status into a reproducible measure that can be used to select (and stratify) patients in clinical practice and clinical trials.
Poor representation in clinical drug development	Limited efficacy/safety data for older patients, uncertainties about benefit-risk, and reliance on data generation in the post-marketing setting.	Focus on systematic inclusion (possibly targeted enrollment) of older patients to establish dosing age/frailty/comorbidity adapted dosing strategies in the earliest phases of drug development.	Develop pivotal trial concepts that allow for differential dosing strategies within the trial, determined by age/frailty/comorbidity-related treatment tolerability.
Poor evidence for chemotherapy dosing strategies in older patients	Suboptimal cure rates due to undertreatment *versus* risk of overtreatment/toxicity.	Increase focus on possible outcomes in older patients and understand clinical risk factors and cultural reasons for undertreatment *versus* overtreatment.	Develop and conduct pragmatic trial designs that enable dose explorations with minimal administrative burdens and trial costs to increase feasibility.
Structural barriers to trial participation for older patients	Trials require activities and trial-related visits that lead to disparities based on residence (rural *vs.* urban), ability to travel, and sufficient physical and cognitive capacity to participate.	Review clinical trials protocols for activities that are not essential for safety and scientific integrity. Facilitate greater geographical diversity of clinical trial sites.	Develop decentralized trial frameworks, home-based treatments and monitoring in hematology/oncology trials.
Trials of older patients have higher bar for success when conventional endpoints such as OS and PFS are used, because of background mortality	Reduced statistical power; type 2 errors and missed efficacy for efficacious therapies. Excess mortality related to issues are more likely to go unnoticed.	Account for high background mortality in studies of the oldest patients. Consider risk of missed efficacy (type 2 error) when subgroup analyses are performed for older patients in pivotal trials.	Develop trial endpoints that separate mortality in deaths caused by lymphoma progression, treatment toxicity and competing background mortality.
Lack of widely agreed and validated prognostic models developed for older patients	Uncertain, possibly poor predictive performance of the models when used in older patients.	Carefully validate existing prognostic tools on older patients and utilize those which generalize best. Agree on a standard model to assess fitness and comorbidity in older patients with lymphoma for use moving forward.	Development of prognostic tools that can predict the wider range of relevant clinical outcomes that are meaningful specifically for the older patients. Explore models as decision support tools for treatment intensity, including dynamic adaptions of treatment intensity during therapy if patients improve/worsen.

OS: overall survival; PFS: progression-free survival.

In modern first-line phase III DLBCL trials, the upper age for inclusion has been 80 years due to perceived poor tolerance to full-dose R-CHOP in patients exceeding this age (NCT06047080, NCT05578976, NCT06356129).[19–21] Eligibility for R-miniCHOP is also pragmatically set at ≥80 years in the recently published European Society for Medical Oncology (ESMO) guidelines for lymphoma.[22] Definitions of old age for expected benefit/risk tipping points are heavily treatment-specific and should change as treatment landscapes evolve to reflect better supportive care and/or less toxic agents. Such decisions are evident in clinical practice for 50- to 60-year-olds with Burkitt lymphoma, for whom trade-offs between tolerability of intensive chemotherapy and potential efficacy must be made. In contrast, no fixed age limits exist for treatment-naïve, low-tumor burden follicular lymphoma in which rituximab monotherapy can be used safely for all ages.[23] Age cut-offs are among key eligibility criteria in clinical trials and often reflect a conservative approach to risks, especially when older patients are excluded on the basis of chronological age alone. While modern first-line studies of DLBCL typically operate with an upper age threshold of 79-80 years (NCT06047080,[24] NCT05578976,[25] NCT06356129[26]) recent first-line studies of mantle cell lymphoma (MCL) used broader definitions of "elderly," including patients as young as 60-65 years of age. For example, the ECHO, SHINE, and ENRICH trials enrolled newly diagnosed patients with MCL with ECOG performance status 0-2 who were older than 60 (ENRICH) or 65 (SHINE and ECHO) years considered transplant-ineligible.[27–29] The eligibility for intensive cytarabine-containing regimens with high-dose therapy and autologous stem cell transplant (HDT/ASCT) was historically <65 years, for example in the Nordic MCL2 and MCL3 trials.[30] However, real-world data studies have shown that treatment with HDT/ASCT is not uncommon in patients with MCL aged >65 years, and that in other lymphomas, such as central nervous system lymphoma, HDT/ASCT has been used in patients up to 70 years of age.[31,32] In contrast to SHINE and ECHO, the TRIANGLE trial, which included patients up to the age of 65 years, documented an OS benefit as well as a PFS benefit when ibrutinib was combined with cytarabine-containing chemotherapy regimens.[33] It is likely that fit patients >65 years old could have been included without safety risks in TRIANGLE, aligning with normal clinical practice and the most recent European MCL guidelines that recommend use of TRIANGLE-based therapy in subjects up to 70 years old.[34] Rather than moving the testing of tolerability to the post-marketing setting, it would be optimal to study older individuals in the clinical trials in order to capture safety data in a systematic manner.

The risk of serious adverse events does increase with age and is a major limitation to effective treatment of older patients, especially for chemotherapy but also targeted therapies.[19,35] However, arbitrary old-age treatment eligibility definitions can potentially derail development of new, effective therapies for elderly populations – particularly for the desperately needed less toxic therapies. Age-based dosing schedules should be explored over age-determined treatment eligibility already early in clinical development programs (Table 1). Unfortunately, older patients with cancer are significantly underrepresented in early phase clinical trials with >75-year-olds accounting for as few as 9-18% of participants but 28-50% of the total cancer patient population.[36] In a review by the Food and Drug Administration (FDA) of hematology trials submitted between 2005-2015 (all phases), <10% of 11,425 patients enrolled in lymphoma trials were >75 years old, although they constitute a much greater proportion of the total patient population.[37] Even in registrational trials submitted to the FDA and European Medicines Agency (EMA) between 2014-2024, the proportion of patients >75 years old (now close to the median age of newly diagnosed patients with DLBCL) was either low or not even reported.[38] Thus, older patients are underrepresented throughout all phases of clinical development of drugs and establishing the benefit/risk for older patients is deferred to the post-marketing setting through clinical experience and in the absence of systematic data collection.

Existing phase I trial dosing schedules also typically rely on early detection of protocol-defined dose-limiting toxicities and not long-term tolerability, despite novel agents often being administered for longer than historical chemotherapy regimens and often intended for use until progression. Objective age-related differences in treatment tolerability in DLBCL have been demonstrated in studies such as the PHOENIX trial,[19] in which ibrutinib plus R-CHOP showed superior OS in patients aged <60 years over R-CHOP alone, yet detrimental OS for patients >60 years old. The latter group experienced more serious adverse events and had higher rates of failed treatment completion for full R-CHOP. Similar observations were made in MCL patients treated with ibrutinib-chemotherapy. Adding ibrutinib to intensive immunochemotherapy provided OS benefit in younger, transplant-eligible MCL patients in TRIANGLE,[39] but no OS benefit was achieved with ibrutinib plus rituximab-bendamustine in transplant-ineligible patients in SHINE.[27] The sizable PFS advantage in SHINE in the ibrutinib-rituximab-bendamustine arm with reduction in deaths from lymphoma progression was offset by a higher risk of toxicity-related deaths.[27] However, it would be wrong to conclude that these treatment combinations are only efficacious in younger patients. The ongoing Arched/GLA 2022-1 study is investigating first-line acalabrutinib combined with R-miniCHOP in older patients with DLBCL (>80 years old or 61-80 years old unfit to receive full-dose R-CHOP) and the combination of a BTK-inhibitor with better tolerability and reduced-dose chemotherapy may lead to a more tolerable regimen for this group.[40,41] Rather than narrowing treatment eligibility, focusing more strongly on dose optimization in older populations prior to pivotal studies could establish more tolerable treatments and inclusive,

successful late-stage clinical development (Table 1). Studies which enrich for elderly populations while simultaneously evaluating new treatments in younger patients have shown promise. The Hodgkin Lymphoma HD21 study randomized young patients between BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) and the more intensive escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy, which is undeliverable to older patients. BreCADD showed both superior PFS and lower toxicity.[42] The deliberate addition of a single-arm cohort of 85 older patients (aged 61-75 years) to receive BreCADD within the HD21 study provided some safety, feasibility, and efficacy data for older patients, in the absence of exposure to the high-intensity control regimen.[43] This study serves as an example of successful inclusion of older patients in a pivotal study, although the data collected were not considered sufficient to establish formally benefit/risk in patients >60 years old.[44]

Unfortunately, the current fast-paced drug development programs give little attention to dose optimization, exploration of true target doses, and strategies to include underrepresented older cohorts. This raises unacceptable ethical issues with missed treatment opportunities for a large population of patients. The growing rationale for rethinking drug development is evidenced by the recent advent of novel, highly effective therapies with predictable and narrow toxicity profiles, such as bispecific antibodies, in the context of surging DLBCL rates in older patients.[45] Strategies for inclusion of older patients with lymphoma in studies of novel therapies should be prioritized by critically reviewing structural barriers to inclusion. For example, a hard upper age-ceiling as an inclusion or exclusion criterion should only be used if some data suggest that there is a strong chronological age-related impact of benefit/risk of the investigational therapy that does not go through age-related fragility measures and comorbidities. Other measures to increase inclusiveness of older populations would be to relax some of the organ-based eligibility criteria. While patients who do not fulfill organ-based eligibility criteria have worse lymphoma outcomes and many of those are older patients, the better approach would be to explore posology adapted to these impairments in the hope of benefiting this population with greater unmet needs rather than excluding them.[46,47]

Inclusion of older patients could also be increased by rethinking the typical setup of clinical trials. which are often performed at selected tertiary academic centers.[48] While this is a burden for younger patients, it can be insurmountable for older patients, who also constitute a larger proportion of the populations in rural areas and may have to travel longer distances to participate.[48] There are now several opportunities to conduct trials with decentralized elements, which means that trial-specific procedures can be performed closer to home and sometimes even at home (Table 1). The increasing use of decentralized elements in clinical trials could facilitate inclusion of older patients, but decentralized elements are unfortunately still rarely used to a larger extent in clinical trials involving novel cancer therapies and there are still logistical and legal challenges that should be addressed.[49,50]

Weak evidence levels for key decisions - the miniCHOP example

Older patients with lymphoma, particularly aggressive subtypes, experience universally inferior outcomes but this does not justify accepting lower levels of evidence or disincentivizing new studies. Randomized trials are feasible and urgently needed to inform clinical care.[51] Dose-reduction for treatment-naïve DLBCL patients ≥80 years old is now common with (R)-miniCHOP (roughly 50% of the full doses of cyclophosphamide, doxorubicin, and vincristine) becoming standard and the control arm in recent DLBCL clinical trials in older and frail adults.[51,52] Replacement of standard R-CHOP with R-miniCHOP is a major decision, as treatment failures were historically associated with very dismal outcomes due to the lack of effective, tolerable salvage therapies, although this is changing with newer therapies.[53] The GELA R-miniCHOP study was a single-arm, phase II study enrolling 149 patients ≥80 years old.[16] All patients had ECOG performance status 0-2 and 47% had no significant limitations of daily function. The 58 on-study deaths were mostly secondary to lymphoma progression, but 12 were due to treatment-related toxicity including infections. The 2-year PFS was 47% (range, 38–56) which is substantially lower than that for full-dose R-CHOP in studies of younger patients.[10] In contrast to patients in the GELA study, older patients now commonly receive granulocyte colony-stimulating factor and viral/antibiotic prophylaxis as well as pre-phase steroids, which likely improve outcomes. Despite the relatively low efficacy, the GELA study led to widespread adoption of R-miniCHOP in patients with DLBCL ≥80 years old. Taken with supportive care improvements, a critical question remains: would a careful increase in dose-intensity lead to better outcomes despite more toxicity? Or are worse outcomes for older DLBCL patients intrinsic to different disease biology that is more resistant to immunochemotherapy? A large proportion of older patients with DLBCL have the activated B-cell (ABC) subtype which confers inferior prognosis: 28-33% of patients aged 50-60 years *versus* 54-67% in patients >80 years old.[54,55] Interestingly, replacing vincristine with polatuzumab vedotin (pola-R-CHP) conferred greater benefit in the ABC subtype of DLBCL than in the germinal center B-cell subtype and greater PFS improvement in patients 70–80 years old.[56, 57] These observations are now being explored in the ongoing Nordic phase III POLAR BEAR study[52] in

which pola-R-miniCHP is being tested against R-miniCHOP in newly diagnosed patients ≥75 years old (NCT04332822). The addition of a BTK-inhibitor (acalabrutinib) to R-miniCHOP is another strategy that may successfully target the prevalent ABC subtypes of DLBCL among older patients.[40]

Worse outcomes in elderly patients could also partially be explained by suboptimal dose-intensity. Although R-miniCHOP is curative in some patients, the optimal R-CHOP dosing strategy has never been explored in prospective randomized studies of the elderly. Real-world studies are mixed. In a systematic review of dosing strategy of 5,188 newly diagnosed cases of DLBCL from 13 studies, multivariable analyses were performed in ten, and six reported significantly poorer outcomes with reduced dose-intensity. However, in subgroups aged ≥80 years old, lower dose-intensity did not consistently impair OS. There was substantial heterogenicity in dose-intensity calculations and definitions of reduced dose-intensity. Furthermore, most studies had very few patients ≥80 years old which limited power to determine smaller, yet clinically important effects of dose reductions in this cohort.[58] Two recent observational studies specifically explored R-miniCHOP *versus* R-CHOP. A UK study included 746 DLBCL patients ≥80 years old receiving R-CHOP and 158 receiving R-mini-CHOP.[59] The patients' characteristics were balanced, with identical 3-year OS (54%) maintained in multivariate analysis (hazard ratio=0.95, 95% confidence interval: 0.73-1.22, with R-CHOP as the reference). Due to R-CHOP definitions including some dosing concessions, the R-CHOP cohort likely included patients who received reduced doses. A Dutch population-based DLBCL study evaluating patients aged ≥65 years reached different conclusions. Using propensity scores 384 R-miniCHOP-treated patients were matched to 384 of the 3,847 R-CHOP-treated patients. R-miniCHOP was associated with statistically significant worse survival (PFS 51% *vs*. 68%; OS 60% *vs*. 75%; relative survival 69% *vs*. 86%). ECOG performance status was not available for either study's matching, despite being strongly predictive of OS. Attributing inferior OS to dose reductions therefore needs caution as it is likely confounded by ECOG performance status and frailty. Whether higher chemotherapy dosing would lead to different outcomes for elderly patients remains unclear. While uncertainties remain around the optimal dosing strategy in older patients, an Italian study focusing on 370 patients ≥80 years old showed that the inclusion of anthracycline, regardless of dosing strategy, correlated with better survival outcomes. Outcomes by R-CHOP intensity (here >70% *vs*. 50-70% of standard-dose intensity) did not impact outcomes, although these comparisons were not adjusted for confounders. In general, escalation/de-escalation strategies warrant prospective, randomized investigations to control for all known and unknown confounders linked to dosing strategy in older patients. Confounding response-adapted treatment decisions during therapy could also impact these analyses. For example, dose-intensity may be reduced more often in patients with signs of poor treatment tolerability if interim response assessment shows remission than in those with partial remissions. Finally, most of the published studies exploring R-CHOP dosing strategies use reduced-dose definitions for doses that were much higher than the conventional R-miniCHOP schedule. For example, a large study in the USA showed no detrimental effects of R-CHOP given at <80% of standard-dose intensity (cyclophosphamide or doxorubicin) to patients with DLBCL >80 years old.[60] However, considering many promising new therapies in development, chemotherapy dose-optimizations may not be a high priority at all. Older patients with DLBCL may potentially look forward to a chemotherapy-free future, as shown by the preliminary data for the triplet treatment with polatuzumab, rituximab, and glofitamab in the AGMT-NHL-16/GLA2022-10 trial in which complete remission was achieved in 82% of patients ineligible for full-dose R-CHOP (median age 80 years, range, 66-92).[61] Numerically, the complete remission rate of >80% is identical to what is achieved with full-dose R-CHOP in younger patients.[20] While durability of response remains to be seen, these early data question the future of chemotherapy in older patients with lymphoma in high-income countries that can afford these expensive combination therapies. However, optimization of the chemotherapy dosing strategies may still be the most cost-effective way of improving outcomes on a global scale. While real-world data may help by providing descriptive data about treatment tolerability, the causal inference between different dosing strategies and outcomes are complex even with advances in statistical methodologies for comparative effectiveness studies and more granular real-world data. Pragmatic clinical trials in which patients are randomized to different dosing strategies but otherwise managed in a setting very close to normal routine practice and in which events are captured in national registries, if possible, could be a cost-efficient way of reaching more firm conclusions concerning dosing strategies.

Trials in older patients with lymphoma risk a higher bar for success and missed safety signals

Treatment- and disease-unrelated deaths in clinical trials are a unique challenge in elderly populations. Highlighting this, a UK study observed a marked difference between OS and lymphoma-specific survival (3-year OS, 54%; lymphoma-specific survival, 80-90%).[59] The exact contributors to cause of death are difficult to elucidate despite OS remaining the most important clinical outcome for industry, policy-makers and regulatory bodies. Background mortality estimates can provide some clarity; the 2020 5-year mortality rates for 80-year-old Danish men and women were 30% and 22%, respectively.[62] Corresponding estimates for 50-year-olds were 2% and 1%. The high background

mortality of elderly populations impacts clinical trial performance and results. Paradoxically, it can raise the bar for success in older lymphoma patients despite higher unmet needs. Our case example illustrates this. Consider a novel immunotherapy which is very effective in combination with first-line chemotherapy for high-risk DLBCL. The experimental therapy reduces the risk of dying from lymphoma by 10% after 5 years regardless of age and has no negative or positive influence on lymphoma-unrelated deaths. Two trials are performed – Trial I exclusively enrolls 50-year-olds and Trial II enrolls only 80-year-olds. The 5-year lymphoma-specific survival is set to 80% and 50% for 50-year-olds and 80-year-olds, respectively.[63] Utilizing Danish background mortality rates,[62] Table 2 illustrates how the two hypothetical trials differ in terms of survival between the arms, with Trial I having a hazard ratio between the arms of 0.50 and Trial II a hazard ratio of 0.82, resulting in Trial I having clearly superior power to Trial II with similar enrollment numbers. Thus, transferring efficacy results (for example observed hazard ratios for OS) from younger to older patients without considering background mortality differences can result in underpowered studies and a higher bar for success. At the same time, high background mortality may inadvertently obscure excess mortality from toxicity. PFS is the common primary endpoint in DLBCL trials, but OS is increasingly considered as a safety endpoint when trends towards worse OS in an experimental arm, even if not statistically significant, would raise concern despite a PFS gain.[64] Again, paradoxically, the bar will be higher for detection of detrimental effects on OS in studies of older patients, despite their excess risk of fatal toxicities. We illustrate this with similar survival assumptions as before, but a fixed number of 500 patients (250 per arm) in a scenario in which the experimental therapy is associated with an excess mortality of 1%, 2%, 3%, 4%, or 5% after 5 years. The corresponding hazard ratios for OS in younger patients would be 1.05 (power: 4%), 1.11 (power: 8%), 1.16 (power: 12%), 1.22 (power: 19%), and 1.27 (power: 25%) whereas hazard ratios for older patients would be 1.02 (power: 4%), 1.04 (power: 5%), 1.06 (power: 8%), 1.08 (power: 19%), and 1.11 (power: 15%). Thus, while excess mortality caused by the experimental therapy is similar, it is more likely to go unnoticed in the oldest patients. Overall, designing and conducting trials in older patients is more complex and associated with lower likelihood of success for several reasons. This may limit pharmaceutical companies' willingness to invest in the development of novel therapies for the oldest patients with lymphoma. The fact that novel therapies are, as a rule, associated with more toxicity in older patients and OS outcomes are worse could also lead to a perception of poorer cost-effectiveness among payers and more questions raised in the post-marketing access discussions. Such negative perceptions will exacerbate the already existing disparity between younger and older cancer patients. Ultimately, there is a role for regulatory agencies, such as the FDA and EMA, as well as ethics review boards to strongly encourage, if not reinforce, inclusion of more elderly patients in clinical development programs already at early stages to optimize dosing strategies for the groups of older patients.

Prognosis and prognostic models in old patients

Prognostic models for older patients require several considerations to maintain clinical relevance. For example, endpoints predominantly related to progression or all-cause mortality do not adequately recognize the broader range of clinically relevant events among older patients, in whom treatment-related mortality and loss of function are substantial risks of interest for the patients themselves. Accurately predicting these outcomes in real-world settings requires models developed on representative patient populations as models developed in younger subjects may not apply (Table 1). The Advanced-stage Hodgkin Lymphoma International Prognostic Index (A-HIPI) developed for patients aged 18-65 years old[65] was applied to patients aged 65-90 years resulting in a C-index for OS of 0.55, indicating low discriminatory power, almost at the level of random guessing.[66] A recent validation study of several commonly used DLBCL prognostic indices also reported lower predictive accuracy in patients >60 years old, likely due to focus on measures of disease burden and failure to account for geriatric performance measures and comorbidities.[67] Dedicated prognostic models for older patients

Table 2. Two hypothetical clinical trial scenarios, one for patients aged 50 years and the other for patients aged 80 years.

	Trial I (patients aged 50)		Trial II (patients aged 80)	
	Control	Experimental	Control	Experimental
5-year BS, %	99	99	74	74
5-year LSS, %	80	90	50	60
5-year OS, %	79	89	37	44
HR	0.50	0.50	0.82	0.82
Power at enrollment, % 200 400 600 800 1,000		47 76 90 96 99		19 34 47 59 69
N to enroll to achieve 80% power		442		1,301

In both scenarios, an experimental treatment increases the 5-year lymphoma-specific survival by 10%. The table shows the resulting overall survival in each arm, the corresponding hazard ratios, and power with different numbers of trial participants randomized in a 1:1 ratio. A two-sided α=0.05 is used. BS: background survival; LSS: lymphoma-specific survival; OS: overall survival; HR: hazard ratio.

have been developed with better performance for outcome predictions.[68–70] Merli *et al.*[69] integrated a simplified geriatric assessment into a prognostic model for older patients with DLBCL, which has been externally validated both in the original publication as well as in a Chinese study.[71] However, caution must be taken when utilizing geriatric assessments in older patients with lymphoma. While the American Society of Clinical Oncology (ASCO) guideline[72] recommends geriatric assessment-guided management of patients ≥65 years planned for systemic therapy when deficits are identified by the assessment, the evidence supporting this practice in lymphoma is insufficient. The ASCO recommendation was based on nine clinical trials, of which only five included patients with lymphoma. Among these, two trials enrolled a very small proportion of lymphoma patients (grouped in the "other cancers"),[73,74] two included fewer than 10% lymphoma patients (N=33 and N=46 patients),[75,76] and only one trial[77] had a substantial proportion of patients with lymphoma (N=50, 31%). Evidence derived from patients with solid cancers may not apply in lymphoma, as patients with lymphoma and deficits in geriatric assessment may improve substantially and fast on lymphoma therapy if the deficits were partially caused by high disease burden. Routine use of geriatric assessments can also be challenging due to limited resources and absence of a simple, commonly agreed standard as-

Table 3. Overview of types of events likely to occur in older patients with lymphoma and their clinical relevance, including how predictions would impact management.

Event	Special consideration for elderly populations	Clinical importance
Toxicity with impact on independent living and daily functioning	With lower baseline functional levels and reserve capacity, older patients are at risk of treatment-related functional decline that eventually reaches levels that severely impact independent living with possible lifelong impact on quality of life.	Impact of toxicity underestimated using 'maximum grade' measures. Benefit/risk as reported in clinical trials may not translate to routine clinical settings and value to patients.
Dose interruptions, substantial dose reductions, or premature termination of treatment	Older patients are more likely to experience toxicities leading to dose reduction or premature treatment discontinuation which may impair treatment efficacy. The threshold for when to reduce doses is lower for older patients.	Reduced dose intensity leading to lower efficacy and perceived lack of benefit in clinical settings. Undertreatment of older patients due to lack of knowledge about optimal dosing strategy/dose modifications for older patients.
Primary refractory disease/early relapse	Frailty and genetically more complex cancer combined with less intensive therapies in older patients increase the risk of refractory disease and early relapse.	Refractory disease in older patients is more often associated with dismal outcomes due to lack of tolerable treatments. More risk in first-line treatment may be justified in older patients who express a wish for curative treatment.
Late relapse and late treatment toxicities	Shorter follow-up due to competing risks makes late relapses more difficult to capture accurately among older patients. Shorter residual life expectancy, pre-existing comorbidities, and selection of fit older patients for treatments complicate evaluation of late treatment toxicities and their implications on the normal age-related decline in general health.	True long-term benefit of therapy and late toxicities are not adequately measured, leading to lack of knowledge about the longer term benefit/risk ratio in older patients.
Deaths	Overall survival is an efficacy measure more difficult to interpret in older patients, especially in diseases with acceptable survival outcomes, due to competing deaths from lymphoma-unrelated causes. Incorporating information on cause of death and expected mortality is essential to respond to observations with relevant changes in clinical practice.	Deaths from unrelated causes" erroneously attributed to treatment can lead to erroneous perceptions about tolerability and undertreatment of older patients. Relevant clinical response to high mortality requires more knowledge about the causes of deaths.

sessment tool.[78] A consensus statement from experts in the field would facilitate more standardized practices and accelerate implementation in clinical trials and routine practice. Alternative ways of assessing comorbidity and fragility through readily available surrogate measures may be an option. For example, prescription drug overviews and polypharmacy can predict various different patient outcomes such as hospitalizations and severe infections and not just OS.[79]

Finally, the validity of geriatric assessment for use in treatment decision algorithms is sensitive to changes in therapy. Newer agents, including small-molecule inhibitors such as BTK-inhibitors and BCL2-inhibitors, as well as bispecific antibodies, and antibody-drug conjugates, bring distinct toxicity profiles compared with chemotherapy. This may fundamentally change the utility of current frailty scores for treatment decisions.

When developing prognostic and predictive models for older patients, considering the relevance of different outcomes and how they may differ between younger and older patients is important (Table 3). Discriminating between these outcomes is clinically important. If treatment-related deaths dominate OS events, increasing dose-intensity would be the solution. In contrast, if a large proportion of deaths is caused by progressive lymphoma with few treatment-related deaths, dose-escalations may be relevant. In general, endpoints should be more nuanced, recognizing that disease progression and death do not carry equal weight, and giving priority to understanding both the cause and timing of death. As a minimum, endpoints focusing on disease- and treatment-related events in older patients should try to account for the significant background mortality and how it contributes to the conventional OS and PFS measures (Table 3). Other survival endpoints, such as cause-specific mortality and relative survival, may provide more meaningful information for older lymphoma patients, although cause-specific mortality requires an exact cause of death, which can be difficult to determine, especially with multimorbidity. Incorporating cause-specific mortality could be combined with integration of prognostic scores that can distinguish treatment-related from disease progression–related mortality. Such prognostic tools could also guide treatment decisions and trial enrollment for older patients, enabling more intensive therapy for those at higher risk of disease progression and less intensive approaches for those at greater risk of treatment-related mortality. In contrast, relative survival relies on life tables for background mortality and is easy to obtain, but depends on model assumptions, which may not be fulfilled in hematology.[80]

Recent developments in the field of multistate modeling[81] allow handling of a wide array of different endpoints and aspects of the elderly health trajectory in a single model. Comprehensive hematology models have yielded clearer overviews of difficulties and adverse events in cohorts of elderly patients, including those with DLBCL.[17,82]

Conclusions

Strict lymphoma therapy age cut-offs serve older patients poorly, both in clinical guidelines as well as a default selection criterion in clinical trials. They are arbitrary, outdated, and risk mismatching benefits and risks in these patients. They also inadequately accommodate patients' wishes or goals of care. We must develop better frameworks for shared decision-making in older patients which focuses on informed therapeutic decisions based on likelihoods of a range of relevant clinical outcomes that can vary in importance according to personal beliefs. Building robust and validated predictive models that account for these outcomes at different timepoints based on patient and disease characteristics will inform this process. Furthermore, a global overhaul of trial design in elderly populations is needed throughout the drug development pathway, from dose optimization in early phases focusing on target doses rather than maximal tolerated doses through to reviewing the backbone of randomized studies and harnessing real-world data to inform applicability to clinical cohorts.

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Contributions

MRS and TCE-G drafted the first version of the manuscript. All authors critically revised the manuscript and approved the final version.

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References

1. Shrestha A, Martin C, Burton M, Walters S, Collins K, Wyld L. Quality of life versus length of life considerations in cancer patients: a systematic literature review. Psychooncology. 2019;28(7):1367-1380.
2. Garner WB, Smith BD, Ludmir EB, et al. Predicting future cancer incidence by age, race, ethnicity, and sex. J Geriatr Oncol. 2023;14(1):101393.
3. Harrysson S, Eloranta S, Antonilli S, et al. Temporal trends in relative survival of diffuse large B-cell lymphoma in Sweden and Denmark in the era of targeted and cellular therapies. Br J Haematol. 2025;206(6):1834-1839.
4. Yang X, Laliberté F, Germain G, et al. Real-world characteristics, treatment patterns, health care resource use, and costs of patients with diffuse large B-cell lymphoma in the U.S. Oncologist. 2021;26(5):e817-e826.
5. Pacis S, Bolzani A, Heuck A, et al. Epidemiology and real-world treatment of incident diffuse large B-cell lymphoma (DLBCL): a German claims data analysis. Oncol Ther. 2024;12(2):293-309.
6. Lamb M, Painter D, Howell D, et al. Lymphoid blood cancers, incidence and survival 2005-2023: a report from the UK's Haematological Malignancy Research Network. Cancer Epidemiol. 2024;88:102513.
7. World Health Organisation. Ageing and Health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health Accessed August 19, 2025.
8. Steel N, Bauer-Staeb CMM, Ford JA, et al. Changing life expectancy in European countries 1990–2021: a subanalysis of causes and risk factors from the Global Burden of Disease Study 2021. Lancet Public Health. 2025;10(3):e172-e188.
9. Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235-242.
10. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9(2):105-116.
11. Solal-Celigny P. Follicular Lymphoma International Prognostic Index. Blood. 2004;104(5):1258-1265.
12. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-994.
13. Gang AO, Pedersen M, D'Amore F, et al. A clinically based prognostic index for diffuse large B-cell lymphoma with a cut-off at 70 years of age significantly improves prognostic stratification: population-based analysis from the Danish Lymphoma Registry. Leuk Lymphoma. 2015;56(9):2556-2562.
14. Biccler J, Eloranta S, de Nully Brown P, et al. Simplicity at the cost of predictive accuracy in diffuse large B-cell lymphoma: a critical assessment of the R-IPI, IPI, and NCCN-IPI. Cancer Med. 2018;7(1):114-122.
15. Juul MB, Jensen PH, Engberg H, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: a Danish population-based cohort study. Eur J Cancer. 2018;99:86-96.
16. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2011;12(5):460-468.
17. Ekberg S, Crowther M, Harrysson S, Jerkeman ME. Smedby K, Eloranta S. Patient trajectories after diagnosis of diffuse large B-cell lymphoma-a multistate modelling approach to estimate the chance of lasting remission. Br J Cancer. 2022;127(9):1642-1649.
18. Shewade A, Olszewski AJ, Pace N, et al. Unmet medical need among elderly patients with previously untreated DLBCL characterized using real-world data in the United States. Blood. 2020;136(Supplement 1):6-8.
19. 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. J Clin Oncol. 2019;37(15):1285-1295.
20. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351-363.
21. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol. 2021;39(12):1317-1328.
22. Eyre TA, Cwynarski K, D'Amore F, et al. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025;36(11):1263-1284.
23. Northend M, Wilson W, Ediriwickrema K, et al. Early rituximab monotherapy versus watchful waiting for advanced stage, asymptomatic, low tumour burden follicular lymphoma: long-term results of a randomised, phase 3 trial. Lancet Haematol. 2025;12(5):e335-e345.
24. Advani RH, Dickinson MJ, Fox CP, et al. SKYGLO: a global phase III randomized study evaluating glofitamab plus polatuzumab vedotin + rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) versus Pola-R-CHP in previously untreated patients with large B-cell lymphoma (LBCL). Blood. 2024;144(Supplement 1):1718.1.
25. Sehn LH, Chamuleau M, Lenz G, et al. Phase 3 trial of subcutaneous epcoritamab + R-CHOP versus R-CHOP in patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL): EPCORE DLBCL-2. J Clin Oncol. 2023;41(16_suppl):TPS7592.
26. Hoffmann M, Vassilakopoulos T, Munoz J, et al. Golseek-1: a phase 3, double-blind, randomized study comparing the efficacy and safety of golcadomide plus R-CHOP vs R-CHOP in patients with previously untreated, high-risk, large B-cell lymphoma. Blood. 2024;144(Supplement 1):1742.2.
27. Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med. 2022;386(26):2482-2494.
28. Wang M, Salek D, Belada D, et al. Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma. J Clin Oncol. 2025;43(20):2276-2284.
29. Lewis DJ, Jerkeman M, Sorrell L, et al. Ibrutinib and rituximab versus immunochemotherapy in patients with previously untreated mantle cell lymphoma (ENRICH): a randomised, open-label, phase 2/3 superiority trial. Lancet. 2025;406(10514):1953-1968.
30. Kolstad A, Pedersen LB, Eskelund CW, et al. Molecular monitoring after autologous stem cell transplantation and preemptive rituximab treatment of molecular relapse; results from the Nordic Mantle Cell Lymphoma studies (MCL2 and MCL3) with median follow-up of 8.5 years. Biol Blood Marrow

Transplant. 2017;23(3):428-435.
31. Martin P, Cohen JB, Wang M, et al. Treatment outcomes and roles of transplantation and maintenance rituximab in patients with previously untreated mantle cell lymphoma: results from large real-world cohorts. J Clin Oncol. 2023;41(3):541-554.
32. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217-e227.
33. Dreyling M, Doorduijn JK, Gine E, et al. Role of autologous stem cell transplantation in the context of ibrutinib-containing first-line treatment in younger patients with mantle cell lymphoma: results from the randomized Triangle trial by the European MCL Network. Blood. 2024;144(Supplement 1):240.
34. Jerkeman M, Aurer I, Campo E, et al. EHA–EU MCL Network guidelines for diagnosis and treatment of mantle cell lymphoma. Hemasphere. 2025;9(10):e70233.
35. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. JAMA Oncol. 2015;1(1):80.
36. Baldini C, Charton E, Schultz E, et al. Access to early-phase clinical trials in older patients with cancer in France: the EGALICAN-2 study. ESMO Open. 2022;7(3):100468.
37. Kanapuru B, Singh H, Myers A, et al. Enrollment of older adults in clinical trials evaluating patients with hematologic malignancies - the Food and Drug Administration (FDA) experience. Blood. 2017;130(Suppl_1):861.
38. Juthani R, Pugh K, Neuendorff NR, Torka P. Representation of older adults in registrational trials associated with therapeutic approvals in diffuse large B-cell lymphoma. J Geriatr Oncol. 2025;16(6):102264.
39. Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomized, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403(10441):2293-2306.
40. Christofyllakis K, Age Kos I, Altmann B, et al. Safety of front-line R-Mini-CHOP with or without acalabrutinib in older adults with DLBCL - an interim analysis of serious adverse events in the Arched / GLA 2022-1 randomized, open-label, phase 3 trial. Blood. 2024;144(Supplement 1):4498.
41. Seymour JF, Byrd JC, Ghia P, et al. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. Blood. 2023;142(8):687-699.
42. Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024;404(10450):341-352.
43. Ferdinandus J, Kaul H, Fosså A, et al. positron emission tomography–guided brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone in older patients with advanced-stage classic Hodgkin lymphoma: a prospective, multicenter, single-arm, phase II cohort of the German Hodgkin Study Group HD21 trial. J Clin Oncol. 2025;43(27):2974-2985.
44. Adcetris: EPAR Product information, European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf Accessed November 12, 2025.
45. Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. Blood. 2023;141(5):467-480.
46. Khurana A, Mwangi R, Nowakowski GS, et al. Impact of organ function-based clinical trial eligibility criteria in patients with diffuse large B-cell lymphoma: who gets left behind? J Clin Oncol. 2021;39(15):1641-1649.
47. Bennedsen TL, Simonsen MR, Jensen P, et al. Impact of trial eligibility criteria on outcomes of 1183 patients with follicular lymphoma treated in the real-world setting. Eur J Haematol. 2025;114(5):832-839.
48. Jones DA, Spencer K, Ramroth J, et al. Inequalities in geographic barriers and patient representation in lymphoma clinical trials across England. Br J Haematol. 2025;206(2):531-540.
49. Thota R, Hurley PA, Miller TM, et al. Improving access to patient-focused, decentralized clinical trials requires streamlined regulatory requirements: an ASCO research statement. J Clin Oncol. 2024;42(33):3986-3995.
50. Park J, Huh KY, Chung WK, Yu K-S. The landscape of decentralized clinical trials (DCTs): focusing on the FDA and EMA guidance. Transl Clin Pharmacol. 2024;32(1):41-51.
51. Oberic L, Peyrade F, Puyade M, et al. Subcutaneous rituximab-MiniCHOP compared with subcutaneous rituximab-MiniCHOP plus lenalidomide in diffuse large B-cell lymphoma for patients age 80 years or older. J Clin Oncol. 2021;39(11):1203-1213.
52. Jerkeman M, Leppä S, Hamfjord J, Brown P, Ekberg S, José María Ferreri A. S227: Initial safety data from the phase 3 POLAR BEAR trial in elderly or frail patients with diffuse large cell lymphoma, comparing R-pola-mini-CHP and R-mini-CHOP. Hemasphere. 2023;7(S3):e91359ec.
53. Abramson JS, Ku M, Hertzberg M, et al. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. Lancet. 2024;404(10466):1940-1954.
54. Mareschal S, Lanic H, Ruminy P, Bastard C, Tilly H, Jardin F. The proportion of activated B-cell like subtype among de novo diffuse large B-cell lymphoma increases with age. Haematologica. 2011;96(12):1888-1890.
55. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(5):649-662.
56. Sehn LH, Martelli M, Trněný M, et al. A randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final analysis of GOYA. J Hematol Oncol. 2020;13(1):71.
57. Hu B, Reagan PM, Sehn LH, et al. Subgroup analysis of older patients ≥60 years with diffuse large B-cell lymphoma in the phase 3 POLARIX study. Blood Adv. 2025;9(10):2489-2499.
58. Bataillard EJ, Cheah CY, Maurer MJ, Khurana A, Eyre TA, El-Galaly TC. Impact of R-CHOP dose intensity on survival outcomes in diffuse large B-cell lymphoma: a systematic review. Blood Adv. 2021;5(9):2426-2437.
59. Hounsome L, Eyre TA, Ireland R, et al. Diffuse large B cell lymphoma (DLBCL) in patients older than 65 years: analysis of 3 year real world data of practice patterns and outcomes in England. Br J Cancer. 2022;126(1):134-143.

60. Bair SM, Narkhede M, Frosch ZA, et al. Treatment intensity and outcomes in elderly patients with DLBCL receiving first line therapy. Blood. 2023;142(Supplement 1):68.
61. Wurm-Kuczera R, Melchardt T, Pichler P, et al. 159 | R-pola-GLO – chemo-light frontline therapy induces high response rates with a favorable safety profile in elderly/frail patients with aggressive lymphoma. Hematol Oncol. 2025;43(S3):207-209.
62. Human Mortality Database. Max Planck Institute for Demographic Research (Germany), University of California, Berkeley (USA), and French Institute for Demographic Studies (France). www.mortality.org Accessed August 19, 2025.
63. Durmaz M, Visser O, Posthuma EFM, et al. Time trends in primary therapy and relative survival of diffuse large B-cell lymphoma by stage: a nationwide, population-based study in the Netherlands, 1989–2018. Blood Cancer J. 2022;12(3):38.
64. Merino M, Kasamon Y, Theoret M, Pazdur R, Kluetz P, Gormley N. Irreconcilable differences: the divorce between response rates, progression-free survival, and overall survival. J Clin Oncol. 2023;41(15):2706-2712.
65. Maurer MJ, Parsons SK, Upshaw JN, et al. The A-HIPI prediction model in advanced-stage Hodgkin lymphoma: identification of risk groups and creation of an online tool. Blood Adv. 2025;9(6):1366-1369.
66. Rask Kragh Jørgensen R, Eloranta S, Christensen JH, et al. Age-based validation of the Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI) in a real-world Danish study: suboptimal performance in older patients. Blood. 2023;142(Supplement 1):4455.
67. Jelicic J, Juul-Jensen K, Bukumiric Z, et al. Validation of prognostic models in elderly patients with diffuse large B-cell lymphoma in a real-world nationwide population-based study – development of a clinical nomogram. Ann Hematol. 2025;104(1):433-444.
68. Scheepers ERM, Vondeling AM, Thielen N, van der Griend R, Stauder R, Hamaker ME. Geriatric assessment in older patients with a hematologic malignancy: a systematic review. Haematologica. 2020;105(6):1484-1493.
69. Merli F, Luminari S, Tucci A, et al. Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the Prospective Elderly Project of the Fondazione Italiana Linfomi. J Clin Oncol. 2021;39(11):1214-1222.
70. Isaksen KT, Galleberg R, Mastroianni MA, et al. The Geriatric Prognostic Index: a clinical prediction model for survival of older diffuse large B-cell lymphoma patients treated with standard immunochemotherapy. Haematologica. 2023;108(9):2454-2466.
71. Yun X, Bai J, Feng R, et al. Validation and modification of simplified Geriatric Assessment and Elderly Prognostic Index: effective tools for older patients with diffuse large B□cell lymphoma. Cancer Med. 2024;13(1):e6856.
72. Dale W, Klepin HD, Williams GR, et al. Practical assessment and management of vulnerabilities in older patients receiving systemic cancer therapy: ASCO guideline update. J Clin Oncol. 2023;41(26):4293-4312.
73. Soo WK, King MT, Pope A, Parente P, Dārziņš P, Davis ID. Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: a multicentre, open-label, randomised controlled trial. Lancet Healthy Longev. 2022;3(9):e617-e627.
74. Mohile SG, Epstein RM, Hurria A, et al. Communication with older patients with cancer using geriatric assessment. JAMA Oncol. 2020;6(2):196.
75. Puts M, Alqurini N, Strohschein F, et al. Impact of geriatric assessment and management on quality of life, unplanned hospitalizations, toxicity, and survival for older adults with cancer: the randomized 5C trial. J Clin Oncol. 2023;41(4):847-858.
76. Mohile SG, Mohamed MR, Xu H, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet. 2021;398(10314):1894-1904.
77. DuMontier C, Uno H, Hshieh T, et al. Randomized controlled trial of geriatric consultation versus standard care in older adults with hematologic malignancies. Haematologica. 2021;107(5):1172-1180.
78. Zuccarino S, Monacelli F, Antognoli R, et al. Exploring cost-effectiveness of the comprehensive geriatric assessment in geriatric oncology: a narrative review. Cancers (Basel). 2022;14(13):3235.
79. Brieghel C, Lacoppidan T, Packness E, et al. Polypharmacy independently predicts survival, hospitalization, and infections in patients with lymphoid cancer. Hemasphere. 2025;9(7):e70172.
80. Pohar Perme M, de Wreede LC, Manevski D. What is relative survival and what is its role in haematology? Best Pract Res Clin Haematol. 2023;36(2):101474.
81. Andersen PK, Ravn H. Models for Multi-State Survival Data. Chapman and Hall/CRC; 2023.
82. Rodday AM, Parsons SK, Cui ZJ, et al. Creation of a multistate model to improve prognostication across the disease course in advanced stage classic Hodgkin Lymphoma (cHL): a report from the Holistic Consortium. Blood. 2024;144(Supplement 1):567.