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ORIGINAL REPORT

Event-Free Survival at 24 Months Is a Robust End Point for Disease-Related Outcome in Diffuse Large B-Cell Lymphoma Treated With Immunochemotherapy

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Studies of diffuse large B-cell lymphoma (DLBCL) are typically evaluated by using a time-to-event approach with relapse, re-treatment, and death commonly used as the events. We evaluated the timing and type of events in newly diagnosed DLBCL and compared patient outcome with reference population data.

Patients and Methods
Patients with newly diagnosed DLBCL treated with immunochemotherapy were prospectively enrolled onto the University of Iowa/Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource (MER) and the North Central Cancer Treatment Group NCCTG-N0489 clinical trial from 2002 to 2009. Patient outcomes were evaluated at diagnosis and in the subsets of patients achieving event-free status at 12 months (EFS12) and 24 months (EFS24) from diagnosis. Overall survival was compared with age- and sex-matched population data. Results were replicated in an external validation cohort from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien 2003 (LNH2003) program and a registry based in Lyon, France.

Results
In all, 767 patients with newly diagnosed DLBCL who had a median age of 63 years were enrolled onto the MER and NCCTG studies. At a median follow-up of 60 months (range, 8 to 116 months), 299 patients had an event and 210 patients had died. Patients achieving EFS24 had an overall survival equivalent to that of the age- and sex-matched general population (standardized mortality ratio [SMR], 1.18; $P = .25$). This result was confirmed in 820 patients from the GELA study and registry in Lyon (SMR, 1.09; $P = .71$). Simulation studies showed that EFS24 has comparable power to continuous EFS when evaluating clinical trials in DLBCL.

Conclusion
Patients with DLBCL who achieve EFS24 have a subsequent overall survival equivalent to that of the age- and sex-matched general population. EFS24 will be useful in patient counseling and should be considered as an end point for future studies of newly diagnosed DLBCL.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma in the United States and Europe and is an aggressive lymphoma with an expected survival of less than 1 year if untreated.[1,2] However, a significant number of patients are potentially cured with the current standard-of-care rituximab (anti-CD20 monoclonal antibody) plus anthracycline-based chemotherapy (immunochemotherapy), most commonly given as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3-6] Although the majority of patients treated with immunochemotherapy respond to treatment, 20% to 40% of patients will either fail to achieve remission or they will relapse. Most relapses occur within the first 12 to 18 months, and outcome for these patients is generally poor with salvage therapies, including platinum-based chemotherapy and stem-cell transplantations, resulting in long-term survival in only a minority of patients.[7-10] Although late relapses may occur, they

are infrequent, with a recent report identifying only 7% of first relapses occurring more than 5 years after diagnosis in the immunochemotherapy era.[8] Traditionally, clinical studies of DLBCL have used progression-free survival and/or overall survival (OS) as outcomes. However, the event rate slows significantly approximately 12 months after diagnosis, and incorporation of late events can be complicated by competing risks, especially in older patients with comorbid health conditions.

On the basis of these clinical observations, we examined the type and timing of events and evaluated OS and cause-specific survival conditional on being alive and disease-free at 12 and 24 months from diagnosis in patients with DLBCL who were treated with immunochemotherapy. Given the competing risk of death in this generally older population (median age at diagnosis, 60 years), we also compared the OS rate to that expected from the general population, accounting for age and sex. We replicated our main results in independent studies from France. Finally, we assessed the impact of using event-free survival status at 24 months from diagnosis (EFS24) as a primary end point for the design of future treatment trials of DLBCL.

PATIENTS AND METHODS

This study was reviewed and approved by the human subjects institutional review board at the Mayo Clinic and the University of Iowa, and written informed consent was obtained from all participants. Patients were prospectively enrolled onto the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE)[11-13] or enrolled onto North Central Cancer Treatment Group NCCTG-N0489.[14] The MER cohort consisted of all patients with newly diagnosed DLBCL who received rituximab and anthracycline-based chemotherapy as their initial therapy. All diagnoses were confirmed by a study hematopathologist. Patients with primary mediastinal lymphoma were included; however, patients with primary CNS lymphoma, post-transplantation lymphoproliferative disorder, transformation of a previously diagnosed lymphoma, or DLBCL in association with HIV infection were excluded. Baseline clinical, laboratory, and treatment data were abstracted from medical records by using a standard protocol (MER) or per clinical trial protocol (NCCTG-N0489 [NCT00301821]). Loss to follow-up was low, since all patients were systematically contacted every 6 months for the first 3 years and then annually (MER)[11-13] or per clinical trial protocol (NCCTG-N0489).[14] Disease progression or relapse, re-treatment, and death were verified through review of pathology and medical records. Unplanned consolidative radiation therapy, but not radiation therapy as part of the initial treatment plan, was considered a re-treatment. Cause of death was determined by review of death certificates and medical records by using a standard definition developed for Eastern Cooperative Oncology Group ECOG-E4494.[4] Death as a result of disease included progressive/refractory disease not responding to treatment irrespective of other causes of death, cardiac deaths attributable to anthracycline toxicity, and deaths secondary to infections for patients actively receiving chemotherapy. Death unrelated to lymphoma included deaths that were considered independent of malignant lymphoma or chemotherapy treatments (eg, stroke, suicide, accidents).

Replication Study

Data for replication were obtained from an external set of patients with DLBCL who were treated with immunochemotherapy from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien 2003B (LNH2003B) program[15-19] and hospital-based registry in Lyon, France. The LNH2003B program of the GELA consisted of six prospective multicenter studies of patients with DLBCL older than age 18 years. Patients were stratified on age and age-adjusted International Prognosis Index for treatment allocation in four randomized phase III and two phase II studies (details in the Data Supplement). All patients had a pathology review confirming the DLBCL diagnosis. In this GELA program, during the first 2 years after treatment, assessment consisted of physical examination and laboratory tests every 3 months and computed tomography scans of the chest, abdomen, and pelvis every 6 months. Thereafter, physical examination and laboratory tests were done every 6 months and computed tomography scans every year for 5 years. The Lyon registry consisted of all patients with newly diagnosed DLBCLs treated with immunochemotherapy in routine clinical practice at the Léon Bérard Cancer Center between August 1998 and December 2008 and observed through 2010. Further details on these studies are in the Data Supplement.

Statistical Methodology

OS was defined as time from diagnosis until death as a result of any cause; cause-specific survival was summarized using common causes of death. Event-free survival (EFS) was defined as time from diagnosis until relapse or progression, unplanned re-treatment of lymphoma after initial immunochemotherapy, or death as a result of any cause. EFS indicators at predefined cut points (ie, EFS at 12 months [EFS12] or EFS at 24 months [EFS24]) were defined on the basis of EFS status at the indicated cut point after date of diagnosis. Kaplan-Meier curves were used to display survival curves. Event decomposition was performed by using a competing risk approach.[20] Expected survival accounting for age and sex was generated in R by using the general US (survexp.us)[21] and French (survexp.fr)[22] populations as reference groups for the US and French studies, respectively.[22-24] Observed versus expected OS was plotted by using a conditional approach[25] and summarized by using standardized mortality ratios (SMRs) of observed to expected deaths.[26] Simulation studies were performed to compare the power of continuous EFS to a dichotomous EFS24 end point (Data Supplement). All analyses were performed by using SAS v9.2 (SAS Institute, Cary, NC) and R v2.13.0.

RESULTS

Patient Characteristics

In all, 767 patients with newly diagnosed DLBCL who were treated with rituximab and anthracycline-based chemotherapy were enrolled onto the SPORE MER from 2002 to 2009 or the NCCTG-N0489 clinical trial from 2006 to 2007. Median age was 63 years (range, 18 to 92 years) and 53% were male (Table 1). At a median follow-up of 60 months (range, 8 to 116 months), 299 patients (39%) had an event and 210 patients (27%) had died. Kaplan-Meier estimates for the percentage of patients achieving EFS12 and EFS24 was 77% (95% CI, 74% to 80%) and 71% (95% CI, 67% to 74%), respectively.

Description of Events

An event decomposition was performed to elucidate the risk of relapse compared with other types of events, such as treatment-related death, relapse with indolent non-Hodgkin lymphoma, and death as a result of other causes. At the time of diagnosis, the vast majority of future events were a result of DLBCL relapse (Fig 1A) with a 5-year risk of relapse of 30% (95% CI, 26% to 33%). Future risk of other event types at the time of diagnosis was low, with 5-year risks no greater than 5% for other event types, including indolent non-Hodgkin lymphoma relapse. Examination of the relapse risk at diagnosis shows that 70% of DLBCL relapses occur within the first year from diagnosis (1-year risk, 21%; 95% CI, 18% to 24%) with a continued declining relapse rate as the time from diagnosis increased. Thus, once a patient completed therapy and achieved EFS12, the risk of future relapse in the following 5 years (Fig 1B) dropped to only 13% (95% CI, 9% to 17%). In patients achieving EFS24, the risk of future DLBCL relapse in the following 5 years improved to 8% (95% CI, 5% to 12%), which was the same as the risk of death as a result of unrelated causes (8%; 95%

Table 1. Patient Characteristics

Characteristic	US Data Sets						French Data Sets						All Patients (N = 1,587)	
	MER (n = 680)		NCCTG-N0489 (n = 87)		All (N = 767)		Lyon, France (n = 220)		GELA (n = 600)		All (N = 820)			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years														
Median	63		60		63		67		61		61		62	
Range	18-92		29-82		18-92		19-90		18-93		18-93		18-93	
> 60	387	57	42	48	429	56	130	59	286	48	416	51	845	53
Male sex	359	53	47	54	406	53	106	48	349	58	455	55	861	54
LDH > ULN	342	55	60	69	402	57	158	72	332	55	490	60	892	58
Stage III to IV	412	61	69	79	481	63	140	64	406	67	546	67	1,027	65
≥ 2 Extranodal sites	127	19	22	25	149	19	57	26	217	36	274	33	423	27
ECOG PS ≥ 2	120	18	9	10	129	17	49	22	103	17	152	19	281	18
IPI score														
0-1	242	36	23	26	265	35	61	28	202	34	263	32	528	33
2	186	27	24	28	210	27	56	25	129	22	185	23	395	25
3	168	25	29	33	197	26	51	23	141	24	192	23	389	25
4-5	84	12	11	13	95	12	52	24	128	21	180	22	275	17
EFS12														
Kaplan-Meier estimate	76		82		77		78		81		80		78	
95% CI	73 to 80		74 to 90		74 to 80		73 to 84		78 to 84		77 to 83		76 to 80	
EFS24														
Kaplan-Meier estimate	70		74		71		71		73		73		71	
95% CI	67 to 74		65 to 83		67 to 74		65 to 77		70 to 77		70 to 76		69 to 73	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS12, event-free survival at 12 months; EFS24, event-free survival at 24 months; GELA, Groupe d'Etude des Lymphomes de l'Adulte; IPI, International Prognostic Index; LDH, lactose dehydrogenase; MER, Molecular Epidemiology Resource; NCCTG, North Central Cancer Treatment Group; ULN, upper limit of normal.

CI, 4% to 12%; Fig 1C). Achieving additional event-free time from diagnosis resulted in only small gains in future DLBCL relapse risk (Data Supplement).

Comparison of Study Group Survival to That of the General Population

At diagnosis, patients had a significantly decreased survival compared with the age- and sex-matched general population, with an SMR of 2.88 (95% CI, 2.51 to 3.30; $P < .001$; Fig 2A). Survival improved as patients remained in a disease-free state, with patients achieving EFS12 having a subsequent SMR of 1.40 (95% CI, 1.10 to 1.76; $P = .0038$; Fig 2B); the SMR was no longer significant when patients achieved EFS24 (SMR, 1.18; 95% CI, 0.89 to 1.57; $P = .25$; Fig 2C). Similar results were seen in cause of death patterns (Fig 3), with little future lymphoma-related mortality in patients achieving EFS12 (Fig 3B) or EFS24 (Fig 3C). In contrast, most patients with an event in the first 12 or 24 months died as a result of lymphoma (Data Supplement). In a sensitivity analysis, results were similar when using a progression-free definition in which consolidative re-treatment was not considered an event (Data Supplement).

Replication of Survival Results

To replicate the survival findings, an external validation data set of 820 patients with newly diagnosed DLBCL who were treated with rituximab and anthracycline-based chemotherapy was assembled consisting of patients from the GELA LNH05-1B, LNH03-1B, LNH03-2B, LNH03-3B, LNH03-6B and LNH03-7B clinical trials and a hospital-based registry in Lyon, France. Event decomposition and cause of death data were not available. Median age was 62 years (range, 18 to 93 years) and 55% were male (Table 1). At a median follow-up of 42 months (range, 1 to 129 months), 290 patients (32%) had an event and 221 (24%) had died. Kaplan-Meier estimates for achieving EFS12 and EFS24 were 80% (95% CI, 77% to 83%) and 73% (95% CI, 70% to 76%), respectively. Results similar to those in the US data set were observed for patient survival when compared with age- and sex-matched survival in the French population. French patients had a larger survival deficit than the US patients at diagnosis (SMR, 4.99; 95% CI, 4.34 to 5.75; $P < .001$; Fig 4A) but showed improvement in survival as the duration of the disease-free period increased (EFS12 SMR, 2.06; 95% CI, 1.57 to 2.70; $P < .001$; Fig 4B). As seen in the US data set, there was no significant difference in subsequent survival compared with that for the general population in patients who were disease-free at 24 months (SMR, 1.09; 95% CI, 0.69 to 1.74; $P = .71$; Fig 4C).

Additional Analyses in the Pooled Data Sets

To increase power, we next pooled the US and French data sets. In the pooled data, survival after a relapse, re-treatment, or progression event (RRPE) was poor, with a median OS of 13 months (95% CI, 10 to 16 months) after an event other than death. Patients with an RRPE within 1 year from diagnosis had inferior survival (median OS, 8 months; 95% CI, 7 to 10 months) compared with patients with an RRPE between 12 and 24 months (median OS, 28 months; 95% CI, 15 to 50 months) or patients with an RRPE after 24 months (median OS, 36 months; 95% CI, 29 to 55 months; $P < .001$). However, 5-year survival rates were similar across the three groups (Data Supplement);

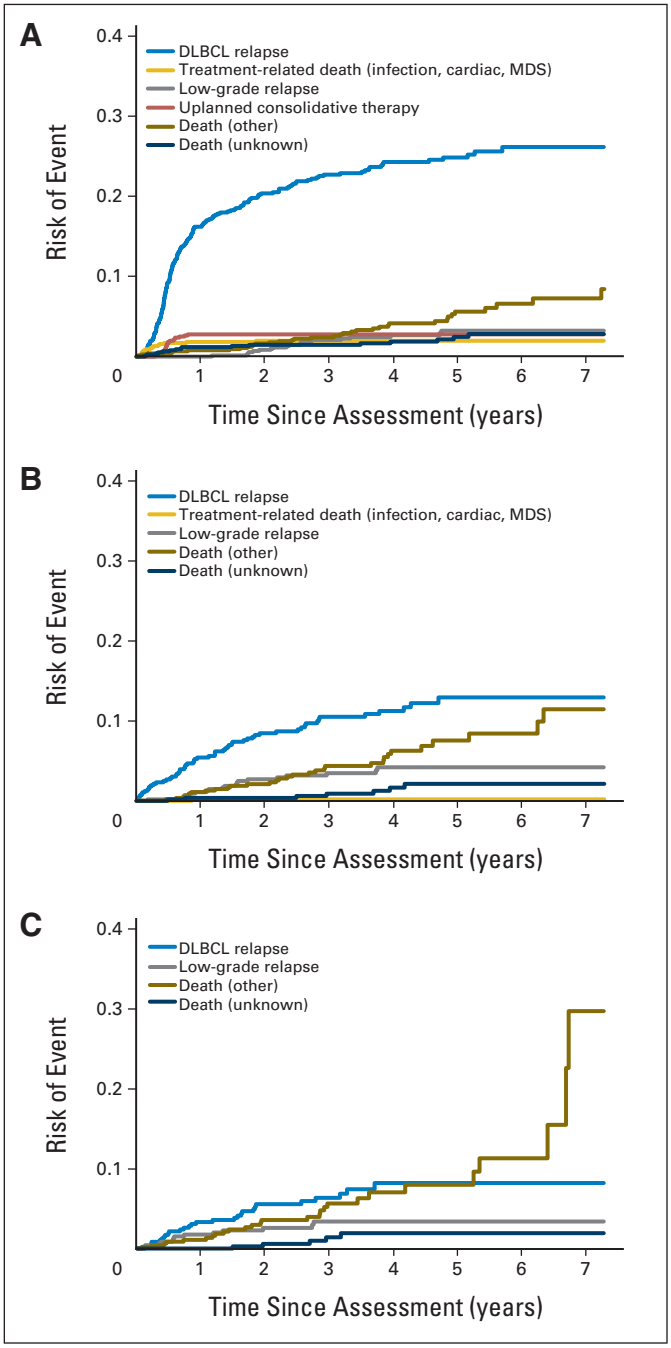

Fig 1. Event description in the US cohort at diagnosis, in patients achieving event-free survival at 12 or 24 months. (A) Assessment at diagnosis; (B) event free 12 months since diagnosis; (C) event free 24 months since diagnosis. DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome.

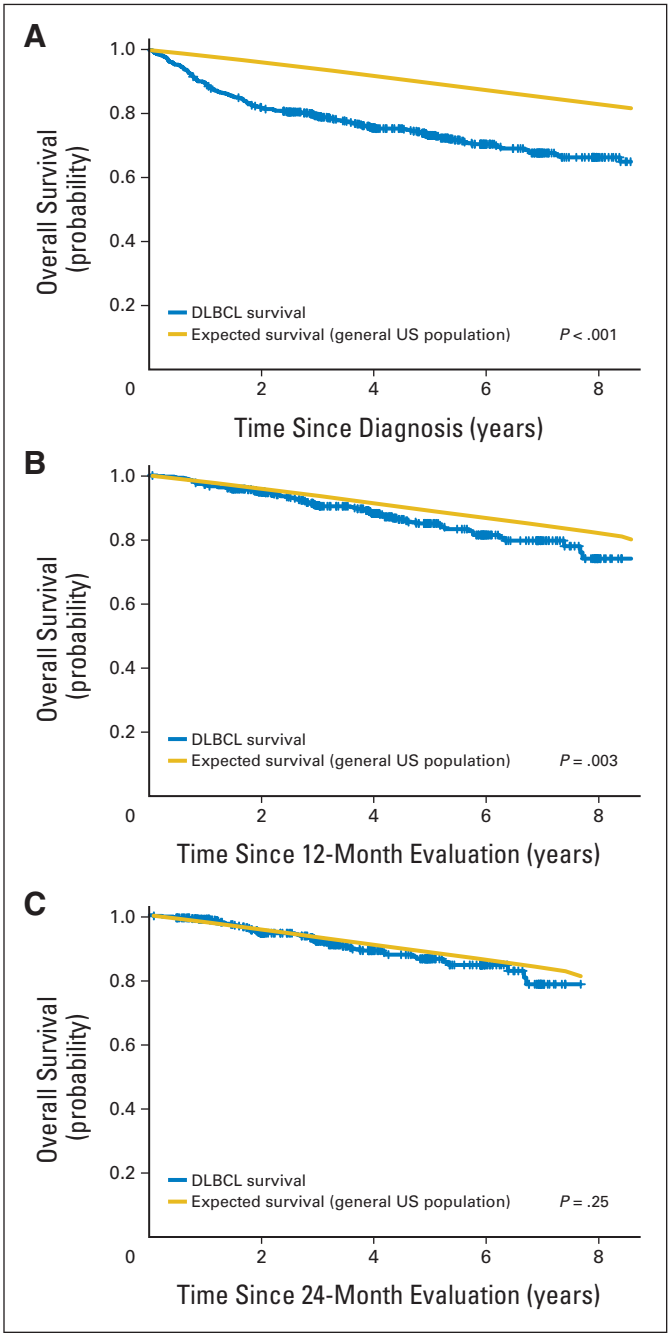

Fig 2. Overall survival versus expected survival in US cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

additional follow-up on these cohorts of patients will be needed to determine whether there is superior long-term survival for late-relapsing patients.

Pretreatment prognostic factors showed an influence on survival, with high-risk subgroups having greater SMR than low-risk subgroups (Fig 5A), and demonstrated continued impact on post-therapy prognosis for patients achieving EFS12 (Fig 5B). The only subgroup that did not show a significantly reduced survival compared with the age- and sex-matched general population was in patients achieving EFS12 with stage I to II disease (US SMR, 1.08; 95% CI, 0.71 to 1.59; $P = .76$; French SMR, 1.35; 95% CI, 0.64 to 2.48; $P = .43$). Pretreatment prognostic factors no longer identified any patient subgroups with reduced survival once patients achieved EFS24 (Fig 5C).

In sensitivity analyses, excluding primary mediastinal B-cell lymphoma and GELA patients who received rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) and consolidation with autologous stem-cell transplantation did not significantly change results (data not shown).

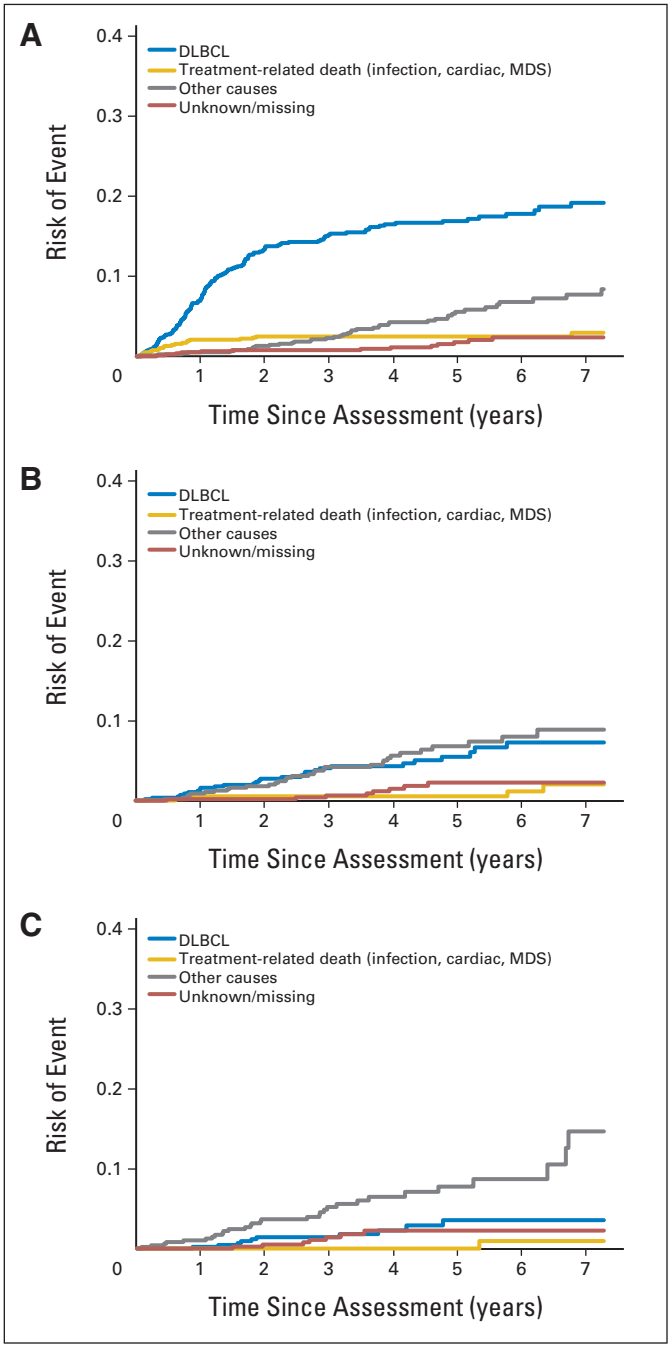

Fig 3. Cause of death in the US cohort at diagnosis, in patients achieving event-free survival at 12 or 24 months. (A) Assessment at diagnosis; (B) event free 12 months since diagnosis; (C) event free 24 months since diagnosis. DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome.

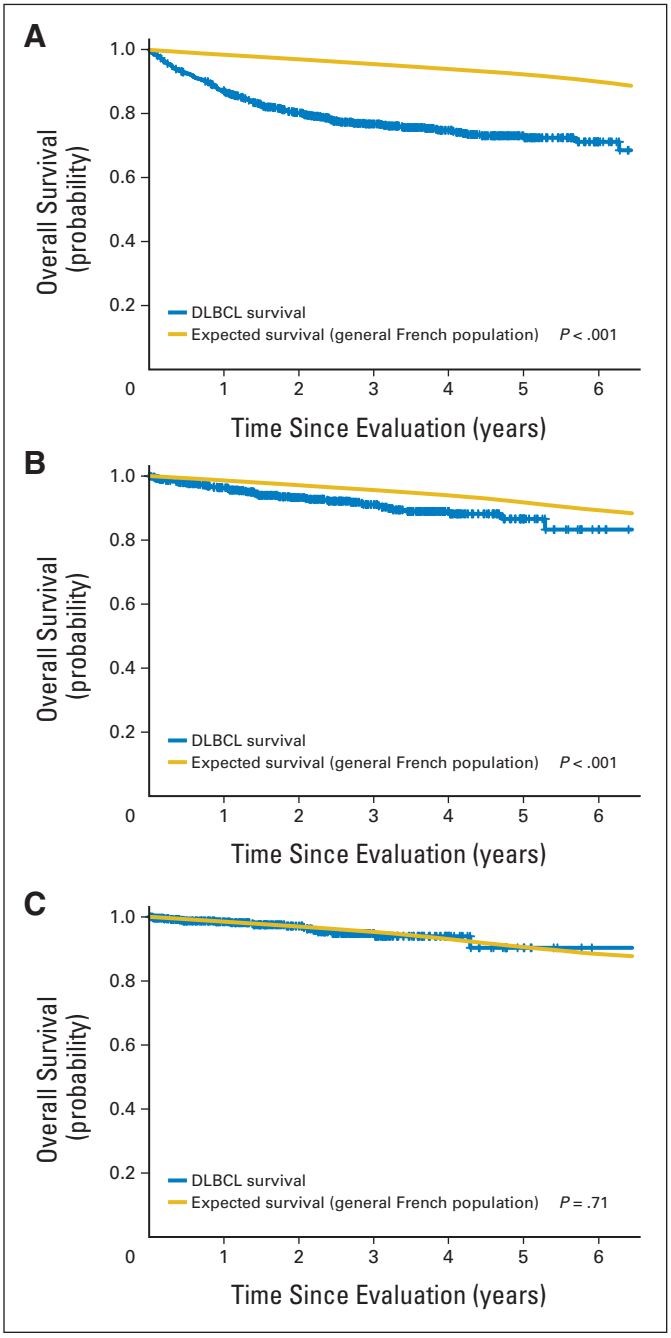

Fig 4. Overall survival versus expected survival in French cohort at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) Overall survival since diagnosis; (B) overall survival since EFS12 evaluation; (C) overall survival since EFS24 evaluation. DLBCL, diffuse large B-cell lymphoma.

Simulation Study of EFS24 and Continuous EFS

Simulated clinical trials were performed to compare the power of EFS24 and continuous EFS to detect a difference in the DLBCL relapse rate of treatment arms in the presence of a competing risk of unrelated death (Data Supplement). Two primary effect models were assumed: one in which the treatment improved the risk of relapse only in the first year following diagnosis (ie, 12 months [12M]) and one in which the treatment improved the risk of relapse during the entire course of follow-up (all follow-up [ALLFU]; Data Supplement). Each simulated trial had an enrollment of 400 patients (200 in each arm) with an enrollment period of 3 years and a varied follow-up period of 24 to 60 months (median follow-up, 3.5 to 6.5 years). Under the 12M model, in which improvement is limited to the first 12 months when the relapse rate is highest, EFS24 (average power of 76% to detect a 50% reduction in DLBCL relapse between arms) was slightly more powerful than continuous EFS (average power of 69%; Data Supplement). Under the ALLFU model, continuous EFS (average power of 95% to

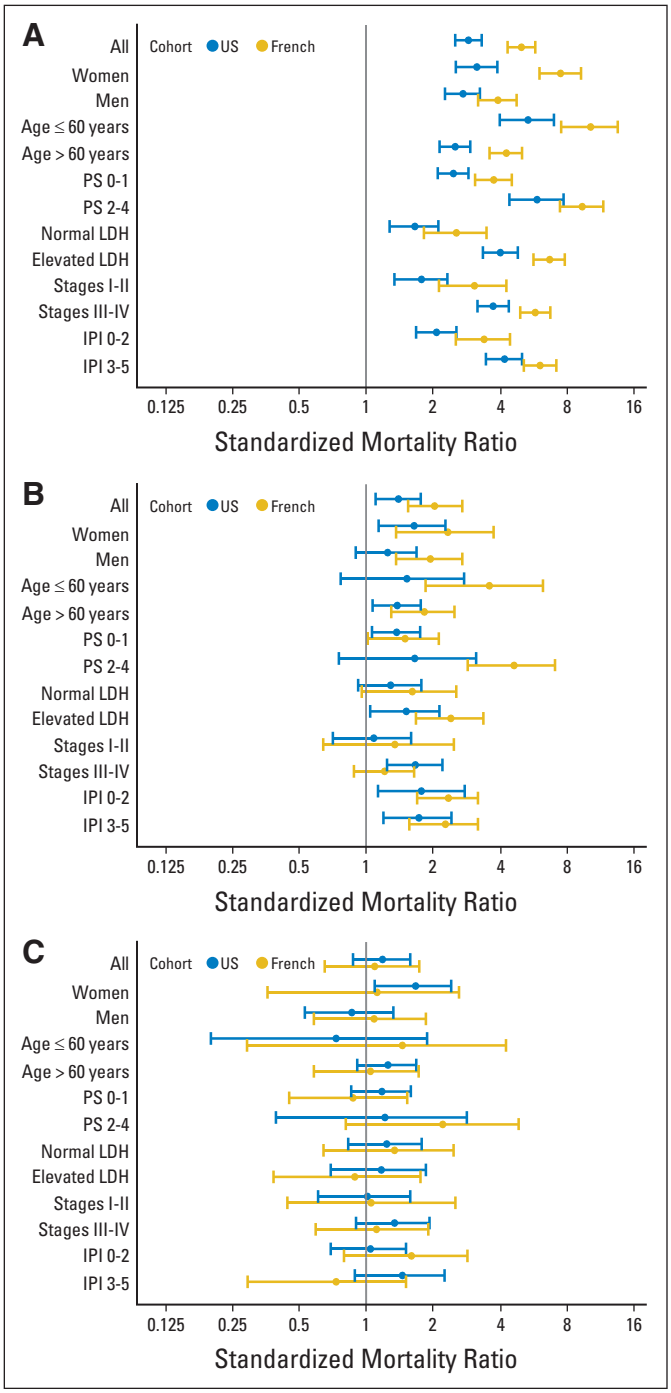

Fig 5. Forest plots of standardized mortality ratio in combined data set by diffuse large B-cell lymphoma subgroups at diagnosis, in patients achieving event-free survival at 12 (EFS12) or 24 (EFS24) months. (A) All patients since diagnosis; (B) EFS12 patients from 12 months since diagnosis; (C) EFS24 patients from 24 months since diagnosis. IPI, International Prognosis Index; LDH, lactate dehydrogenase; PS, performance status.

detect a 50% reduction in DLBCL relapse between arms) was slightly more powerful than EFS24 (average power of 91%). The models simulated were selected to be at the extreme ends of potential treatment effects. It is likely that the effect measured in future trials will lie somewhere in between, suggesting that there is comparable power between the two end points. Of note, the power for continuous EFS decreased with additional follow-up time under the 12M effect model and remained relatively consistent under the ALLFU effect model.

DISCUSSION

This study demonstrates that patients with DLBCL treated with standard immunochemotherapy who remain event-free 2 years after diagnosis have excellent long-term outcome with little lymphoma-related mortality in the follow-up period observed in this study. In other words, patients who have achieved EFS24 have subsequent survival comparable to that of the age- and sex-matched general population (ie, a normal life expectancy).

The strengths of the study include the large series of prospectively enrolled patients treated with immunochemotherapy, replication in an independent data set, and patients enrolled onto both registry and trial-based studies from the United States and Europe. This is one of the largest series of patients with DLBCL studied for outcome in the immunochemotherapy era and should have excellent generalizability. The major limitations of this analysis are the under-representation of very elderly patients (older than age 85 years) in our cohort and the lack of long-term (ie, > 10 years) follow-up since the immunochemotherapy era began in the early 2000s, and our study includes patients prospectively enrolled from the start of this treatment period.[27] In addition, these findings were in patients treated with anthracycline-based immunochemotherapy regimens, and extrapolation of results to other treatments would be speculative. We also did not assess the impact of management after relapse, which was beyond the scope of this study. It is important to note, as well as communicate to patients, that achieving EFS24 does not establish cure, since approximately 8% of patients event-free at 24 months had a subsequent relapse of DLBCL in the US data set. However; for the roughly 70% of newly diagnosed patients achieving EFS24, as well as perhaps stage I to II patients achieving EFS12, this does mean that the patient now has an OS from that point forward that is equivalent to that of the general non-DLBCL population. In other words, these patients now have a normal life expectancy, and they are now also at greater risk of dying from causes other than their DLBCL. For most patient groups, there is still a reduced survival in patients achieving the EFS12 end point; most of this added mortality in our series was from lymphoma resulting in death (results not shown). Importantly, these survival deficits appear to be resolved in patients once they achieve EFS24. Further follow-up will be needed to look for potential effects of long-term treatment on survival.

These results have important implications in planning new prospective clinical trials for DLBCL, and they support the use of EFS24 as the primary end point. Analysis of DLBCL can be challenging in that the majority of patients can be cured by their initial therapy, and the validity of time-to-event end points such as EFS is influenced by causes other than the intended element being studied (ie, DLBCL relapse/progression). Event decomposition in the US data shows that once patients achieve 24 months of follow-up, at least 50% of any future events will be deaths unrelated to DLBCL from patients in remission. Thus, in contrast to the general rule of thumb "the more follow-up the better," observing patients with DLBCL beyond 24 months for relapse provides little benefit, confirmed by our simulation studies. In addition, examination of the EFS curves in the

practice-changing GELA LNH 98-5,[3] ECOG-E4494,[4] and MabThera International Trial (MiNT) group[6] trials shows that the separation of outcome between arms occurs within 24 months on each study. Given that the vast majority of DLBCL relapses occur in the first 24 months, any improvement in outcome is expected to manifest in the first 24 months and thus would be captured by the EFS24 end point. EFS24 is also an appealing end point for clinical trial design in DLBCL. It requires only 2 years of follow-up, and studies can be evaluated sooner than when using continuous EFS. It can potentially make trial design more accurate since the standard exponential model used for power calculations is a poor fit for the typical event distribution of DLBCL; the use of EFS24 also avoids potential violations of Cox proportional hazards models. Thus, when the primary goal is comparison of disease-related events, we recommend using EFS24 as the end point for outcome studies or clinical trials of patients with newly diagnosed DLBCL. Additional follow-up beyond 24 months is still needed for assessment of overall survival and to monitor for late complications such as progressive multifocal leukoencephalopathy or cardiomyopathy.

These data provide important insight into developing informed clinical strategies for post-therapy surveillance and management. The excellent outcome of patients achieving EFS24, and perhaps patients with low-stage disease who achieve EFS12, call into question the utility of routine surveillance imaging for patients in remission beyond these time points. Investigation of strategies involving prolonged postremission therapy will also benefit from a more precise understanding of expected outcomes from key landmark time points. Clinical risk prediction models for achieving EFS24 should be developed to identify patients at high risk of early relapse to help prioritize patients for clinical trials or alternative management strategies. Finally, these results will help physicians and patients develop a survivorship care plan, which will also need to address nonlymphoma health issues and potential late effects of therapy that are perhaps more likely to have an impact on life expectancy.

In conclusion, patients with newly diagnosed DLBCL who were treated with immunochemotherapy who are event-free 24 months after diagnosis have excellent outcome, with an OS equivalent to that of the age- and sex-matched general population in both US and French data sets. Consideration of EFS24 as an end point in clinical trials and biologic studies of newly diagnosed DLBCL is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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GLOSSARY TERMS

immunochemotherapy: a combination of immunotherapy (eg, anti-CD20) and chemotherapy.