original reports

Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

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abstract

PURPOSE Diffuse large B-cell lymphoma (DLBCL) presents as a limited-stage disease in 25% to 30% of patients, with better overall survival (OS) than that for advanced-stage disease but with continuous relapse regardless of treatment approach. The preferred treatment is abbreviated rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and radiation therapy. On the basis of promising results of positron emission tomography (PET)–directed treatment approaches, we designed a National Clinical Trials Network (NCTN) study to improve outcomes and decrease toxicity.

METHODS Patients with nonbulky (< 10 cm) stage I/II untreated DLBCL received 3 cycles of standard R-CHOP therapy and underwent a centrally reviewed interim PET/computed tomography scan (iPET). Those with a negative iPET proceeded with 1 additional cycle of R-CHOP, whereas those with a positive iPET received involved field radiation therapy followed by ibritumomab tiuxetan radioimmunotherapy.

RESULTS Of 158 patients enrolled, 132 were eligible and 128 underwent iPET, which was positive in 14 (11%) of the patients. With a median follow-up of 4.92 years (range, 1.1-7.7 years), only 6 patients progressed and 3 died as a result of lymphoma. Eleven patients died as a result of nonlymphoma causes at a median age of 80 years. The 5-year progression-free survival estimate was 87% (95% CI, 79% to 92%) and the OS estimate was 89% (95% CI, 82% to 94%), with iPET-positive and iPET-negative patients having similar outcomes.

CONCLUSION To our knowledge, S1001 is the largest prospective study in the United States of limited-stage DLBCL in the rituximab era, with the best NCTN results in this disease subset. With PET-directed therapy, 89% of the patients with a negative iPET received R-CHOP × 4, and only 11% had a positive iPET and required radiation, with both groups having excellent outcomes. The trial establishes R-CHOP × 4 alone as the new standard approach to limited-stage disease for the absolute majority of patients.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma diagnosed in the United States, representing 30% to 40% of all cases.[1] DLBCL presents as limited stage approximately 25% to 30% of the time. Our study in the pre-rituximab era, SWOG S8736, established that 3 courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) followed by radiation therapy (RT; CHOP × 3 + RT) had superior progression-free and overall survival (PFS and OS) compared with 8 courses of CHOP, but the differences disappeared by year 9 because of late relapses, without a plateau in the survival curve.[2,3] S8736 also established the stage-modified (Miller) international prognostic index (smIPI) by demonstrating that patients without adverse risk factors had an excellent 10-year OS of at least 90%, whereas patients with risk factors had excess mortality because of relapse and death, with a 5-year OS of approximately 70%.[2,4,5]

In follow-up studies, SWOG S0014 demonstrated that adding rituximab to CHOP × 3 + RT (R-CHOP × 3 + RT) had a positive effect on the high-risk group,[6] and radioimmunotherapy consolidation with ibritumomab tiuxetan after CHOP × 3 + RT seemed to decrease long-term relapses in S0313.[7] On the basis of S0014 and extrapolation from other DLBCL studies,[8] R-CHOP × 3 + RT has remained a standard therapy approach in this setting and holds a category 1 recommendation from the National Comprehensive Cancer Network.

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

To use an interim positron emission tomography (PET) scan after 3 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) to stratify therapy for patients with limited-stage diffuse large B-cell lymphoma.

Knowledge Generated

With a median follow-up of almost 5 years, only 6 of 132 eligible patients progressed, and 3 died as a result of lymphoma, for a 5-year progression-free survival estimate of 87% and an OS estimate of 89%. Eighty-nine percent of the patients with a negative interim PET/computed tomography scan (iPET) received R-CHOP × 4, whereas only 11% had a positive iPET and required radiation-based therapy, with both groups having excellent outcomes.

Relevance

The trial establishes R-CHOP × 4 alone as the new standard approach to limited-stage disease for the absolute majority of patients

Midtreatment interim positron emission tomography (PET)/computed tomography (CT) scan (iPET) is prognostic in DLBCL.[9,10] Preliminary results of a retrospective experience from the BC Cancer Lymphoid Cancer Database demonstrated that 80% of patients were PET negative after 3 cycles of R-CHOP (defined as Deauville 1-2[11]), and only 8% of them relapsed after receiving 1 more cycle of R-CHOP without RT.[12]

We designed S1001, a prospective National Clinical Trials Network (NCTN) PET-directed study, to tailor therapy in limited-stage DLBCL after 3 cycles of R-CHOP. Our goal was to eliminate the short- and long-term toxicities associated with RT[3,13,14] for the majority of patients with a negative PET scan after 3 cycles of R-CHOP and to improve the outcome in the minority of patients with a positive interim PET scan.

METHODS

Patients

S1001 was a phase II NCTN study for previously untreated patients with nonbulky (< 10 cm) stage I/II CD20-positive DLBCL. Since the WHO classification underwent a change over the study period, new categories of high-grade B-cell lymphoma (HGBL) with or without *MYC* and *BCL2* or/and *BCL6* rearrangements were also eligible. Staging was based on both CT and PET/CT scans. Patients with primary mediastinal, HIV-associated, post-transplantation, testicular, CNS, primary cutaneous, and indolent lymphoma were excluded. Patients, including those whose disease was grossly resected at diagnosis, could have either measurable or evaluable disease. Patients had to have a WHO performance status of 0-2, adequate organ function, a left ventricular ejection fraction of at least the lower level of normal, and a negative bone marrow biopsy within 6 weeks of registration. Patients had to be at least 18 years old, with no upper age limit. The protocol had to be approved by institutional review boards. All patients provided written informed consent in accordance with their institutional policies and according to the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01359592).

All patients received 3 cycles of standard R-CHOP treatment given every 3 weeks, with rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (capped at 2 mg) IV, and prednisone 100 mg a day by mouth for 5 days. Patients had an iPET between day 15 and 18 of cycle 3, which was centrally reviewed in real time at Imaging and Radiation Oncology Core Rhode Island. Those with a negative iPET, defined as Deauville 1-3, proceeded with 1 additional cycle of R-CHOP. Patients with a positive iPET (Deauville 4-5) initiated 36 Gy of involved field radiation therapy (IFRT), plus an additional boost to fluorodeoxyglucose (FDG)-avid areas of up to 9 Gy, within 5 weeks of cycle 3 of R-CHOP. Three to 6 weeks after completing IFRT, patients received ibritumomab tiuxetan administered per standard protocol, with rituximab 250 mg/m^2 on day 1 and day 7, 8, or 9, and ibritumomab tiuxetan 0.4 mCi/kg on day 7, 8, or 9, after rituximab. A final PET scan was performed 12 weeks after treatment completion. Patients were observed with examination and testing, including CT scans every 6 months for the first 2 years and then annually for up to 7 years or death, whichever came first.

Pathology Procedures

Pathology was centrally reviewed by 2 expert hematopathologists after the study completed enrollment. The cell of origin (COO) was first assessed on immunohistochemistry by the Hans algorithm[15] and subsequently by Nanostring using Lymph2Cx.[16] If not performed locally, additional immunohistochemistry slides were stained to establish the double protein expressor (DPE) status, defined as having both positive MYC staining of at least 40% and BCL2 staining of at least 50% of malignant cells.[17] Similarly, additional fluorescence in situ hybridization (FISH) studies for *MYC*, *BCL2*, and *BCL6* using the LSI dual

color break-apart probes (Abbott Molecular, Des Plaines, IL) were performed centrally as needed to establish the diagnosis of HGBL with or without *MYC* and *BCL2* or/and *BCL6* rearrangements. In 9 cases, outside FISH results were confirmed with a central FISH study.

Statistical Plan

The primary end point was the 5-year PFS rate, whereas secondary end points included OS rate, PFS and OS rates for iPET-positive and iPET-negative subgroups, toxicity, and response rates. Assuming a 10% ineligibility rate, 155 enrolled patients were needed to obtain 140 eligible patients. This would be sufficient to estimate the 5-year PFS rate to within 6% (95% CI), to test the historical 5-year PFS estimate of 85% against an alternative hypothesis of 93%. Using an exact binomial test, this design had a type I error of .057 and 93% power.

Analysis was performed on all eligible patients. PFS and OS were estimated using the Kaplan-Meier method.[18] Adjustment for prognostic factors for PFS and OS was performed using Cox regression analysis.[19] The cumulative incidence of progression was estimated accounting for the competing risk of nonlymphoma death.[20] Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria, version 4. Eligible patients receiving at least 1 dose of drug were included in the assessment of adverse events. Response was assessed using revised Cheson criteria.[21]

RESULTS

Patient Characteristics

S1001 was activated on July 15, 2011, and accrual was completed on June 1, 2016. Of 158 patients enrolled, 26 were ineligible because of incorrect histology (the majority [21] had concurrent indolent or follicular lymphoma grade 3B), lack of diagnostic tissue submission for central pathology review (3), or bulky evaluable bone disease (2; Fig 1).

The clinical and disease characteristics of the 132 eligible patients are summarized in Table 1. The median age was 62 years, 62% had stage I disease, 17% had B symptoms, 14% had elevated lactate dehydrogenase (LDH), 43% had extranodal involvement, 66% had exclusive involvement of the head and neck region, and 10% had their disease fully resected at baseline. smIPI was 0 in 27%, 1 in 42%, 2 in 28%, and 3 in 4% of the patients. Overall, 72% of the patients had DLBCL, NOS not otherwise specified (NOS);

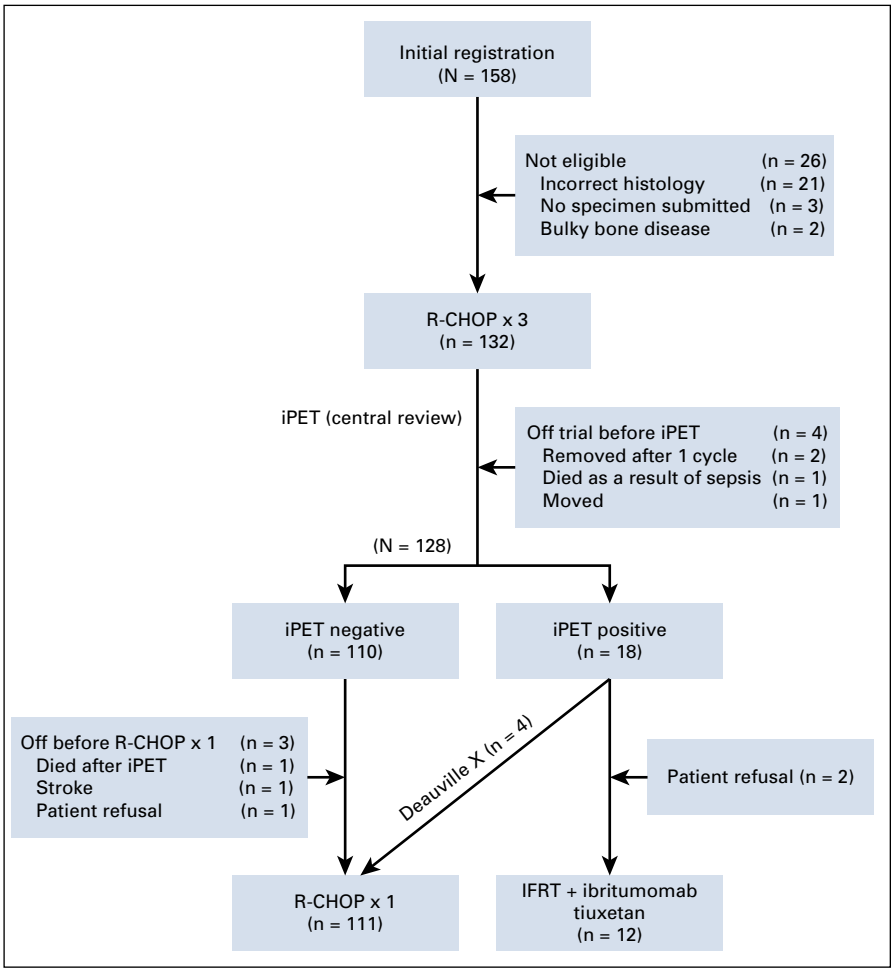

FIG 1. CONSORT diagram. IFRT, involved field radiation therapy; iPET, interim positron emission tomography/computed tomography scan; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

TABLE 1. Patient Characteristics

Characteristic	S1001 (N = 132)
Age, years, median (range)	62 (18-86)
Age > 60 years	71 (54)
Male	70 (53)
WHO performance status	
0	89 (67)
1	39 (30)
2	4 (3)
Stage I (rest stage II)	82 (62)
Elevated LDH	19 (14)
Systemic (B) symptoms	23 (17)
Largest diameter, cm, median (range; n = 121)	3.5 (1.0-9.7)
Head and neck–only involvement	87 (66)
Extranodal involvement	57 (43)
Stage-modified IPI risk factors	
0	35 (27)
1	55 (42)
2	37 (28)
3	5 (4)
Histologic subtype	
Diffuse large B-cell lymphoma, NOS	95 (72)
High-grade B-cell lymphoma with *MYC* and *BCL2* or/and *BCL6* rearrangements	4 (3)
High-grade B-cell lymphoma, NOS	22 (17)
T cell/histiocyte-rich large B-cell lymphoma	2 (2)
Central pathologic review not performed	9 (7)
Cell of origin by Lymph2Cx	
GCB	59 of 87 (68)
ABC	20 of 87 (23)
Unclassifiable	8 of 87 (9)
Double protein expressors	
DPE	21 of 123 (17)
Non-DPE	97 of 123 (79)
Indeterminate	5 of 123 (4)
FISH	
BCL2 positive (n = 43)	4 of 43 (9)
BCL6 positive (n = 38)	8 of 38 (21)
MYC positive (n = 77)	7 of 77 (9)
MYC/*BCL2* double hit (n = 42)	2 of 42 (5)
MYC/*BCL6* double hit (n = 38)	2 of 38 (5)

NOTE. Data are presented as No. (%) or No. of Total (%) unless otherwise specified.

Abbreviations: ABC, activated B-cell; DPE, double protein expressor; FISH, fluorescence in situ hybridization; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified.

17% had HGBL, NOS; and 3% had HGBL with *MYC* and *BCL2* or/and *BCL6* rearrangements ("double-hit" lymphoma [DHL] or "triple-hit" lymphoma). COO by Lymph2Cx was assessable in 87 patients; 68% had germinal center B-cell (GCB), 23% had activated B-cell (ABC), and 9% had unclassifiable. DPE was present in 16%. None of the patients with DHL (2 with *MYC*/*BCL2* and 2 with *MYC*/*BCL6* rearrangements) had dual protein overexpression.

Treatment

Of the 132 eligible patients, 128 had central review of their interim PET scan, of which 110 were iPET negative (Fig 1). Only 18 were iPET positive, 4 because of infection (Deauville X), which were treated as iPET negative with 1 additional cycle of R-CHOP. Of 14 patients (11%) with truly positive iPET, 2 refused radiation and 12 received IFRT followed by ibritumomab tiuxetan. Eight of the 12 patients (67%) converted from partial response (PR) to complete response (CR) after IFRT plus ibritumomab tiuxetan, and 4 (33%) had PR. Overall, CR was 92%, PR was 4%, and stable disease (SD) was 1% (with 4 [3%] unevaluable, 3 because the patient was coming off treatment before assessment and 1 because the patient had inadequate measurements on follow-up).

Median time from the date of diagnosis to the date of treatment initiation (the diagnosis-to-treatment interval)[22] was 31 days, similar to the 32 days reported in the FLYER trial in limited-stage DLBCL.[23] Ninety-eight percent of patients completed R-CHOP as planned. Two iPET-negative patients did not receive a subsequent cycle of R-CHOP (1 patient refused and 1 patient had a stroke). Radiation was initiated at a median of 30 days after R-CHOP (range, 23-44 days). There were no major radiation administration deviations or known ibritumomab tiuxetan deviations.

Safety

Adverse events are summarized in Table 2. Among the 132 patients, 1 patient died as a result of sepsis and 1 as a result of hypoxia. Thirteen patients (10%) had febrile neutropenia, 57 (31%) had grade 3-4 neutropenia, 10 (8%) had grade 3 anemia, 10 (8%) had grade 3-4 thrombocytopenia, 2 (2%) had grade 3 lung infection, 3 (2%) had grade 3 urinary tract infection, and 2 (2%) had grade 3 peripheral neuropathy. Of the 12 patients who received IFRT followed by ibritumomab tiuxetan, 2 had grade 3-4 neutropenia, 3 had grade 3-4 thrombocytopenia, and 2 experienced radiation dermatitis.[24]

Outcomes

With a median follow-up of 4.92 years (range, 1.1 to 7.7 years), only 6 patients have progressed and 3 have died as a result of lymphoma. Of the 6 patients who progressed, 4 were iPET negative and received R-CHOP × 4, 1 was iPET positive but declined radiation, and 1 went off treatment after 1 cycle of R-CHOP because of treatment delay. One of

the 6 patients progressed in CNS. There was no primary refractory disease. The median time to progression was 1.1 years (range, 0.2-6.2 years), with a continuous pattern of relapse. Of the 3 patients who had progression but remained alive, 1 had excision, 1 was retreated with R-CHOP, and in 1, the details of additional treatment were unknown. Eleven patients have died as a result of non-lymphoma causes, including 1 patient as a result of acute myeloid leukemia (AML) (in the iPET-negative arm) and 1 as a result of lung adenocarcinoma diagnosed on iPET (all deaths are listed in Appendix Table A1, online only). The median age of patients who died as a result of non-lymphoma causes was 80 years (range, 56-86 years). All 4 patients with DHL had a negative iPET and maintain remission.

The 5-year PFS estimate is 87% (95% CI, 79% to 92%), and the OS estimate is 89% (95% CI, 82% to 94%; Figs 2A and 2B). iPET-positive and iPET-negative patients had similar outcomes, with PFS of 86% versus 89% and OS of 85% versus 91%, respectively, as shown by the landmark analysis from the time of iPET (Fig 3). Three of 30 patients with Deauville 3 iPET relapsed, compared with 1 in 80 with Deauville 1-2, but the difference was not statistically significant. Although histology (DLBCL *v* HGBL, NOS) did not predict outcomes, COO, DPE, and smIPI were prognostic of PFS and OS. Five-year PFS by smIPI was 97% for smIPI of 0, 86% for smIPI of 1-2, and 30% for smIPI of 3. GCB had a 5-year PFS of 95% versus 72% for ABC and 49% for unclassifiable. DPE patients had a 5-year PFS of 70% versus 89% for non-DPE patients. However, COO, DPE, and smIPI are also known to correlate with more advanced age.[17,25] Using a Cox regression model adjusting for age, DPE retained statistical significance for OS ($P = .045$) but not for PFS (Table 3).

Considering that the majority of events in the study were driven by nonlymphoma deaths, competing risk modeling was performed in an exploratory analysis. The model showed that the 5-year cumulative incidence of lymphoma progression, with death as a result of other causes as a competing risk, was 4.5% (95% CI, 1.6% to 9.9%), whereas the 5-year cumulative incidence of progression or death as a result of other causes was 12.8% (95% CI, 7.4% to 19.8%).

Because of a high proportion of exclusive head and neck involvement, the sites of presentation from the prior SWOG study S0313 were reviewed and showed that 29 of 43 patients with DLBCL (67%) had head and neck–only involvement, confirming this finding. Patients with head and neck–only involvement had a lower probability of elevated LDH (9% *v* 24%, $P = .034$) and of B symptoms (10% *v* 31%, $P = .007$) than did other patients. In addition, the median diameter of the largest lymph node was smaller in such patients: 3 cm versus 5.2 cm in others ($P = .0002$). Neither head and neck–only presentation nor extranodal involvement predicted outcome.

TABLE 2. Adverse Events, in Order of Decreasing Frequency of Any Grade, up to 15% (n = 132)

	Any Grade		Grades 3 or 4	
Adverse Event	**No.**	**%**	**No.**	**%**
By individual toxicity type				
Fatigue	97	73	3	2
Anemia	73	55	10	8
Lymphocyte count decreased	67	51	23	17
Nausea	64	48	1	1
WBC decreased	62	47	36	27
Neutrophil count decreased	57	43	41	31
Febrile neutropenia	14	10	14	10
Alopecia	52	39	0	0
Constipation	49	37	0	0
Peripheral sensory neuropathy	41	31	2	2
Platelet count decreased	36	27	10	8
Oral mucositis	22	17	0	0
Insomnia	20	15	0	0
By toxicity category				
GI	108	82	3	2
Hematologic	101	77	55	42
Nervous system	71	54	4	3
Skin and subcutaneous tissue	66	50	0	0
Metabolism and nutrition	49	37	9	7
Musculoskeletal and connective	41	31	2	2
Infections	38	29	8	6
Respiratory	33	25	4	3
Psychiatric	27	20	0	0

NOTE. There were 2 grade 5 events: 1 sepsis and 1 hypoxia.

DISCUSSION

To our knowledge, NCTN S1001 is the largest prospective study in the United States of limited-stage DLBCL in the rituximab era, with the best NCTN results reported in this disease subset. Patients who were iPET negative after 3 cycles of R-CHOP (89%) received 1 additional cycle of R-CHOP, whereas patients who were iPET positive (11%) received IFRT followed by ibritumomab tiuxetan, with similarly excellent long-term outcomes. With a median follow-up of almost 5 years, only 6 patients in total have experienced disease progression, and only 3 have died as a result of lymphoma.

Our results are similar to those reported by a BC Cancer retrospective experience of PET-adapted therapy.[12] S1001 had a lower rate of iPET positivity (11% *v* 18%) than that reported by BC Cancer, likely because of Deauville 3 being classified as iPET negative rather than positive in S1001, without showing any higher risk of relapse in patients

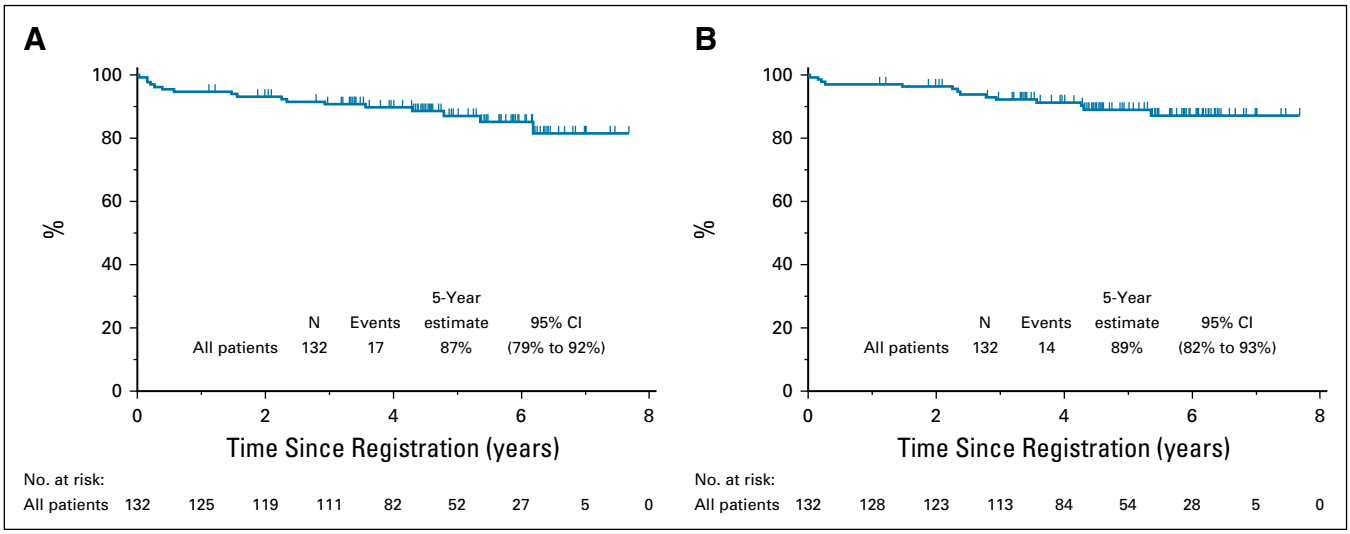

FIG 2. (A) Progression-free survival and (B) overall survival estimates.

with Deauville 3 iPET (3 out of 30). There are other trials prospectively investigating PET-directed therapy in DLBCL, including OPTIMAL > 60 (ClinicalTrials.gov identifier: NCT01478542) and LNH 2009-1B (ClinicalTrials.gov identifier: NCT01285765). Our data demonstrate the feasibility of real-time PET analysis and support the timing of scans at between days 15 and 18 of the third cycle of R-CHOP.

Several large European rituximab-based studies in limited-stage DLBCL have focused on patients with more favorable risk than those treated in S1001. The MabThera International Trial defined a cohort of 101 patients with favorable outcome to 6 cycles of R-CHOP or R-CHOP with etoposide (R-CHOEP) × 6 with radiation to bulky disease; with a median age of 47 years (all < 60 years), IPI of 0, and disease bulk < 7.5 cm, this group had a 6-year PFS rate of 90% and OS of 95%.[26] The FLYER trial randomly assigned patients with a median age 48 years, age-adjusted IPI (aaIPI) of 0, and bulk < 7.5 cm to 6 cycles of R-CHOP or 4 cycles of R-CHOP plus 2 additional rituximab doses, and showed similar PFS (3-year, 94% *v* 96%) and OS (98% *v* 99%),[23] establishing the role of R-CHOP × 4 without radiation for these younger, favorable-risk patients. LYSA/GOELAMS 02-03 randomly assigned patients who achieved CR after 4 cycles of R-CHOP administered every 14 days, with smIPI of 0 and bulk < 7 cm, to observation (n = 76) or to 40 Gy of IFRT (n = 82).[27] Including those patients with an smIPI of 1 who received an additional 2 cycles of R-CHOP before RT resulted in a 5-year event-free survival (EFS) of 89% versus 92% and a 5-year OS of 92% versus 96%.

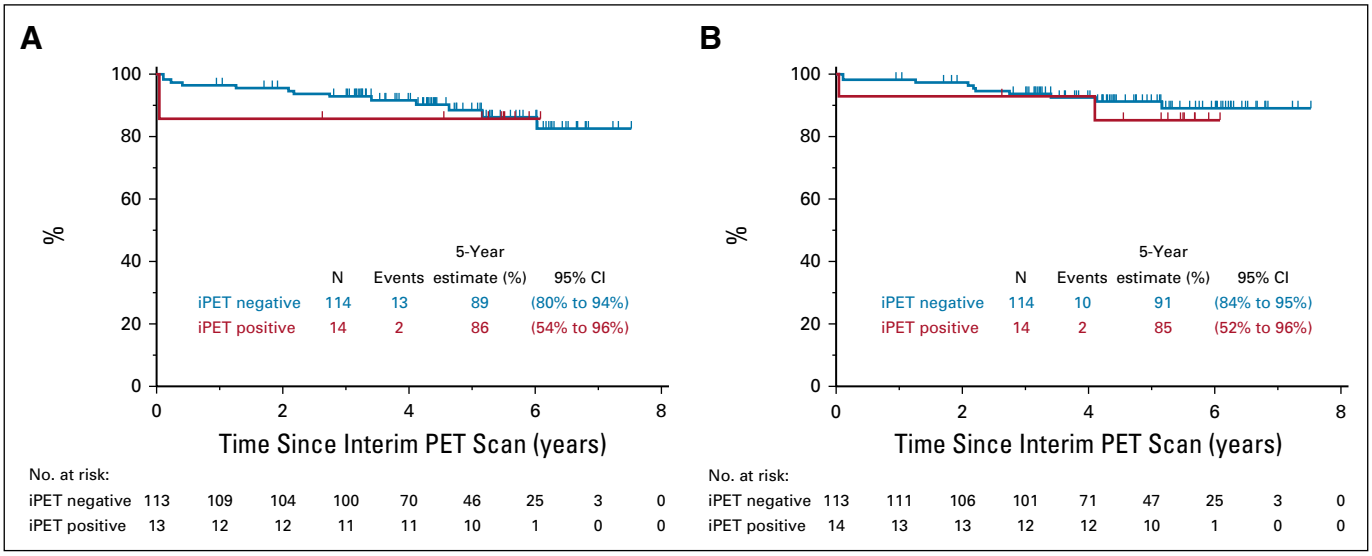

FIG 3. Landmark analysis at interim positron emission tomography (iPET)/computed tomography scan. (A) Progression-free survival. (B) Overall survival.

TABLE 3. Cox Regression Analysis for Prognostic Factors, With and Without Adjustment for Age

	Progression-Free Survival				Overall Survival			
	Univariate		Multivariate Adjusting for Age		Univariate		Multivariate Adjusting for Age	
Covariate	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Stage-modified IPI (n = 132)								
0	Reference		—		—		—	
> 0	5.9 (0.8 to 44.3)	.09	—		4.7 (0.6 to 35.7)	.14	—	
Histology subtype (n = 123)								
DLBCL	Reference		—		—		—	
Other[a]	0.6 (0.2 to 2.2)	.46	0.6 (0.2 to 2.1)	.44	0.9 (0.2 to 3.2)	.84	0.8 (0.2 to 3.1)	.80
COO by Lymph2Cx (n = 87)								
GCB	Reference		—		—		—	
ABC	4.4 (1.2 to 16.5)	.03	3.0 (0.8 to 11.4)	.12	5.4 (1.3 to 22.4)	.02	4.1 (.96 to 17.4)	.058
Unclassifiable	5.4 (1.2 to 24.3)	.03	3.7 (0.8 to 17.2)	.09	4.6 (0.8 to 27.8)	.09	3.4 (0.6 to 20.6)	.18
DPE (n = 118)								
Non-DPE	Reference		—		—		—	
DPE	2.6 (.95 to 7.02)	.06	2.0 (0.7 to 5.5)	.17	3.5 (1.2 to 10.2)	.02	3.0 (1.0 to 8.6)	.0454

Abbreviations: ABC, activated B-cell; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; DPE, double protein expressor; GCB, germinal center B-cell; HR, hazard ratio; IPI, international prognostic index.

[a]Other histology subtype includes high-grade B-cell lymphoma (22), high-grade B-cell lymphoma, with *MYC* and *BCL2* or/and *BCL6* translocations (4), and T-cell/histiocyte-rich large B-cell lymphoma (2).

In comparison with the patients in these trials, patients in S1001 were considerably older, with a median age of 62 years; 73% had an elevated smIPI, with 14% having elevated LDH and 17% having systemic symptoms, making our results applicable to all patients with limited-stage DLBCL, as opposed to the younger and more favorable–risk patients in the European studies. Given our relatively long follow-up, we observed several nonlymphoma deaths, particularly in older patients. Indeed, our observed 5-year PFS rate of 87% did not meet our original goal of 93%, primarily because of the competing risk of death as a result of nonlymphoma causes (12.8% at 5 years) occurring in patients at a median age of 80 years. Considering these competing risks of death in an older population over a prolonged time period, we feel that the traditional end point of PFS does not adequately reflect the observed treatment effects, which was supported by our competing risk modeling.

Remarkably, no patient in S1001 who received RT has relapsed to date, despite having positive iPET. We used a relatively high radiation dose (36 Gy plus a 9 Gy boost *v* 30-35 Gy in other studies) and a larger radiation field (IFRT *v* involved-site RT) for these patients, which is no longer standard. In addition, ibritumomab tiuxetan is not approved in DLBCL. However, ibritumomab tiuxetan could have eliminated residual disease through the crossfire of radioisotope.[28] Given the small number of patients who required radiation in our study, additional studies are needed to confirm this favorable outcome in patients who had a positive iPET and to better understand the degree to which radiation and radioimmunotherapy contributed to favorable outcomes.

As part of S1001, we demonstrated a distinct biology of limited-stage DLBCL, such as a predominance of GCB origin (68%) as defined rigorously by Lymph2Cx, confirming retrospective evidence using immunohistochemistry surrogates for GCB.[29,30] Similarly, DHL, which carries an unfavorable prognosis in advanced-stage DLBCL, did not portend a worse outcome in S1001, similar to the findings of previously published retrospective studies.[29,31,32] Although double-protein expression predicted worse OS in Cox regression analysis, the importance of this finding with so few lymphoma-related events must also be interpreted with caution. HGBL, NOS, was present in 17% of S1001 patients and was not prognostic. Only 1 of 6 patients progressed in CNS, despite prohibition of CNS prophylaxis, demonstrating that limited-stage DLBCL does not routinely require CNS prophylaxis, with the exception of testicular DLBCL, which was excluded from the study.

Head and neck involvement at such a high proportion (66%) has not been reported previously in studies of patients with limited-stage DLBCL, although this definition includes both nodal and extranodal disease. This finding was confirmed on review of S0313 (67%; unpublished data). Head and neck–only presentation had more favorable features, such as a lower rate of elevated LDH and B symptoms, and having a smaller median

diameter of the largest lymph node could suggest that its presentation at a palpable location resulted in earlier detection.

In summary, S1001 showed excellent outcomes in patients with limited-stage DLBCL, including older patients and those with moderate disease bulk. Together with the FLYER results in younger, more favorable risk–patients, the findings of our study have established that R-CHOP × 4 is a new standard, less morbid approach in limited-stage DLBCL for the absolute majority of patients, reserving radiation for the small subset of patients with interim PET-positive disease. The results were also favorable in subgroups defined by age, smIPI, cell of origin, and histology and were marginally unfavorable for DPE.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

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APPENDIX

TABLE A1. Details of Progression or/and Death

Progression	Status	Cause
No	Dead	AML
No	Dead	Developed orthodeoxia and died as a result of pneumonia while receiving treatment, family history of respiratory illnesses
No	Dead	Cause of death unknown
No	Dead	Cause of death unknown but was in CR last visit
No	Dead	Cause of death unknown but had Parkinson disease and was in assisted living
No	Dead	Cause of death unknown, learned from obituary
No	Dead	Died as a result of sepsis after cycle 1 of R-CHOP
No	Dead	Cause of death unknown, learned from obituary
No	Dead	Died the day of interim PET (negative) scan in his sleep
No	Dead	Treating physician took off trial after step 1 because of inadequate response (PR, Deauville 4), received R-ICE, found dead at home, suspect sepsis
No	Dead	Diagnosed with lung adenocarcinoma after step 1 PET (DLBCL in CR), died as a result of lung cancer; in retrospect, had lung cancer same time as DLBCL
Yes	Alive	Relapse in right thyroid gland, on final PET, excised, no additional treatment
Yes	Alive	Biopsy-proven progression in brain parenchyma, subsequent treatment not known
Yes	Alive	Relapse in same location, late, R-CHOP with plan for RT
Yes	Dead	Declined step 2, progressed in the stomach, received BR in June 2016, died in December 2018
Yes	Dead	Off trial after 1 cycle of R-CHOP because of delay; got cycle 2 6 weeks later, then 45 Gy RT, relapsed 14 months later, R-CHOP × 6 + BEAM/ASCT, relapsed 6 months later, lenalidomide for 2 weeks, died
Yes	Dead	Relapse in same location, RT, R-ICE × 4; second relapse in left temporalis muscle (outside radiation field), then renal/pulmonary/hilar metastases, RT to chest, R-Gem-Ox, died

Abbreviations: AML, acute myeloid leukemia; BEAM/ASCT, carmustine, etoposide, cytarabine, and melphalan/autologous stem cell transplantation; BR, bendamustine, rituximab; CR, complete response; DLBCL, diffuse large B-cell lymphoma; PET, positron emission tomography; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-Gem-Ox, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; RT, radiation therapy.