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[18F] Positron emission tomography response after rituximab-containing induction therapy in follicular lymphoma is an independent predictor of survival after adjustment for FLIPI in academic and community-based practice

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Abstract

Positron emission tomography (PET) after induction therapy in follicular lymphoma (FL) is predictive of survival in clinical trials. We describe use of PET and computed tomography (CT) after rituximab-based induction therapy in FL patients followed by the National LymphoCare Study, and explore the association between imaging response assessment and survival. Among 1289 patients, imaging consisted of: PET±CT (35%), CT alone (42%), other/no imaging (24%). Median follow-up was 7.6 years. In unadjusted analyses, positive PET±CT and CT were prognostic of inferior OS (HR 1.78; 95% CI: 1.16–2.72 and HR 1.61, 95% CI: 1.13–2.29, respectively) and PFS (HR 1.63, 95% CI: 1.21–2.20 and HR 1.45, 95% CI: 1.12–1.89, respectively). Adjusting for FL International Prognostic Index, PET remained predictive of OS (HR 1.54, 95% CI: 1.01–2.36) and PFS (HR 1.54, 95% CI: 1.14–2.07). Residual disease via PET in FL is prognostic of survival in clinical practice.

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DECLARATIONS OF INTERESTS

M.B. and K.L.D. are employees of Genentech Inc. and hold stock options with F. Hoffmann-La Roche Ltd/Genentech Inc. X.Z. is an employee of RTI Health Solutions, which has a contract with Genentech Inc. C.R.F. has performed consulting/advisory roles with Algeta, OptumRx, Biogen Idec, Genentech BioOncology, Roche, and Celgene, and has received research funding from Abbott, Celgene, Millennium/Takeda, Spectrum, Gilead and Janssen/Pharmacyclics. A.D.Z. has performed consulting/advisory roles for Genentech, Celgene, Gilead, Amgen, Hospira, and Reddy Laboratories, and has received research funding from Genentech/Roche, Gilead, and BMS. I.W-S., E.R. and J.W.F. have declared no conflicts of interest.

Keywords

Follicular lymphoma; PET; survival; prognostic

INTRODUCTION

Follicular lymphoma (FL) is a common, indolent lymphoma with a wide range of clinical behaviors [1,2]. General characteristics of FL include multiple relapses and risk of transformation to aggressive high-grade lymphoma [2]. FL patients often undergo imaging studies during watchful waiting, treatment, and after treatment conclusion.

The high sensitivity of [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) in FL is well recognized [3,4], and residual FDG-avidity at the end of front-line chemoimmunotherapy for FL may portend poorer progression-free survival (PFS) [3–8], and most recently, overall survival (OS) [9,10] in patients on clinical trials. Utilizing data from patients on clinical trials, retrospective studies comparing PET to computed tomography (CT) scans have also shown that PET-assessed response may be better in predicting PFS and OS than conventional imaging response by CT scans alone [6,9]. Recent Lugano Classification formally included PET in assessments of FDG-avid non-Hodgkin lymphoma (NHL) such as FL [11]. The Lugano Classification proposed using PET response for end-of-treatment assessment, reserving CT-based response in low or variable FDG-avid lymphomas [12]. By providing standardization for PET imaging response, the revised Lugano Classification aimed to provide recommendations that could lead to improved therapies for NHL.

The prospective, observational National LymphoCare Study (NLCS) database, in which more than 2700 newly diagnosed FL patients from over 200 practice sites in the US were monitored for presentation, prognosis, treatment, and clinical outcomes from 2004–2007, is a distinctive opportunity to evaluate the use of imaging in FL in clinical practice. This study first describes imaging patterns and clinical use of PET and CT after first-line rituximab (R)-based induction therapy, and then examines and compares the prognostic impact of end-of-induction (EOI) imaging choice and response assessments on PFS and OS in clinical practice.

PATIENTS AND METHODS

Study Design, Patients, and Assessment Imaging

This retrospective cohort study was determined by an analysis of prospectively collected data from the NLCS. Full details of the NLCS study design have been published elsewhere [13]. The NLCS is an observational study that includes 2740 newly diagnosed FL patients enrolled between March 2004 and March 2007 at participating sites. There was no central pathology review; the local pathology report defined FL diagnosis after investigator education on World Health Organization definitions of FL. Given that this was an observational study, there was no central imaging review; stage and response were determined and reported by the treating physician(s). Since the data were collected before

the Lugano Classification (Deauville criteria), PET response was reported as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CT response was reported as CR, CR unconfirmed (CRu), PR, SD, and PD. Treatment and outcomes (including response, time to progression, and survival) were collected quarterly. Follow-up data were actively solicited from providers at the time of clinical follow-up. Enrolled patients were followed for 10 years from enrollment or until death, withdrawal of consent, or loss to follow-up. Staging procedures (including bone marrow biopsy, diagnostic CT, and/or PET with or without CT scans), were recorded in the database. For this study, we included patients in the NLCS who completed R-based induction therapy and who met all of the following criteria: evaluable; stage II–IV [14]; FL without large-cell histology at diagnosis; received initial therapy (as assigned by the physician) with R-monotherapy or R-chemotherapy, including R-CHOP (rituximab plus cyclophosphamide, vincristine, and prednisone), R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone), rituximab plus fludarabine, and R-other chemotherapy; completed planned (not terminated early, as reported by clinical sites) therapy; reported treatment end date (last dose date). Patients were checked for EOI assessments, specified in this study as imaging performed between two cycles before and 12 weeks after completion of first-line treatment. Assessments included PET, CT, other response evaluations (physical exam, lab exam, bone marrow biopsy, and/or imaging other than PET or CT), and no evaluation. All imaging was done at the physician's discretion. PET and CT scans were done per protocol at individual institutions. Each patient was classified into one of five groups determined by the method used to make assessments at completion of the first-line treatment: PET alone, CT alone, PET with CT, other image evaluation, and no image evaluation. Given imaging was done at the provider's discretion, and multiple images could be ordered and reported, patients were classified as PET with CT if the PET and CT scans were done on the same day, or within 28 days of each other; responses were classified as the best response via PET during the assessment period. Similarly, for PET (or CT) alone, responses were classified as the best response via PET (or CT) during the assessment period. To examine EOI PET as a predictor of outcome, patients who received a PET with CT or PET alone were combined for analysis and labeled as "PET±CT." For the purposes of this article, a "negative PET (or CT)" result indicates the assessed response was CR /CRu (if CT) and a "positive PET (or CT)" result indicates the assessed response was PR, SD, and PD.

NLCS data management and analysis are guided by an advisory board comprising academic investigators and a patient advocate, some of whom co-authored this article (C.R.F., J.W.F., and A.D.Z.). The advisory board participated in all study phases, including initial protocol design, prospective determination of data for collection, and consideration of participating sites. The advisory board collaborated with the primary author (I.W-S.) and sponsor regarding data interpretation and publication. This article was written *de novo* by the primary author (I.W-S.) and members of the advisory board following approval of a protocol with prespecified endpoints, hypotheses, and plans for analysis.

Statistics

Baseline patient demographics and disease features, center, type, geographic region, therapy regimen, and duration were summarized by imaging group. Between imaging groups, the

overall and pairwise comparisons were examined using the Pearson χ^2 test. Logistic regression was then used to identify factors related to imaging choice, with covariates included through a backwards selection ($p > 0.10$).

Descriptive statistics of OS and PFS (calculated from the date of EOI response) were estimated using Kaplan Meier methods. Cox regression models including positive-negative response status, assessment method, and their two-way interaction were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) with and without propensity score (PS) matching; additional models also adjusted for the Follicular Lymphoma International Prognostic Index (FLIPI) risk groups. To adjust for potential baseline characteristic imbalances, patients were scored and then matched based on their propensity of being assigned to an imaging modality. Cox proportional hazards models with PS matching were used to compare the impact of PET±CT response with CT response on OS/PFS. All available variables potentially related to outcome or imaging selection (i.e. age group, sex, race, histology grade, stage, lactate dehydrogenase, hemoglobin, nodal sites, extra-nodal sites, Eastern Cooperative Oncology Group performance status, B symptoms, bone marrow involvement, geographic region, center type, and induction treatment) were included in the calculation of the PS.

RESULTS

Characteristics of Patients and EOI Assessment Choice

A total of 1289 stage II-IV subjects completed induction R-monotherapy or R-chemotherapy. Among those who completed induction therapy, 447 (35%) had PET±CT, 537 (42%) had CT alone, 10 (1%) had imaging other than PET or CT, and 295 (23%) had no EOI imaging (Supplementary Figure 1).

Factors Associated with EOI Assessment Choice

EOI assessment by either PET±CT was performed on average 183 days after diagnosis, and 25 days after the end of therapy. CT alone was obtained on average 169 days after diagnosis, and 26 days after the end of therapy. Imaging via PET or CT scans was more common in patients: aged less than 70 years; with at least five nodal sites; at academic sites; who had received R-chemotherapy; or who had therapy for at least 85 days; it was less common in the West ($p < 0.01$, Supplementary Table I). Nearly half of the patients who did not receive imaging via PET or CT were treated for less than 85 days. In a generalized logits model evaluating the association of baseline factors and the choice of assessment method (PET alone, CT alone, PET and CT, or no imaging), region, center type, duration, choice of induction therapy, and histologic grade were associated with whether imaging was performed and which type of imaging was obtained ($p < 0.10$).

The baseline characteristics of evaluable patients who received imaging via PET±CT and CT alone and the percentages of patients receiving PET±CT compared with CT alone are presented in Table I. From the logistic regression analysis of those who received PET or CT imaging, grade 3 histology and R-CHOP induction were associated with greater likelihood of receiving PET±CT vs. CT alone, while the Midwest region was less likely to receive PET

($p < 0.05$). In view of the marked differences among patients who received a PET±CT or CT alone, PS matching was used to remove potential bias in the comparison of imaging methodologies. A total of 361 pairs were matched using PS for comparative evaluation of OS and PFS. Table I provides the demographics and clinical factors for the PS-matched population.

EOI Response

Of 447 patients who received PET±CT scans performed at EOI, 292 (65%) were reported as negative and 155 as positive. Of 537 responses evaluated at EOI by CT scans alone, 211 (39%) were reported as negative and 326 as positive. Responses for the PS-matched population were similar to the non-matched population (Supplementary Table II).

Effect of Imaging Results on Survival

With a median follow-up of 7.6 years, the 5-year OS and PFS for PET-negative patients were 88% and 65%, respectively. PET-positive patients had a 5-year OS of 78% and PFS of 51%. The OS and PFS at 5 years for CT-negative patients were 87% and 64%, respectively. CT-positive patients had a 5-year OS of 78% and a PFS of 54% (Table II). Five-year OS and PFS within the PS-matched population were comparable to those in the non-matched population (Table II). Similar to the 5-year survival, PET-negativity also predicted 2-year PFS, 83% vs. 68% in the PET-positive patients (p-value 0.002). Among all evaluable patients, positive EOI PET±CT and positive EOI CT were both associated with inferior OS (HR 1.78, 95% CI: 1.16–2.72 and HR 1.61, 95% CI: 1.13–2.29, respectively) and PFS (HR 1.63, 95% CI: 1.21–2.20 and HR 1.45, 95% CI: 1.12–1.89, respectively) in unadjusted analysis (Table III). After adjustment for FLIPI scores, PET response remained associated with inferior OS (HR 1.54, 95% CI: 1.01–2.36) and PFS (HR 1.54, 95% CI: 1.14–2.07). However, after adjustment for FLIPI, CT responses were only associated with inferior PFS (HR 1.34, 95% CI: 1.03–1.75), but not OS (HR 1.38, 95% CI: 0.96–1.97; Table III).

In the PS-matched subset, there was not a statistically significant improvement with PET vs. CT in the association with OS or PFS (imaging assessment by response interaction p-values 0.77 and 0.65, respectively); Table III). Kaplan–Meier curves comparing the two imaging assessments are presented in Supplementary Figure 2.

Role of the Funding Source

This study was funded by Genentech Inc. (South San Francisco, CA, USA).

DISCUSSION

The NLCS registered more than 2700 patients with FL, and then prospectively followed the patients for more than a decade. This is the largest observational cohort in FL, and it allows for a unique chance to explore practice in a non-clinical trial setting, and explore whether practice in the “real world” leads to similar outcomes to those in clinical trials. This large, multicenter observational study supports PET response as a strong predictor of OS and PFS after R-induction therapy in FL. Importantly, PET response provided additional prognostic

information beyond the FLIPI score, the primary clinical tool employed in prognostication of FL.

Our results confirm those from previous studies demonstrating the ability of PET to predict survival after R-induction therapy for FL. In the one prospective study assessing the prognostic value of PET performed at the end of treatment, 121 patients with FL treated with first-line R-CHOP and two cycles of R, 2-year OS rate was 100% for PET-negative vs. 88% for PET-positive patients ($p = 0.0128$), and 2-year PFS rate was 87% for PET-negative vs. 51% for PET-positive patients ($p < 0.001$) [9]. Our larger study demonstrated even longer-term impact of post-induction PET-response status on survival: a negative PET portended a better 5-year OS (87% vs. 78%) and PFS (65% vs. 51%) compared with a positive PET. In the study by Trotman *et al.* which had a median follow-up of 54.6 months, the HR for OS for patients with a positive PET scan vs. a negative scan was 6.7 (2.4–18.5); this predictive power was independent of FLIPI and FLIPI-2, and stronger than conventional CT [10]. With a follow-up of 7.6 years in NLCS, our study showed that similarly, in clinical practice, PET response is associated with OS after accounting for FLIPI.

The PRIMA and GOELAMS trials both underwent secondary analyses where PET response remained highly predictive of outcomes in patients after assessment by 1999 International Standardized Response Criteria [5,6]; in contrast, CT response in PET-negative and PET-positive patients was not prognostically significant. In our study using PS-matching, though PET response had numerically greater association with outcome than did CT response, we were not able to show that PET response compared to CT response portended a superior survival. Because the NLCS was an observational study of FL treatment, practices, and outcomes, in which imaging were ordered per provider preference, most patients did not receive a concurrent PET and diagnostic CT scan; therefore, we were unable to directly compare PET and CT responses in individuals. With the intention of reducing known bias in this study, including choice of imaging, we applied PS-matching to compare those who received a PET versus CT. As a result, the findings from these two former studies differed from our finding due in part to this methodologic difference.

While the observational nature of our study has limitations, including bias associated with treatment decisions and imaging choices, no reported EOI imaging from almost a quarter of patients treated, and conclusions that cannot be accounted for in the analysis, our study reflects a much larger scope of academic and community clinical practices countrywide. This makes the findings of this study more broadly applicable to general oncology care. In the GOELAMS/GELA and LYSA/FIL analyses, PET scans were centrally reviewed and the results reported using the Deauville 5-point scale [9,10]. The lack of central review, absence of the Deauville criteria to assist providers in response assessments at the time of this study, and the number of PET scans done without a CT correlate could have accounted for the relatively increased PET-positive patients in this study, dampening this study's predictive power of PET. However, despite an absence of central review and the advantages of defined criteria for PET response at the time of the study, this study confirmed the benefit of PET imaging for PFS and OS based on local interpretation of the scan and outside of a clinical trial, reflecting general clinical practice in the "real world". In addition, the follow-up in this

study was also relatively long compared with other studies, a meaningful aspect of this study given FL is typically an indolent disease.

This is the only known study to examine FL imaging patterns after R-induction therapy. Our data demonstrated that, despite current recommendations, PET is commonly utilized with non-clinical factors, including duration, region, center type, therapy, and driving assessment choice. Whereas most previous studies included patients primarily treated with R-CHOP [5,6,9], NLCS incorporated all R-based induction treatment regimens commonly used in clinical practice. We established that PET's prognostic value is independent of FLIPI scores, which is most relevant given the FLIPI score is the primary prognostic tool used in upfront FL. Finally, disease progression within 2 years after diagnosis in chemoimmunotherapy-treated patients is predictive of poorer OS [15]. Our data showed that EOI-PET response was predictive of 2-year PFS (from time of EOI response assessment); therefore, PET response may be an acceptable surrogate for OS in FL. Although 2-year PFS as a predictor of OS has never been validated in R-monotherapy-treated patients, 12-month event-free survival was a predictor of OS in patients treated with R-monotherapy or R-chemotherapy [16]. Our conclusion mirrors the LYSA/FIL results, which demonstrated that PET-CT was predictive of OS in prospective studies [10]. Consequently our results not only confirmed the revised Lugano Classification's recommendation for PET imaging to assess response in FDG-avid lymphomas such as FL, but indicate that in clinical practice, PET response assessment should be the preferred mode of response assessment and performed in patients after induction treatment for FL.

In conclusion, this study showed that use of PET after completion of R-containing therapy for FL was prevalent but varied by center and region. Our data confirmed that PET provides important prognostic information after treatment initiation by highlighting the inferior OS in patients remaining PET positive after therapy, independent of FLIPI scores, supporting and confirming use of PET imaging at the end of R-induction therapy outside of a clinical trial, even in an indolent lymphoma like FL. Further study of EOI PET imaging in FL could facilitate major changes in FL treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table I

Demographics and characteristics of evaluable and propensity score-matched patients.

		Evaluable patients			Propensity score-matched patients		
Variable	**Statistics or category**	**PET±CT (*n* = 447)**	**CT alone (*n* = 537)**	***p*-value***	**PET±CT (*n* = 361)**	**CT alone (*n* = 361)**	***p*-value***
Age (years)	≤ 60	247 (50%)	250 (50%)	0.0478	186 (50%)	184 (50%)	0.8973
	61–70	108 (43%)	146 (57%)		92 (51%)	90 (49%)	
	71–80	70 (40%)	105 (60%)		63 (50%)	62 (50%)	
	> 80	22 (38%)	36 (62%)		20 (44%)	25 (56%)	
Gender	Female	241 (46%)	286 (54%)	0.8372	197 (51%)	186 (49%)	0.4121
	Male	206 (45%)	251 (55%)		164 (48%)	175 (52%)	
Race	White	404 (45%)	485 (55%)	0.7914	322 (50%)	322 (50%)	0.9048
	African American	19 (50%)	19 (50%)		18 (55%)	15 (45%)	
	Hispanic	17 (40%)	26 (60%)		14 (45%)	17 (55%)	
	Other	7 (50%)	7 (50%)		7 (50%)	7 (50%)	
Histology by grade	Follicular grade 1 or 2	277 (41%)	396 (59%)	< 0.0001	238 (50%)	241 (50%)	0.8911
	Follicular grade 3	122 (59%)	85 (41%)		81 (50%)	80 (50%)	
	Missing	48	56		42	40	
FLIPI risk group	Good (0–1)	81 (42%)	113 (58%)	0.3111	66 (49%)	68 (51%)	0.8911
	Intermediate (2)	138 (49%)	145 (51%)		110 (53%)	96 (47%)	
	Poor (3–5)	161 (45%)	196 (55%)		130 (49%)	137 (51%)	
	Missing	67	83		55	60	
Stage	Stage II	69 (43%)	92 (57%)	0.4740	55 (51%)	52 (49%)	0.7533
	Stage III or IV	378 (46%)	445 (54%)		306 (50%)	309 (50%)	
LDH	Normal	258 (44%)	329 (56%)	0.0951	214 (51.0%)	206 (49%)	0.4906
	> ULN	102 (51%)	99 (49%)		72 (48%)	79 (52%)	
	Missing	87	109		75	76	
Hemoglobin	< 12 g/dL	110 (47%)	125 (53%)	0.6453	87 (48%)	94 (52%)	0.5152
	≥ 12 g/dL	321 (45%)	391 (55%)		260 (51%)	251 (49%)	
	Missing	16	21		14	16	
Nodal sites	< 5	224 (42%)	305 (58%)	0.0338	189 (50%)	190 (50%)	0.9399

Leuk Lymphoma. Author manuscript; available in PMC 2018 April 01.

		Evaluable patients			Propensity score-matched patients		
Variable	**Statistics or category**	**PET±CT (*n* = 447)**	**CT alone (*n* = 537)**	***p*-value***	**PET±CT (*n* = 361)**	**CT alone (*n* = 361)**	***p*-value***
	≥ 5	213 (49%)	220 (51%)		165 (50%)	164 (50%)	
	Missing	16	21		7	7	
Extranodal sites	None	169 (46%)	195 (54%)	0.2694	131 (49%)	136 (51%)	0.8645
	1	114 (42%)	201 (58%)		130 (51%)	123 (49%)	
	≥ 2	123 (48%)	134 (53%)		95 (50%)	96 (50%)	
	Missing	11	7		5	6	
ECOG	0: 100–90	214 (50%)	216 (50%)	0.2946	159 (50%)	158 (50%)	0.7092
	1: 80–70	106 (46%)	126 (54%)		84 (47%)	93 (53%)	
	≥ 2: 60–10	15 (38%)	24 (62%)		14 (44%)	18 (56%)	
	Missing	112	171		104	92	
B symptoms	Yes	145 (47%)	166 (53%)	0.6082	115 (49%)	120 (51%)	0.6913
	No	302 (45%)	371 (55%)		246 (51%)	241 (49%)	
Bone marrow involvement	Yes	166 (46%)	197 (54%)	0.3773	135 (51%)	132 (49%)	0.7451
	No	201 (49%)	210 (51%)		156 (49%)	161 (51%)	
	Missing	80	130		70	68	
Geographic region	Midwest	112 (36%)	202 (64%)	< 0.0001	103 (50%)	101 (50%)	0.9924
	Northeast	60 (49%)	63 (51%)		49 (50%)	49 (50%)	
	Southeast	166 (46%)	193 (54%)		141 (49%)	145 (51%)	
	Southwest	53 (67%)	26 (33%)		28 (53%)	25 (47%)	
	West	56 (51%)	53 (49%)		40 (49%)	41 (51%)	
Center type	Academic	72 (39%)	113 (61%)	0.0485	68 (49%)	70 (51%)	0.8499
	Community	375 (47%)	424 (53%)		293 (50%)	291 (50%)	
Induction treatment	R-monotherapy	49 (31%)	111 (69%)	< 0.0001	46 (49%)	48 (51%)	0.8249
	R-chemotherapy	398 (48%)	426 (52%)		315 (50%)	313 (50%)	
	R-CHOP	232 (54%)	201 (46%)	0.0071	175 (51%)	166 (49%)	0.8713
	R-CVP	91 (45%)	109 (55%)		76 (49%)	80 (51%)	
	R-Flu	53 (41%)	77 (59%)		45 (47%)	50 (53%)	
	R-Other	22 (36%)	39 (64%)		19 (53%)	17 (47%)	
Duration of induction treatment	≤ 84 days	67 (34%)	133 (67%)	0.0006	58 (48%)	63 (52%)	0.6188

		Evaluable patients			Propensity score-matched patients		
Variable	**Statistics or category**	**PET±CT (*n* = 447)**	**CT alone (*n* = 537)**	***p*-value***	**PET±CT (*n* = 361)**	**CT alone (*n* = 361)**	***p*-value***
	85–126 days	226 (48%)	248 (52%)		181 (49%)	188 (51%)	
	> 126 days	154 (50%)	156 (50%)		122 (53%)	110 (47%)	

[a]Pearson chi-squared test.

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; PET, positron emission tomography; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisone; R-Flu, rituximab plus fludarabine; R-Other, rituximab plus other chemotherapy; ULN, upper limit of normal.

Table II

Five-year survival for the whole cohort and propensity score-matched cohort.

	Evaluable patients		Propensity-score matched patients	
Imaging response	**OS (%)**	**PFS (%)**	**OS (%)**	**PFS (%)**
PET-negative	88	65	88	65
PET-positive	78	51	77	53
CT-negative	87	64	87	65
CT-positive	78	54	77	57

CT, computed tomography; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

Table III

Hazard ratios for survival via PET and CT response.

Comparison	Evaluable patients, unadjusted		Evaluable patients, FLIPI-adjusted		Propensity score-matched patients	
	OS HR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)	PFS HR (95% CI)
CT-negative	Ref	Ref	Ref	Ref	Ref	Ref
CT-positive	1.61 (1.13, 2.29)	1.45 (1.12, 1.89)	1.38 (0.96, 1.97)	1.34 (1.03, 1.75)	1.76 (1.15, 2.69)	1.32 (0.96, 1.82)
PET-negative	Ref	Ref	Ref	Ref	Ref	Ref
PET-positive	1.78 (1.16, 2.72)	1.63 (1.21, 2.20)	1.54 (1.01, 2.36)	1.54 (1.14, 2.07)	1.94 (1.22, 3.08)	1.48 (1.06, 2.07)
CT-negative					Ref	Ref
PET-negative	–	–	–	–	0.80 (0.49, 1.31)	0.99 (0.71, 1.38)
CT-positive	–	–	–	–	Ref	Ref
PET-positive					0.88 (0.58, 1.35)	1.10 (0.78, 1.55)

CI, confidence interval; CT, computed tomography; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; Ref, reference