European Journal of Cancer 126 (2020) 78–90

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Positron-emission tomography–based staging reduces the prognostic impact of early disease progression in patients with follicular lymphoma

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Received 29 August 2019; received in revised form 14 November 2019; accepted 2 December 2019

KEYWORDS
PET;
Follicular lymphoma;
Early progression;
PFS24;
R-CHOP

Abstract ***Background:*** Previous studies reported that early progression of disease (POD) after initial therapy predicted poor overall survival (OS) in patients with follicular lymphoma (FL). Here, we investigated whether pre-treatment imaging modality had an impact on prognostic significance of POD.
Methods: In this retrospective study, we identified 1088 patients with grade I–IIIA FL; of whom, 238 patients with stage II–IV disease were initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), and 346 patients were treated

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https://doi.org/10.1016/j.ejca.2019.12.006

with rituximab-based chemotherapy. Patients (N = 484) from the FOLL05 study served as an independent validation cohort. We risk-stratified patients based on pre-treatment radiographic imaging (positron-emission tomography [PET] versus computed tomography [CT]) and early POD status using event-defining and landmark analyses. A competing risk analysis evaluated the association between early POD and histologic transformation.

Results: In the discovery cohort, patients with POD within 24 months (PFS24) of initiating R-CHOP therapy had a 5-year OS of 57.6% for CT-staged patients compared with 70.6% for PET-staged patients. In the validation cohort, the 5-year OS for patients with early POD was 53.9% and 100% in CT- and PET-staged patients, respectively. The risk of histologic transformation in patients whose disease progressed within one year of initiating therapy was higher in CT-staged patients than in PET-staged patients (16.7% versus 6.3%, respectively), which was associated with a 9.7-fold higher risk of death.

Conclusion: In FL, pre-treatment PET staging reduced the prognostic impact of early POD compared with CT staging. Patients with early POD and no histologic transformation have an extended OS with standard therapy.

1. Introduction

FL is the second most common lymphoma in the United States, compromising approximately 30% of all lymphomas [1,2]. As treatment outcomes and OS continue to improve, surrogate end-points are increasingly needed to predict OS in prospective clinical trials.

Previous studies proposed early progression or an early event was the surrogate end-point predicting poor OS in patients with newly diagnosed FL. In one study, patients with FL whose disease progressed within 24 months from diagnosis (progression-free survival at 24 months [PFS24]) after treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) had a 5-year OS of 50%, compared with 90% for those without early POD [3]. In a different study, patients with an event within 12 months (event-free survival at 12 months) after treatment with immunochemotherapy also had a poor OS [4]. These two studies shared similar but distinct definitions of early POD. One study based the analysis on event-free survival, which included the start of new lymphoma therapy as an event, whereas the other study used progression-free survival; therefore, early POD lacks a common definition. Nonetheless, the studies identified patients with early POD as a subgroup of patients with FL with inferior outcomes and represented an area of unmet medical needs. These observations suggested utilisation of a new clinical end-point to evaluate new treatment strategies, possibly leading to rapid approval by regulatory agencies. Furthermore, these observations suggested more intensive treatment approaches, including salvage chemoimmunotherapy followed by consolidative autologous stem cell transplantation, may be needed to improve the treatment outcome [3,5,6].

However, the imaging modality used at diagnosis and before treatment initiation in the earlier studies was not described [3,4]. Whether the prognostic significance is maintained in the PET-based staging era is currently unknown. PET with 2-[^{18}F]-flouro-2-deoxyglucose integrated with CT (FDG-PET, hereafter referred to as PET) has emerged as an important imaging tool for staging, response assessment and predicting treatment outcomes of FL [7]. PET imaging is more sensitive than CT imaging in identifying extranodal disease and facilitates more accurate clinical staging or response assessment [8–11]. Furthermore, several studies highlight the ability of PET imaging to identify sites of suspected transformation for targeted biopsy, which may influence the choice of initial therapy and treatment outcome [12–15].

With this background, we examined the impact of PET staging on the treatment outcome and prognosis of FL. We also compared the prognostic significance of PFS24 after first-line therapy in patients with FL whose disease was assessed by CT or PET imaging modalities.

2. Methods

2.1. Study design

This is a retrospective study of adult patients (aged ≥18 years) diagnosed between the years of 1998 and 2009 with FL managed at Memorial Sloan Kettering Cancer Center (MSKCC). This time frame was selected to include patients who were treated in the rituximab era

and to allow adequate follow-up. The institutional review board approved this study.

2.2. Participants

Patients with FL grade IIIB, composite histology or *de novo* disease transformation at diagnosis, with fewer than 3 clinic visits (indicative of a consultative role without long-term follow-up) or harbouring an active concurrent malignancy were excluded. For the MSKCC cohort, pathology slides were confirmed at MSKCC. Radiographic modality used for staging was captured at both diagnosis and at the time of first treatment. Transformation to diffuse large B cell lymphoma (DLBCL) at the time of relapse was confirmed by biopsy. From a database of 1088 patients with FL (grade I, II and IIIA), we excluded 31 patients with histologic transformation to DLBCL before treatment; 164 patients were observed and did not require treatment. Eight hundred ninety-three patients were evaluable at first treatment; of which, 754 patients had stage II–IV disease (Fig. 1). We identified 346 patients with stage II–IV grade I–IIIA FL treated with rituximab and chemotherapy for analysis of the impact of PFS24 status on OS: 118 patients with pre-treatment CT and 228 patients with pre-treatment PET (Fig. 1). A subgroup of 238 patients with stage II–IV grade I–IIIA FL who were initially treated with R-CHOP chemotherapy were identified for separate analysis: 84 patients with pre-treatment CT and 154 patients with pre-treatment PET. An independent cohort of 484 patients with FL treated with rituximab-based chemotherapy regimens between 2006 and 2010 in the prospective FOLL05 clinical trial conducted by the Fondazione Italiana Linfomi was used for validation [16,17]. From the FOLL05 study, 161 patients with FL treated with R-CHOP were identified for replication: 114 patients with pre-treatment CT and 47 patients with pre-treatment PET.

2.3. Statistical analysis

PFS24 failures were defined as patients with disease progression within 24 months of treatment initiation (PFS24). PFS24 achievers were defined as patients without disease progression within 24 months of treatment initiation. We selected time of initiating therapy instead of time of diagnosis as our landmark because our population included patients who were initially managed with observation but who subsequently required therapy. Two methods were used independently to risk stratify patients based on early progression status. First, we conducted an event-defining analysis to directly compare with the methods previously followed by by Casulo et al. [3] and Maurer et al. [4]. Accordingly, OS for PFS24 failures was defined as the time from PFS24 failure to death or last follow-up. OS for the PFS24 achievers was defined as the survival time from achieving PFS24 (i.e. 24 months after treatment initiation) until death or last follow-up. Patients were excluded from this analysis if they died within 24 months without disease progression or were lost to follow-up within 24 months of first-line therapy. Second, we used a landmark analysis proposed by Anderson et al. [18] to compare the outcomes of the PFS24 failures and PFS24 achievers. Using a common time origin for both groups allows comparison of outcomes to be more clinically interpretable and eliminates immortal time bias that arises when an event such as relapse occurs during the time of follow-up [18]. OS in the landmark analysis was calculated from 24 months after treatment initiation to last follow-up or death. Patients were excluded from the landmark analysis if they died from any cause or were lost to follow-up within 24 months of starting first-line therapy. Kaplan–Meier methods were used to estimate survival probability.

To understand the association between early progression and transformation, we conducted a competing risk analysis for patients treated with rituximab-based chemotherapy (R-CHEMO), in which a patient can experience one of the two different events: transformation or death without transformation. The time origin was set at the time of progression or two years for patients who were progression-free for two years. The cause-specific event rates were estimated for three groups of patients: those who progress in the first year, those who progress in the second year or those who are progression-free in the first 2 years. The rate of death without transformation is compared with the survival rates from the risk-defining event to quantify the rates of death after transformation within the time interval of interest [19].

Continuous variables were summarised by medians and ranges. Categorical variables were summarised by frequencies and percentages. OS and PFS were estimated using the Kaplan–Meier method and compared using log-rank tests. All tests are two-sided. P values less than or equal to 0.05 were considered statistically significant. All statistical analyses were conducted using R3.5.0 [20].

3. Results

The median age of all 1088 patients was 57 years (range: 20–94). The median follow-up of the population was 8.3 years (range: 0.2–17.5), was 9.5 years (range: 0.3–17.5) for patients staged with CT and was 7.9 years (range: 0.2–17.2) for patients staged with PET. There was a trend of increased utilisation of PET imaging over time (Supplemental Fig. 1).

In the MSKCC cohort, patients were not evaluable if they had incomplete radiographic records (N = 57), missing treatment data (N = 1), were deceased within

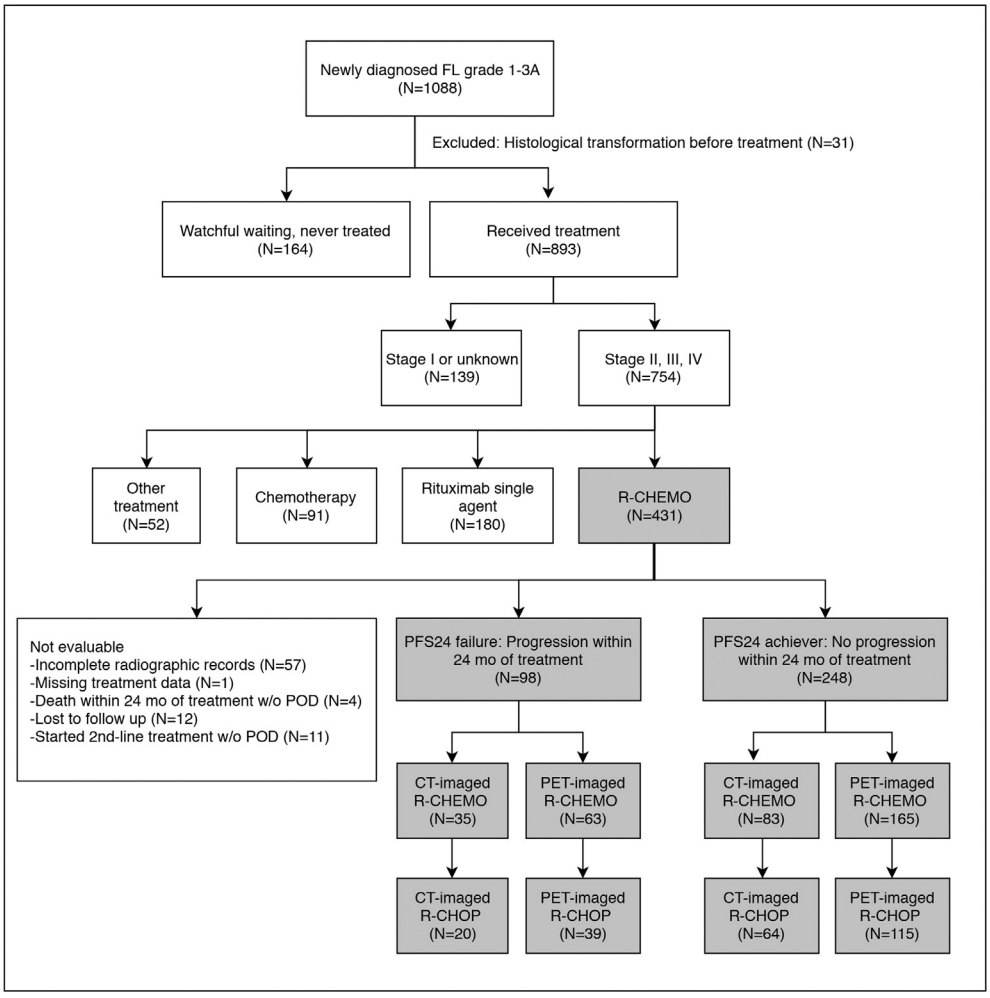

Fig. 1. Consort diagram of patients at initial treatment who were evaluable for progression-free survival (PFS) status at 24 months in the MSKCC cohort. MSKCC, Memorial Sloan Kettering Cancer Center; CT, computed tomography; PET, positron-emission tomography; R-CHEMO, rituximab-based chemotherapy; FL, follicular lymphoma; PFS24, progression-free survival at 24 months; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; POD, progression of disease.

24 months of treatment without progression (N = 4), were lost to follow-up (N = 12) or started second-line treatment without progression (N = 11) (Fig. 1). Of four patients who died within 24 months without progression, 1 patient died from treatment-related infection, whereas 3 patients died from causes unrelated to treatment or lymphoma. The 11 patients who started second-line therapy without progression included 9 patients who had suboptimal or stable responses to treatment with associated change of therapy and 2 patients who suffered treatment toxicity. A total of 346 patients in the MSKCC cohort who had stage II–IV disease and were treated with rituximab and chemotherapy regimens were evaluable for PFS24 status (Fig. 1, Table 1). Patient characteristics were similar to those of 754 patients with stage II–IV disease who required treatment in the MSKCC cohort (Supplemental Table 1). The median age of the 346 patients treated with R-CHEMO was 56 years (range: 24–80 years). Five percent of the patients had stage II disease, whereas 95% had stage III or IV disease before treatment initiation. The Follicular Lymphoma International Prognostic Index (FLIPI) risk score at the time of treatment initiation was available for 80% of the CT-imaged and 86% of the PET-imaged patients. A high FLIPI was represented by 45% (154/346) of patients.

R-CHOP was the primary treatment regimen making up 71% (N = 84) of CT-staged and 68% (N = 154) of PET-staged patients. Patients not achieving PFS24 represented 30% (N = 35) of CT-imaged and 28% (N = 63) of PET-imaged patients.

The validation cohort consisted of 484 patients from the FOLL05 clinical trial treated with rituximab in combination with chemotherapy (Table 1). The median follow-up for the validation cohort was 6.8 years (range: 0.1–9.9). Nine percent of patients had stage II disease and 91% of patients had stage III or IV disease at time of treatment. A high FLIPI was represented by 37% of the population. Treatment was evenly distributed between R-CHOP (33%), R-CVP (rituximab,

Table 1
Patient characteristics at treatment initiation.

Characteristic	MSKCC (N = 346)					FOLL05 (N = 484)				
	CT-staged (N = 118)		PET-staged (n = 228)		*P*	CT-staged (N = 345)		PET-staged (n = 139)		*P*
	No.	%	No.	%		No.	%	No.	%	
Age (years), median (range)	56 (24–80)		55 (23–85)		0.95	55 (29–75)		56 (32–74)		0.24
Gender										
Female	54	46%	99	43%	0.73	164	48%	72	52%	0.42
Male	64	54%	129	57%		181	52%	67	48%	
Stage										
II	6	5%	13	6%	1.00	33	10%	9	6%	0.37
III/IV	112	95%	215	94%		312	90%	130	94%	
FLIPI										
Low	15	16%	24	12%	0.69	74	21%	31	22%	0.98
Intermediate	30	32%	66	34%		144	42%	57	41%	
High	49	52%	105	54%		127	37%	51	37%	
Unknown	24		33							
LDH										
Elevated	31	35%	68	37%	0.89	67	19%	28	20%	0.90
Normal	57	65%	117	63%		278	81%	111	80%	
Unknown	30		43							
Treatment										
R-CHOP	84	71%	154	68%	0.93	114	33%	47	34%	0.85
R-CVP	21	18%	41	18%		116	34%	43	31%	
R-FM	1	1%	4	2%		115	33%	49	35%	
R-bendamustine	6	5%	14	6%						
Other	6	5%	15	7%						
Rituximab maintenance										
Yes	27	23%	74	32%		0	0%	0	0%	1.00
No	91	77%	154	68%		345	100%	139	100%	
Subsequent HDT/SCT					0.84					
Autologous	7	6%	20	9%		–		–		
Allogeneic	6	5%	12	5%						
Both	3	3%	7	3%						
No	102	86%	189	83%		–		–		
PFS24 status										
PFS24 achievers	83	70%	165	72%	0.71	235	68%	104	75%	0.16
PFS24 failures	35	30%	63	28%		110	32%	35	25%	

CT, computed tomography; PET, positron-emission tomography; PFS24, progression-free survival at 24 months; MSKCC, Memorial Sloan Kettering Cancer Center; R-CHEMO, rituximab-based chemotherapy; FLIPI, Follicular Lymphoma International Prognostic Index; HDT/SCT, high-dose therapy and stem cell transplant; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisone; R-FM, rituximab plus fludarabine and mitoxantrone.
In the MSKCC cohort, 346 patients with stage II–IV disease treated with R-CHEMO were evaluable for PFS24 status after first-line treatment. In the validation FOLL05 cohort, 484 patients with stage II–IV disease treated with R-CHEMO were evaluable for PFS24 status after first-line treatment.

cyclophosphamide, vincristine and prednisone; 33%) and R-FM (rituximab, fludarabine and mitoxantrone; 34%). Patients not achieving PFS24 included 32% (N = 110) in the CT-imaged group and 25% (N = 35) in the PET-imaged group.

We initially analysed PFS24 based on pre-treatment radiographic staging in patients treated with R-CHOP using an event-defining analysis to facilitate comparison with previously published studies [3,4] (Fig. 2). In the MSKCC cohort, 238 evaluable patients with stage II–IV disease were treated with R-CHOP. PFS24 failure was observed in 24% (20/84) of CT-imaged and 25% (39/154) of PET-imaged patients. A replication cohort of 161 patients treated with R-CHOP in the FOLL05 study was also analysed. PFS24 failure was associated with inferior OS in the MSKCC cohort regardless of modality of staging (Fig. 2A). However, the impact of PFS24 failure on OS was lessened with PET-based radiologic staging (Fig. 2A). In CT-imaged patients, PFS24 failures demonstrated an estimated 5- and 10-year OS of 57.6% (95% confidence interval [CI]: 39–85) and 43.2% (95% CI, 22–86), respectively. In contrast, patients achieving PFS24 demonstrated an estimated 5- and 10-year OS of 90.2% (95% CI, 83–98) and 84.0% (95% CI, 75–94), respectively (Fig. 2A). With PET-based imaging before initiating treatment, PFS24 failures demonstrated an estimated 5- and 10-year OS of 70.6% (95% CI, 57–87) and 67.1%

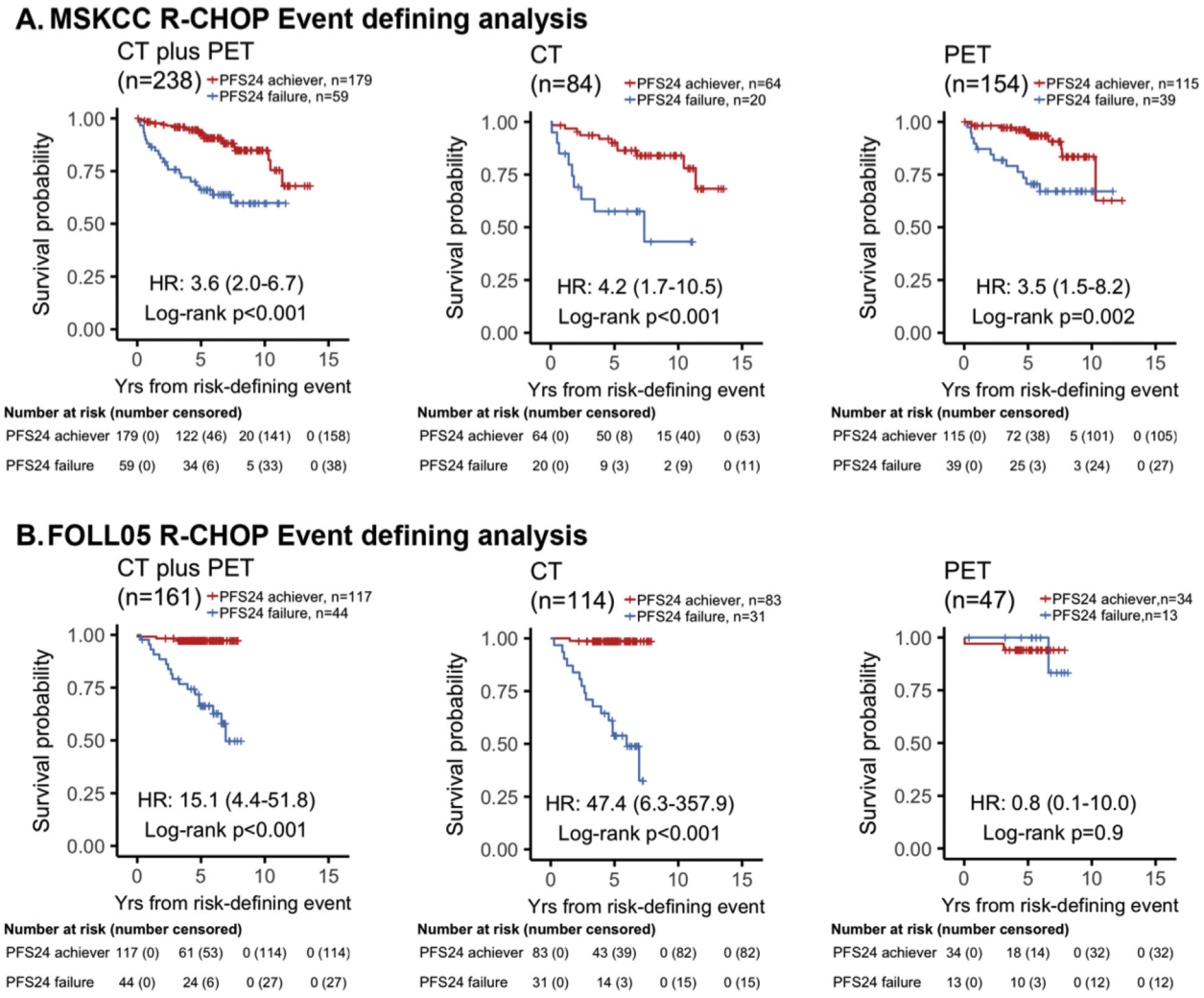

Fig. 2. Event-defining analysis of PFS24 based on radiographic imaging at time of treatment in patients treated with R-CHOP. Kaplan–Meier plots of overall survival (OS) since the risk-defining event stratified by PFS24 status in patients with stage II–IV disease treated with R-CHOP. (A) MSKCC cohort. (B) Validation FOLL05 cohort. When comparing OS by PFS24 status, PFS24 failures staged by CT had a worse outcome than those who were staged by PET. For CT-staged patients who failed to achieve PFS24, the estimated 10-year OS rate was 43% compared with that of 67% for PET-staged patients. The results were reproduced in the validation cohort in which CT-imaged PFS24 failures had an estimated 5-year OS rate of 54% compared with PET-imaged PFS24 failures who had an estimated 5-year OS rate of 100%. MSKCC, Memorial Sloan Kettering Cancer Center; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; CT, computed tomography; PET, positron-emission tomography; PFS24, progression-free survival at 24 months; HR, hazard ratio.

(95% CI, 53–85), respectively (Fig. 2A). Among patients achieving PFS24 imaged with PET, the estimated 5- and 10-year OS were 95.0% (95% CI, 91–99) and 83.6% (95% CI, 73–96), respectively. The FOLL05 validation cohort confirmed the improvement of the outcome in PET-imaged patients who failed to achieve PFS24 ($P = 0.857$, Fig. 2B).

We next applied a landmark analysis using a 24-month post-treatment landmark to evaluate the prognosis in patients who are alive but failed to achieve PFS24. This analysis excluded 7 patients from the MSKCC cohort and 3 patients from the FOLL05 cohort for progression before the 24-month landmark. Applying this method, PET-based staging further blunted the impact of PFS24 status on OS, whereas failure to achieve PFS24 continued to predict a poor OS in the CT-staged patients (Fig. 3A), In the CT-imaged patients treated with R-CHOP, PFS24 failures had an estimated 5- and 10-year OS of 63.2% (95% CI, 44–92) and 47.4% (95% CI, 24–93) respectively, whereas PFS24 achievers had an estimated 5- and 10-year OS of 90.2 (95% CI, 83–98) and 84.0% (95% CI, 75–94), respectively (Fig. 3A). Patients with PET-based imaging and who experienced PFS24 failures demonstrated an estimated 5- and 10-year OS of 80.8% (95% CI, 68–96) and 76.1% (95% CI, 62–94), respectively (Fig. 3A), compared with 95% (95% CI, 91–99) and 83.6% (95% CI, 73–96) in patients who achieved PFS24 (Fig. 3A).

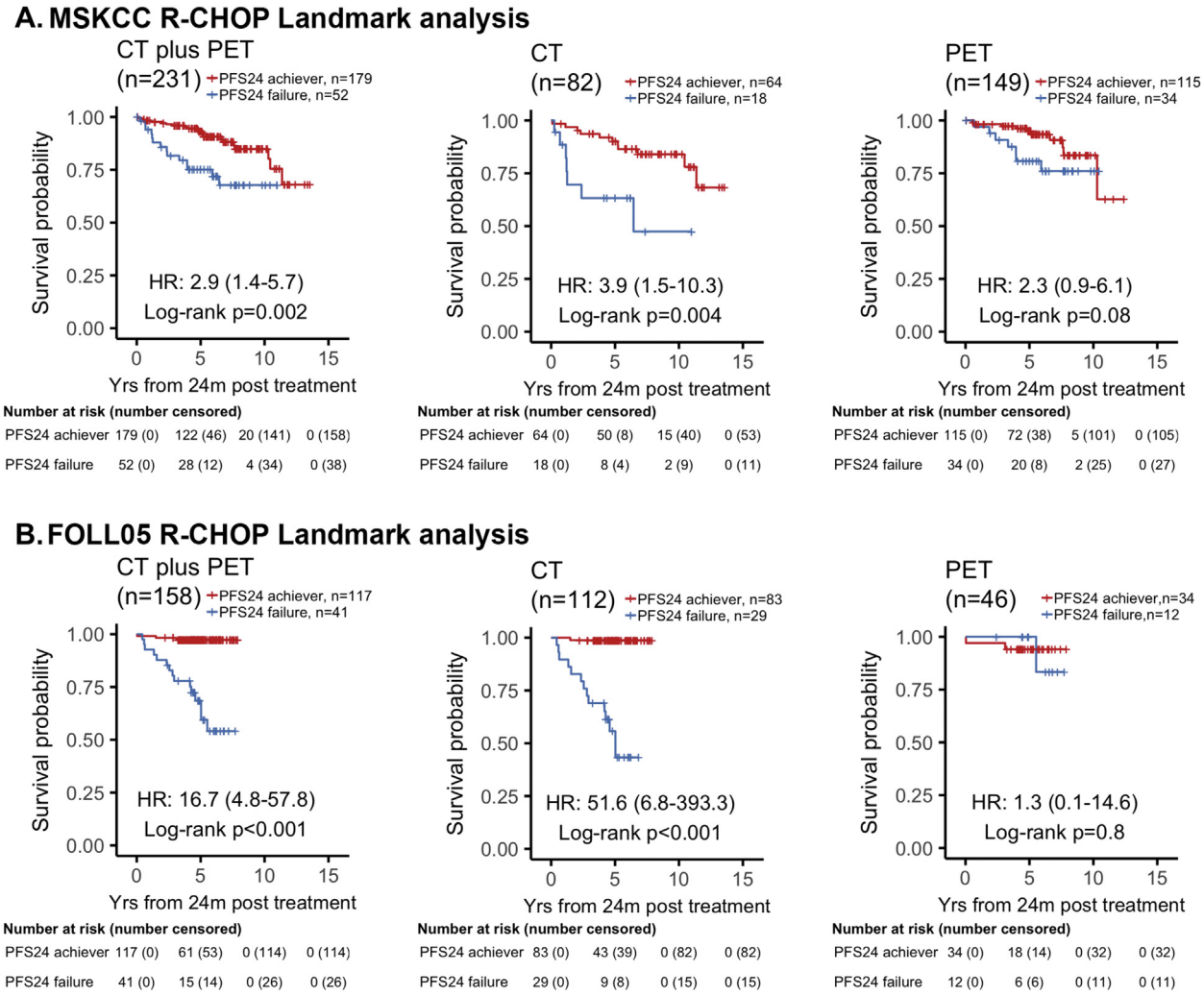

Fig. 3. Landmark analysis of PFS24 based on radiographic imaging at time of treatment in patients treated with R-CHOP. Kaplan–Meier plots of overall survival (OS) since 2-year landmark stratified by PFS24 status in patients with stage II–IV disease treated with R-CHOP. (A) MSKCC cohort. (B) Validation FOLL05 cohort. When comparing OS by PFS24 status, PFS24 failures staged by CT had a worse outcome than those who were staged by PET. For CT-staged patients who failed to achieve PFS24, the estimated 10-year OS rate was 47% compared with that of 76% for PET-staged patients. The results were reproduced in the validation cohort in which CT-imaged PFS24 failures had an estimated 5-year OS rate of 56% compared with PET-imaged PFS24 failures who had an estimated 5-year OS rate of 100%. MSKCC, Memorial Sloan Kettering Cancer Center; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; CT, computed tomography; PET, positron-emission tomography; PFS24, progression-free survival at 24 months; HR, hazard ratio.

Similar results were observed in the FOLL05 validation cohort (Fig. 3B, Supplemental Table 3).

Next, we investigated whether the data obtained from R-CHOP could be generalised to other R-CHEMO regimens. In the MSKCC cohort, we identified 330 patients treated with R-CHEMO regimens who were evaluable for the landmark analysis, and 16 patients were excluded for progression within the 24-month landmark (Fig. 4). In patients imaged with CT before treatment, the estimated 5-year OS in patients who exceeded PFS24 was 92.3% (95% CI, 86.5–98.4) compared with 62.0% (95% CI, 45.9–83.7) for those not achieving PFS24 (Fig. 4A). In the PET-imaged patients, the estimated 5-year OS in patients who exceeded PFS24 was 94.2% (95% CI, 90.4–98.2) compared with 79.4% (95% CI, 68.7–91.7) for those who failed to achieve PFS24 (Fig. 4A). The validation FOLL05 cohort included 473 evaluable patients treated with R-CHEMO, and 11 patients were excluded from the 24-month landmark. In the CT-imaged patients, the estimated 5-year OS was 95.7% (95% CI, 92.9–98.5) for patients who exceeded PFS24 compared with 66.9% (95% CI, 57.6–77.7) for those who failed to achieve PFS24 (Fig. 4B). In contrast, PET-imaged patients who exceeded PFS24 had an estimated 5-year OS of 95.6% (95% CI, 91.5–99.9) compared with 84.3% (95% CI, 72.5–98.0) for those who failed to achieve PFS24 (Fig. 4B, Supplemental Table 4). Patients treated with R-CHEMO and analysed using the event-defining analysis supported the pattern that PET-based staging

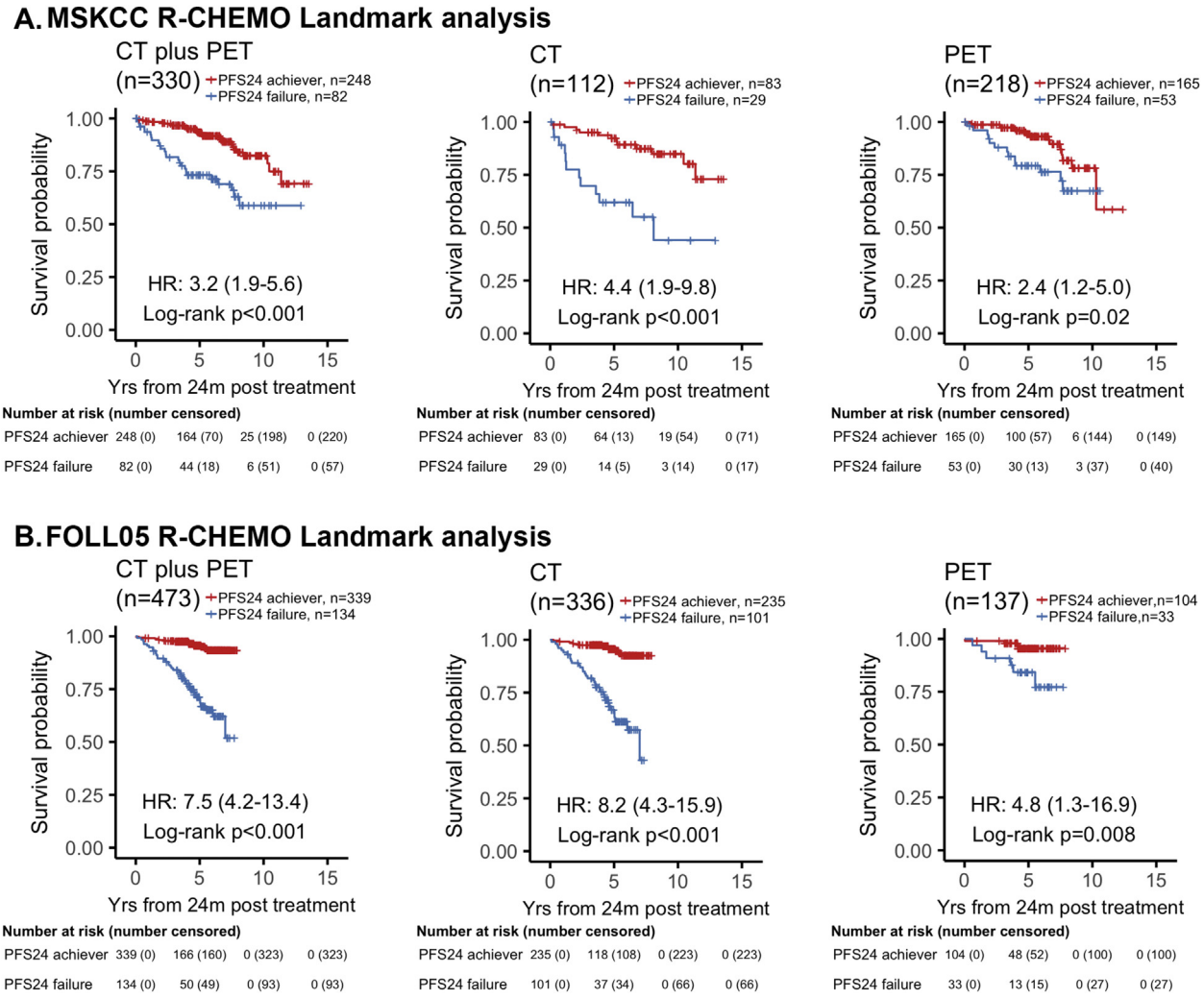

Fig. 4. Landmark analysis of PFS24 based on radiographic imaging at time of treatment in patients treated with R-CHEMO. Kaplan–Meier plots of overall survival (OS) since 2-year landmark stratified by PFS24 status in patients with stage II–IV disease treated with rituximab plus chemotherapy (R-CHEMO). (A) MSKCC cohort. (B) FOLL05 cohort. When comparing OS by PFS24 status, PFS24 failures staged by CT had a worse outcome than those who were staged by PET. For CT-staged patients who failed to achieve PFS24, the estimated 10-year OS rate was 44% compared with that of 67% for PET-staged patients. The results were reproduced in the validation cohort in which CT-imaged PFS24 failures had an estimated 5-year OS rate of 67% compared with PET-imaged PFS24 failures who had an estimated 5-year OS rate of 84%. R-CHEMO, rituximab-based chemotherapy; MSKCC, Memorial Sloan Kettering Cancer Center; CT, computed tomography; PET, positron-emission tomography; PFS24, progression-free survival at 24 months; HR, hazard ratio.

blunted the poor prognostic effect of early progression in both the MSKCC and the FOLL05 validation cohorts (Supplemental Fig. 2).

Early disease transformation has been shown to negatively impact OS in patients with FL [21–24]. Therefore, we performed a competing risk analysis of transformation and early death to determine if early transformation after initial treatment is associated with poor outcomes (Fig. 5). Patients were categorised into three groups based on their early progression status: (1) PFS24 achiever, (2) progression within 1 year after treatment and (3) progression between 1 and 2 years after treatment. In patients who achieved PFS24, the cumulative risk of biopsy-proven transformation at 3 years was 3.4%, and all-cause mortality risk at 3 years was also 3.4%, with <1% attributed to transformation- and 2.5% attributed to non-transformation–associated causes. For patients who progress within 1 year after treatment, the cumulative risk of biopsy-proven transformation was 31.9% at 1 year and 42.4% at 3 years. The all-cause mortality risk was 33%, with almost 60% (18.6/33) of patient deaths attributed to transformation, whereas 40% (14.4/33) of patient deaths were unrelated to transformation. Transformation is a significant contribution to progression and early death during the first two years after treatment (Table 2).

In patients staged with CT before treatment, the cumulative risk of transformation at the time of progression for patients who progressed within 1 year and 1–2 years was 16.7% and 8.7%, respectively. In contrast,

patients staged with PET before treatment demonstrated that a lower cumulative risk of transformation at the time of progression for patients who progressed within 1 year and 1–2 years was 6.3% and 3.2%, respectively (Supplemental Table 5). This supports the hypothesis that PET imaging at diagnosis and treatment excludes patients with transformation, which previously would have gone undetected by CT.

4. Discussion

Our study provides evidence of the importance of pre-treatment PET–based staging in the current management of FL. Although early progression remains a predictor of poor outcomes in FL, the observed difference in outcomes is blunted in the era of PET-based staging. Patients who fail to achieve PFS24 and are alive at 24 months without evidence of transformation may enjoy a prolonged OS without the need for more intensive, and potentially more toxic, therapy. In the MSKCC cohort, less than 20% of patients received a stem cell transplant at any line of subsequent therapy. Thirty-eight percent of stem cell transplant recipients harboured disease transformation. Consistent with our data, a recent study from MD Anderson Cancer Center of 342 patients with advanced-stage, grade I–II FL without histologic transformation during their disease course demonstrated a 5-year OS of >75% regardless of PFS24 status [25]. The diverse treatment landscape using a variety of non-intensive, targeted therapy regimens similarly demonstrates favourable OS in patients with early disease progression but without histologic transformation [26–33]. For example, a recent update of the CHRONOS-1 study showed patients with relapsed or refractory FL, without evidence of disease transformation treated with single-agent copanlisib, demonstrated similar OS regardless of their PFS24 status [34]. A combined analysis of three clinical trials using rituximab-based doublets showed a significant but blunted impact of PFS24 on 5-year OS [5]. Therefore, caution should be used before considering PFS24 broadly without regard to transformation status as a surrogate end-point for OS or applying this surrogate end-point to evaluate the efficacy of new therapeutic agents.

The discrepancy in OS between CT- and PET-based imaging in patients with PFS24 failure is likely from a multitude of factors including improving prognosis afforded by recent advances and ability of PET-based imaging to identify areas of disease transformation. With pre-treatment CT imaging alone, a diagnostic biopsy is typically obtained from a less invasive peripheral

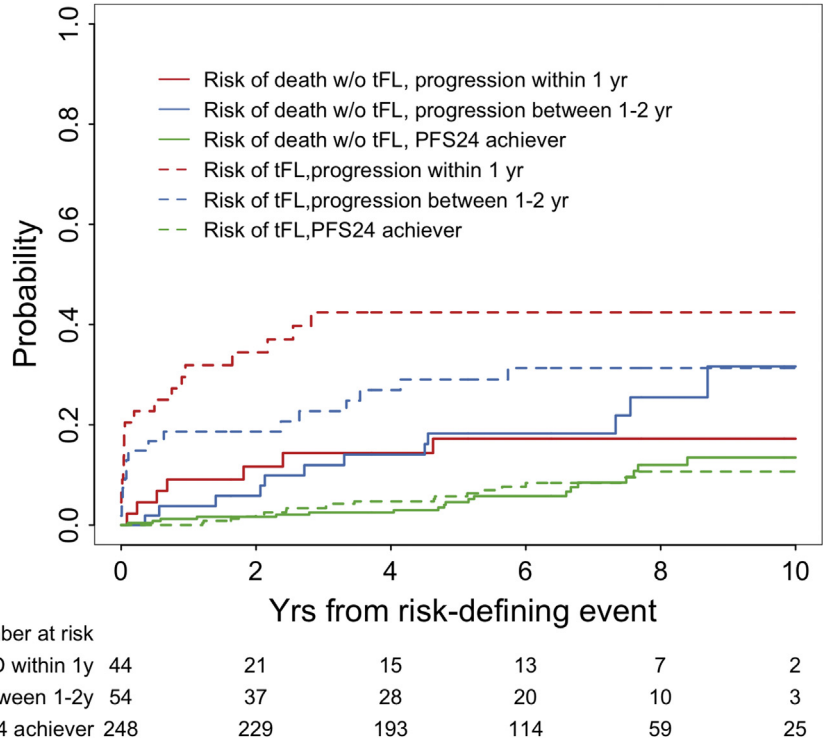

Fig. 5. Competing risk analysis to assess association between early progression and transformation in MSKCC patients treated with R-CHEMO. Patients were categorised as early progressors within 1 year, early progressors between 1 and 2 years and PFS24 achievers who lack progression within 2 years. The competing events were transformation or death without transformation. The risk of transformation based on time from the risk-defining event (dashed lines) was compared with the risk of death not attributed to transformation (solid lines). POD, progression of disease; PFS24, progression-free survival at 24 months; tFL, transformed follicular lymphoma; R-CHEMO, rituximab-based chemotherapy; MSKCC, Memorial Sloan Kettering Cancer Center.

Table 2
Rate of histological transformation and risk of death based on PFS24 status.

Risk	Years after the risk-defining event	Progression within 1 year (n = 44); cumulative risk (cumulative cases)	Progression between 1 and 2 years (n = 54); cumulative risk (cumulative cases)	PFS24 achievers (n = 248); cumulative risk (cumulative cases)
Risk of tFL, %	0.02 (1 week)	9.1 (4)	5.6 (3)	0 (0)
	1	31.9 (14)	18.6 (10)	0 (0)
	2	34.5 (15)	18.6 (10)	2.1 (5)
	3	42.4 (18)	22.7 (12)	3.4 (8)
Risk of death because of tFL, %	0.02 (1 week)	0 (0)	0 (0)	0 (0)
	1	11.4 (5)	5.7 (3)	0 (0)
	2	16.2 (7)	7.7 (4)	0 (0)
	3	18.6 (8)	9.8 (5)	0.9 (2)
Risk of death without tFL, %	0.02 (1 week)	0 (0)	0 (0)	0 (0)
	1	9.1 (4)	3.8 (2)	1.2 (3)
	2	11.7 (5)	5.8 (3)	1.6 (4)
	3	14.4 (6)	12.0 (6)	2.5 (6)
Total risk of death (sum of risk of death from tFL and without tFL), %	0.02 (1 week)	0 (0)	0 (0)	0 (0)
	1	20.5 (9)	9.4 (5)	1.2 (3)
	2	27.8 (12)	13.6 (7)	1.6 (4)
	3	33.0 (14)	21.8 (11)	3.4 (8)

FL, follicular lymphoma; PFS24, progression-free survival at 24 months; tFL, transformed FL.
Risk of transformed FL denotes the cumulative risk of biopsy-proven transformation at the time of the relapse. The cumulative risk of death without transformation is provided using a competing risk analysis. The risk of death because of transformation is calculated by the total risk of death minus the risk of death without transformation.

lymph node. This approach may miss other diseased areas involved with *de novo* histologic transformation, which carries a poor prognosis. With pre-treatment PET imaging, disease sites with high FDG-PET uptake are typically biopsied, and if *de novo* disease transformation is found, those patients are typically excluded from FL-based therapy and databases. Accordingly, in our retrospective data analysis, *de novo* transformed FL was not included in the FL database, and this likely impacted the better OS in our report compared with other published series.

In our study, we demonstrate that patients who fail to achieve PFS24 after treatment and undergo histologic transformation suffered the highest risk of early mortality. In a retrospective pooled analysis with more than 8000 patients with FL, the 5-year survival after transformation was 34% for patients experiencing early ($\leq$1 year) histological transformation and was 48% for those with late histological transformation [24]. In addition, a study by the British Columbia Cancer Agency showed that 77% of patients treated with rituximab and bendamustine with an early progression had a transformative event [35]. In the PRIMA trial, more than half (58%) of the transformations were documented during the first year after induction, and 38% of the biopsies performed during the first year identified transformations [21]. These results support the hypothesis that the majority of transformations occur in patients with early progression after frontline treatment. Co-occurrence of early progression and transformation is a major contributor to early mortality. Both studies incorporated subsets of patients with PET imaging. On early recurrence, PET-based imaging and biopsy is warranted to identify possible areas of transformation. Admittedly, our data contrast with results from a GALLIUM substudy that evaluated patients with PET imaging and showed that overall transformation in CT-staged patients was 2.5% and high uptake on PET did not predict transformation [36].

Limitations of this study include its retrospective nature, and the histological transformation rate may also be underestimated because of the lack of systemic biopsies at the time of progression. In addition, the blunted prognostic value of PFS24 in the PET era can be partly attributed to the evolved treatment paradigm in recent years. Better outcomes were observed from patients in the FOLL05 cohort than in the MSKCC cohort. We hypothesised that the survival difference between the MSKCC and FOLL05 cohorts may be caused by the nuances in the patient population. For example, fewer patients in the FOLL05 cohort had a high-risk FLIPI (37% versus 53%) or elevated levels of lactate dehydrogenase (20% versus 36%). In addition, patients enrolled in the FOLL05 clinical trial were required to have a centrally reviewed pathology sample which confirmed FL, and a better survival could be expected by excluding *de novo* transformed biology. Both PET- and CT-imaged cohorts demonstrated a similar absolute rate of PFS24 failures. Ultimately, our patients were treated with a wide range of first-line and maintenance strategies over 10 years, therefore evaluating that the absolute rate of PFS24 failure may provide less nuance than understanding the timing and transformation status of the relapses. The existing data

are also not suitable to associate PET utilisation at time of treatment with identification of transformation before treatment. However, this may be an important question to address in the future.

Our study reveals staging with PET imaging at diagnosis and treatment may provide valuable information that impacts the outcomes of patients with FL. Consistent with previous reports, we found that early POD in CT-staged patients confers a poor OS. The poor prognosis associated with early POD is predominantly driven by early histologic transformation, which can be missed before initiating therapy in CT-staged patients. When modern PET imaging was used before initiating therapy, early POD was less frequently associated with histologic transformation, and therefore, early POD had a lower impact on OS. Management of patients with early progression without histologic transformation needs to be better studied as this population demonstrates a more favourable prognosis than patients with early progression and transformation of disease. Our study supports the incorporation of PET imaging to guide clinical decisions in the management of patients with FL. In addition, our study highlights the need for repeated biopsies in patients with early POD to guide treatment decisions. Future studies are needed to prospectively identify patients at risk of early progression and disease transformation and to design pre-emptive therapy aimed at improving treatment outcomes and OS.

Author contributions

C.L.B., F.S., A.A. and A.Y. contributed to conception and design; C.L.B., A.A., F.S., K.S., Z.Y., S.L., L.M. and M.F. contributed to collection and assembly of data; C.L.B., A.Y., F.S., V.E.S., A.N., A.A., S.L., L.M. and M.F. contributed to data analysis and interpretation; C.L.B., F.S., A.A. and A.Y contributed to writing the first draft of the manuscript. All authors provided a critical review of the manuscript's content and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding

This work was supported in part by National cancer institute (NCI) Cancer Center Support Grant (P30 CA008748). The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Conflict of interest statement

C.L.B. reports research support from Janssen, Novartis, Epizyme, Xynomic and Bayer; reports honoraria from Dava Oncology and is a consultant for from Kite and Juno. J.F.G. is presently employed by Janssen and reports honoraria from Bayer, Epizyme, Roche, Genentech and AbbVie. P.A.H. reports research support from Portola, Molecular Templates, Incyte and J&J Pharmaceuticals and is a consultant for Portola Pharmaceutics, Celgene, Karyopharm and Juno Therapeutics. S.M.H. reports research support from ADCT Therapeutics, Aileron, Celgene, Forty Seven, Infinity/Verastem, Kyowa Hakka Kirin, Millenium/Takeda, Seattle Genetics and Trillium and is a consultant for ADCT Therapeutics, Aileron, Corvus, Forty Seven, Innate Pharma, Kyowa Hakka Kirin, Millenium/Takeda, Mundipharma, Portola and Seattle Genetics. A.K. reports research support from AbbVie, Adaptive Biotechnologies, Celgene, Pharmacyclics and Seattle Genetics and serves on the scientific advisory board for Celgene. M.J.M. reports research support from Genentech, Roche, GlaxoSmithKline, Bayer, Pharmacyclics, Janssen, Rocket Medical and Seattle Genetics; reports honoraria from Genentech, Roche, Bayer, Pharmacyclics, Janssen, Seattle Genetics and GlaxoSmithKline and is a consultant for Genentech, Bayer, Merck, Juno, Roche, Teva, Rocket Medical, Seattle Genetics, Genentech, Roche, Seattle Genetics and Bayer. A.J.M. reports research support from Incyte, Seattle Genetics, BMS and Merck and is a consultant for Kyowa Hakko Kirin Pharma, Miragen Therapeutics, Takeda Pharmaceuticals, ADC Therapeutics, Seattle Genetics, Cell Medica, Bristol-Myers Squibb and Erytech Pharma. C.H.M. reports research support from BMS, Merck and Seattle Genetics; is a consultant for AstraZeneca, BMS, Karyopharm Therapeutics, Merck, Seattle Genetics, Takeda and Vaniam Group and serves on the scientific advisory board for AstraZeneca, Karyopharm Therapeutics, Merck, Seattle Genetics, Takeda and Vaniam Group. A.N. reports research support from Pharmacyclics, NIH and Rafael Pharma and is a consultant for Janssen, Pharmacyclics, Medscape and Targeted Oncology. M.L.P. reports research support from Genentech, Juno and Regeneron; reports honoraria from Novartis, Merck, Celgene, Juno and Pharmacyclics and is not a consultant for any firms. D.S. reports research support from and serves on the scientific advisory board for Seattle Genetics. G.v.K. reports research support from Pharmacyclics, Genentech and Bayer. A.D.Z. reports research support from MEI Pharma, MorphoSys, Sandoz, Celgene, Roche and Gilead; is a consultant for Genentech/Roche, Gilead, Celgene, Janssen, Amgen, Novartis and Adaptive Biotechnology and serves on the board of directors (DMC Chair) for BeiGene. S.L. is a consultant for and serves on the scientific advisory board for Roche, Celgene, Sandoz and Gilead. M.F. reports research support from Mundipharma s.r.l., Cephalon/Teva, Celgene, Millennium/Takeda and Roche and is a consultant for and serves on the scientific advisory boards for Takeda, Roche, Celgene,

Sandoz and Spectrum. A.Y. reports research support from Janssen, Curis, Merck, BMS, Syndax and Roche; reports honorarium from Janssen, AbbVie, Merck, Curis, Epizyme, Roche and Takeda and is a consultant for BioPath, Xynomic, Epizyme and Roche. F.S., A.A., A.N., K.S., L.M., V.E.S., E.J., C.O. and Z.Y. declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.12.006.

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