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Follicular Lymphoma Treated with First-line Immunochemotherapy: a Review of PET-CT in Patients who did Not Achieve CMR in the GALLIUM Study

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Running Title: PET-CT in patients with FL without CMR

ABSTRACT

Complete metabolic response (CMR) on positron emission tomography-computed tomography (PET-CT) was the sole independent predictor of overall survival in the PET sub-study of the phase III GALLIUM trial (NCT01332968) in first-line treatment of high tumour burden follicular lymphoma (FL). The aim of this analysis was to investigate further the outcome of patients not achieving CMR.

Methods: Two international experts re-reviewed PET-CT scans from patients failing to achieve CMR assessed by the Independent Review Committee (IRC) blinded otherwise to IRC results. Metabolic response category and Deauville score (DS) were assigned. Progression-free survival (PFS) was investigator assessed with contrast-enhanced CT (ceCT). Kaplan–Meier methodology was used to estimate landmark PFS and time-to-next treatment (TTNT) from end-of-induction by DS. Patients who experienced CT-based progressive disease at end-of-induction were excluded.

Results: Fifty-four patients were reviewed. Six had CMR, 37 partial metabolic response, two no metabolic response and nine progressive metabolic disease. Patients were reassigned to CMR because fluorodeoxyglucose uptake was considered as i) inflammatory (*n* = 2), ii) incidental neoplasia (*n* = 2) or iii) where fluorodeoxyglucose uptake was visually close to liver uptake but quantitatively lower (*n* = 2). There was a trend for shorter PFS and TTNT for patients with DS-5 than DS-4. High-grade mesenteric uptake at end-of-induction was common, occurring in 20 patients with non-CMR, fourteen of whom achieved CMR at all other sites. Only 3/14 (21%) patients with mesenteric uptake as the only site of disease experienced progression or death within 24 months (PFS24) whereas 4/6 patients (67%) with mesenteric and additional sites of fluorodeoxyglucose-avid disease had a PFS24 event. All patients with early progression had measurable disease on ceCT at fluorodeoxyglucose-avid sites at end-of-induction.

Conclusion: After induction immunochemotherapy, CMR was assigned after reassessment in some patients, where increased fluorodeoxyglucose uptake was considered due to inflammation/incidental neoplasia rather than lymphoma. Quantitative assessment to confirm the visual impression of residual

uptake in lesions is suggested. Isolated mesenteric fluorodeoxyglucose uptake is likely a common false-positive finding at end-of-induction and does not warrant changes in clinical management nor disease surveillance unless there is measurable disease on ceCT or clinical suspicion of active disease.

Keywords: Follicular lymphoma, positron emission tomography, response assessment

INTRODUCTION

Patients with follicular lymphoma treated with first-line immunochemotherapy with complete metabolic response (CMR) on positron emission tomography (PET) using the five-point Deauville score have a better prognosis than patients who do not achieve CMR *(1)*. In a landmark analysis of 508 patients with baseline and end-of-induction positron emission tomography-computed tomography (PET-CT) scans in the prospective phase III GALLIUM study (NCT01332968), the progression-free survival (PFS) 2.5 years from randomisation for patients achieving CMR (Deauville score 1, 2 or 3) was 87.4% (95% confidence interval [CI], 83.7-90.2) compared with 54.9% (95% CI, 40.5-67.3) for patients failing to do so, with (Deauville score 4 or 5) assigned as non-CMR *(2)*. PET-CT was superior to contrast-enhanced CT for predicting PFS and overall survival. The 2014 Lugano response criteria *(3,4)* incorporating the Deauville score were superior to the previous standard, the 2007 international harmonisation project criteria *(5)*. The Lugano criteria also proposed combining the Deauville score with interval changes in fluorodeoxyglucose (FDG) uptake to assign metabolic response categories *(3,4)*, analogous to the anatomical response categories used for CT reporting.

The Lugano criteria have been suggested as a suitable platform for response-adapted therapy in follicular lymphoma *(2)* with different management strategies already being tested for patients with advanced follicular lymphoma with CMR versus non-CMR following first-line immunochemotherapy using the Deauville score as a binary measure of response *(6,7)*. This may be partly because there are no published data to our knowledge about ordinal Deauville score or metabolic response category, nor information about patterns of FDG uptake that might be associated (or not) with early progression or death in patients with follicular lymphoma and non-CMR at the end of induction. Patients with lymphoma usually have high response rates, which makes analysis of the small numbers of patients with non-CMR challenging. It is becoming clear however that a 'positive' PET scan may not carry uniform

prognostic weight, with clinical trials in aggressive lymphomas reporting that patients with a PET score of 5 have inferior outcomes to patients with a PET score of 4 and treating this group differently *(8-11)*. The aims of this ancillary analysis from the GALLIUM PET study were therefore i) to report PFS according to Deauville score and metabolic response category and ii) to evaluate any PET-CT findings, such as disease distribution, on end-of-induction scans that might be associated (or not) with early progression or death in patients with non-CMR.

MATERIALS AND METHODS

The details of the GALLIUM trial *(12)* and the PET analysis *(2)* have been reported, but in brief, previously untreated patients with advanced stage grade 1-3a follicular lymphoma requiring immunochemotherapy were eligible. Patients were randomised 1:1 to receive either obinutuzumab or rituximab followed by the same maintenance antibody for up to two years. The chemotherapy was cyclophosphamide, vincristine, and prednisone, cyclophosphamide, doxorubicin, vincristine and prednisone, or bendamustine, decided by the treating site. PFS was assessed by investigators using contrast-enhanced CT scans. PFS24 was defined as progression or death within 24 months from the end of induction.

PET-CT response was a secondary endpoint with scans mandated for the first 170 patients and optional thereafter. All PET-CT scans were performed according to a standardised study protocol with pre-specified time windows. The GALLIUM study was approved by local Institutional Review Boards and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent.

Baseline and end-of-induction PET-CT and contrast-enhanced CT scans were read prospectively by an independent review committee using the international harmonisation project criteria, which were the international standard at the time. The PET-CT scans were retrospectively reviewed by the independent review committee using the 2014 Lugano criteria *(3,4)*. Patients with progressive metabolic disease in GALLIUM had an unexpectedly longer PFS than patients with partial metabolic response on independent review committee evaluation, though this did not reach statistical significance. Two international experts (SFB, MM) were invited to re-review baseline and end-of-induction PET-CT scans that had been assessed as non-CMR by the independent review committee. Deauville score and metabolic response category were assigned blinded to independent review committee results and any clinical information at the time of scan review, with differences between the two reviewers resolved by consensus. A Deauville score of 5 was assigned where uptake in baseline lesions was ≥3 times higher than the maximum standardized uptake (SUVmax) in the liver at response and/or in the presence of new lesions considered to be lymphoma related. Lymphomatous lesions were considered measurable if two dimensions were recorded on contrast-enhanced CT, with the longest diameter at least 15 mm for nodal sites and at least 10 mm for extranodal sites *(4).*

Statistical Methods

Kaplan–Meier methodology was used to estimate landmark PFS distributions and time-to-next anti-lymphoma treatment from end-of-induction therapy for each response category. Patients who experienced progressive disease (CT-based assessment) at the end of induction were excluded from the landmark analyses.

RESULTS

There were 55 patients with non-CMR by independent review committee assessment without CT-defined progressive disease at the end of induction. One patient was excluded from further analysis, as not all FDG-avid sites present on the baseline scan were included on the end-of-induction PET-CT scan. Median follow-up for these 54 patients was 75.1 (range 5.9–92.3) months from the end of induction.

Six of the remaining 54 patients in the current analysis were reassigned to CMR. Thirty-seven patients had partial metabolic response, two patients had no metabolic response and nine patients had progressive metabolic disease.

Two of the six patients reassigned to CMR by both reviewers compared to the independent review committee had new uptake at sites not involved at baseline. These areas of new uptake were considered to be more in keeping with a sarcoid-like reaction and inflammatory uptake in degenerative disease at a facet joint, than new sites of follicular lymphoma, with CMR at all other sites. Two patients had abnormal uptake determined by the reviewers to be due to a different neoplasm than follicular lymphoma, also in the context of CMR elsewhere. One of these patients had unchanged uptake in an incidental thyroid nodule, in keeping with a probable thyroid neoplasm. Follow-up information was not available. The second patient had increasing FDG uptake in a focus in the caecum and in a probable liver metastasis. The caecal uptake was later confirmed to be colonic adenocarcinoma on biopsy (Fig. 1). Two patients had low grade residual uptake in the mesentery and the subpectoral region, respectively, which were close to the intensity of maximum uptake in the liver visually but less than the liver on quantitative measurement and hence reassigned as CMR. Five of the six patients reassigned to CMR did not experience PFS24. The remaining patient with inflammatory arthropathy experienced progression,

presenting with a new parotid node 11 months after the end of induction, a site of initial disease on the baseline scan that had responded at the end of induction on both PET-CT and contrast-enhanced CT.

Forty-eight patients were assigned as non-CMR by the current reviewers, 26 with a Deauville score of 4 and 22 patients with a Deauville score of 5. The PFS and time-to-next anti-lymphoma treatment for patients with a Deauville score of 5 was shorter than for patients with a Deauville score of 4, but the differences did not reach statistical significance: hazard ratio (HR): 1.33 (95% CI: 0.69–2.59); *P* = 0.39 and HR: 1.37 (95% CI: 0.64–2.92); *P* = 0.41, for PFS and time-to-next anti-lymphoma treatment, respectively (Fig. 2). Fourteen of 37 (37.8%) patients with a partial metabolic response, 2/2 patients with no metabolic response and 2/9 (22.2%) patients assessed as progressive metabolic disease experienced PFS24 (Fig. 3) prompting a careful review of appearances that might not represent lymphoma and could represent 'false positive' uptake. Six of the nine patients with progressive metabolic disease had increased or new uptake in the mesentery, two with measurable disease on CT. In five of these patients, the mesentery was the only site of disease and only one of the nine patients with the largest residual mesenteric node measuring 42mm x 24mm experienced progression from follicular lymphoma, 5.5 months after end-of-induction PET scans within the residual mesenteric site, at which time the patient commenced anti-lymphoma treatment (Fig. 4). The remaining five patients were observed and did not experience early progression (Fig.5). One patient died without progression. Median follow-up for non-progressing patients was 74.5 (range 16.5–0.9) months.

In the current analysis of a subgroup of patients assigned as non-CMR, high residual and/or new mesenteric uptake associated with lymph nodes and/or mesenteric stranding was a common finding. Twenty out of 48 (41.7%) patients had abnormal FDG uptake in the mesentery at the end of induction (Fig. 6). All 20 patients had mesenteric involvement at baseline. The location of mesenteric uptake was not always identical at baseline and response but, allowing for bowel/mesenteric movement and

reduction in other nodal responding masses, was concerning for the presence of residual lymphoma. Fourteen out of 20 (70.0%) patients had mesenteric uptake in the context of CMR at all other baseline FDG-avid sites with median mesenteric SUVmax = 10.6 (range 3.1–18.7), only three of whom (21.0%) progressed; all had measurable mesenteric disease on CT and commenced anti-lymphoma treatment within 3 months of progression. Six out of 20 patients had mesenteric uptake and additional sites of abnormal FDG uptake, four of whom progressed within 24 months (66.7%), two at mesenteric sites, one of whom also had progression of renal disease, all with measurable mesenteric disease on CT. Three of these patients with PFS24 commenced anti-lymphoma treatment within 3 months of progressive disease, and one was observed and commenced treatment 26 months after progression on contrast-enhanced CT. The presence of measurable disease in the mesentery was difficult to assess on the low-dose CT acquired as part of the PET-CT examination and the size of lesions measured during this post-hoc review was not reliable when compared with the measurements obtained on dedicated contrast-enhanced CT scans of the abdomen and pelvis.

The delta SUV, which is the change in the SUVmax with treatment has been suggested as a marker of inadequate response in aggressive non-Hodgkin lymphoma *(13,14)*. The mean reduction in SUVmax was 35.5% amongst patients who had a PFS24 event (range -91.4 to +12.1%) and 34.3% (-91.1 to +121.3%) amongst those who remained alive without progression.

DISCUSSION

Few patients treated with immunochemotherapy for high tumour burden follicular lymphoma fail to achieve a CMR at the end of induction. In this ancillary analysis of the 12% (55) of patients with non-CMR, as assessed by the independent review committee, from the GALLIUM PET study, the current reviewers reassigned six patients to CMR. Four were reassigned by virtue of new or persistent sites of

FDG uptake not considered to be follicular lymphoma (new uptake was considered to be due to a sarcoid-like reaction and an inflammatory arthropathy in two patients, and persistent uptake due to an incidental thyroid nodule and colonic cancer in another two). New areas of uptake unlikely to be related to lymphoma, especially in the context of response elsewhere, are not considered to represent progressive metabolic disease in the Lugano criteria and are designated by the suffix 'X' after the PET score given to residual lymphomatous lesions *(3)* e.g. Score 3X, 4X, and by implication to sites of persistent or increased uptake attributable to other aetiologies. Two patients with residual uptake close in intensity to the liver visually but measured as quantitatively lower than maximum liver uptake were also reassigned to CMR. It is recommended to confirm visual assessment using quantitative assessment to avoid misinterpretation, which can be influenced by the adjacent background *(15,16)*. Only the patient with inflammatory arthropathy experienced progression, at a different nodal site.

Nine patients in this analysis using Lugano criteria were assigned as progressive metabolic disease by expert reviewers and the observation that seven of these patients did not experience early progression was surprising and prompted scrutiny of all scans of patients with non-CMR. Persistent and/or new focal uptake in the mesentery was relatively common (20/48; 42%) in this non-CMR population, only one of these patients did not have baseline abnormal mesenteric uptake. An important finding was that just three of the fourteen patients (21%) with mesenteric uptake who had CMR at all other sites developed early progression and among patients who progressed in mesenteric sites, all had measurable disease on CT at the time of first non-CMR assignment. Mesenteric uptake with CMR elsewhere was observed in three patients who received obinutuzumab and eleven with rituximab suggesting it was not related to mesenteric reactivity to the administration of a more potent antibody. This suggests that mesenteric uptake has a high likelihood of being 'false positive' uptake, perhaps inflammatory or representing a delayed metabolic response, especially in the context of CMR

elsewhere. In our series, disease progression never occurred in mesenteric sites in the absence of measurable disease on CT at the end of induction. Regression of mesenteric lesions however also occurred in four patients who had measurable mesenteric disease on the contrast-enhanced CT at the end of induction with CMR at other sites, only one of whom progressed at another site 4 months after the end of induction. By comparison, 15/34 patients with non-mesenteric FDG uptake had a PFS24 event (44%), which was similar to the rate of progression or death of 45% previously reported in the non-CMR population at 2.5 years.

Mesenteric panniculitis on CT has been reported in around 2% of patients with non-Hodgkin's lymphoma *(17)* most commonly follicular lymphoma *(18)* and is also associated with solid cancers, autoimmune disease, infection and abdominal trauma. It is more commonly found in males *(18-20)*. On biopsy these appearances are associated with inflammation and fat necrosis *(19)*. Radiological features that help to distinguish lymphomatous involvement from inflammatory uptake at diagnosis are reported to be nodules at least 1cm in size, increased attenuation giving the appearance of a 'misty mesentery', sometimes calcification and the absence of a fat ring or 'halo' around the mesenteric vessels or a pseudocapsule *(17,19)*. FDG uptake was reported in only 2 of 44 patients who underwent PET scanning in a retrospective review of all patients with appearances of mesenteric panniculitis on abdominal CT scans over a 5-year period in one United States radiology network and has been used as a feature to differentiate lymphoma from other causes of panniculitis *(18,20)*. After treatment for lymphoma, distinguishing CT features may disappear, and calcification may occur within nodal masses. Case reports have suggested that follow-up CT imaging may be helpful to determine whether CT changes suggestive of panniculitis resolve, remain stable or progress along with the underlying lymphoma *(17,18,20)*. Stable changes were reported in 80%, and improvement in appearances in 9%, of cases using CT in one series *(18)*. Ishiyama et al recently reported three patients with lymphoma, where new mesenteric uptake on

PET-CT with CMR elsewhere, similar to our findings, showed reduced FDG uptake over time, with an excisional biopsy in one patient with follicular lymphoma demonstrating fat necrosis and histiocyte infiltration *(21)*. Four patients in our series with abnormal FDG uptake in the mesentery in isolation and measurable disease on CT who did not experience disease progression showed regression of lesions on contrast-enhanced CT suggesting an inflammatory component that may be treatment related. Delayed response in the bone marrow and large nodal masses, also likely inflammatory, is recognised in aggressive lymphomas with focal FDG uptake at diagnosis *(16,22)*. The Lugano classification considered that 'in the case of persistent focal changes in the bone marrow in the context of nodal response consideration should be given to further evaluation with MRI, biopsy or an interval scan'*(4)*. Our findings suggest that similar caution should be exercised in the case of persistent or new sites of mesenteric uptake in patients with follicular lymphoma, especially in the context of response at other disease sites. The use of delta SUV did not appear to be helpful for response discrimination or determining whether mesenteric uptake was a 'false positive'.

This review was limited by the small number of patients who fail to achieve CMR with effective treatment of follicular lymphoma. The reviewers in the current analysis were blinded to independent review committee results but were aware that patients had been categorised as non-CMR. The review was not powered to determine the association of Deauville score nor metabolic response category with patient outcomes, although there was a trend for shorter PFS and time-to-next anti-lymphoma treatment in patients with a Deauville score of 5 as previously reported in aggressive lymphomas *(8-11)*.

CONCLUSION

In some patients initially considered as non-CMR, CMR was assigned on re-review because alternative pathology was considered to be the cause of new or increased FDG uptake rather than

lymphoma, and use of the suffix ‘X’ in this circumstance is recommended as per international guidelines *(3)*. Quantitative assessment to confirm the visual impression of residual uptake in lesions is also suggested to avoid erroneous classification of non-CMR *(14,16)*.

Mesenteric FDG uptake is a common false-positive finding at the end of induction in patients with follicular lymphoma, who fail to achieve CMR, most likely due to inflammatory uptake rather than residual lymphoma, especially in the context of CMR at all other disease sites. Based on our results, contrast-enhanced CT is recommended to determine whether mesenteric uptake is accompanied by measurable disease on CT, as early progressions did not occur in patients without corresponding CT abnormalities. Furthermore, no changes in clinical management nor disease surveillance strategy are recommended when isolated mesenteric FDG uptake is present at the end of induction without measurable disease on CT or a clinical suspicion of active disease. These patients and their families can be reassured and managed as other patients with CMR.

DECLARATIONS

Availability of Data and Materials

Data availability: Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here: (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Authors' Contributions

- Study design: JT, MM, MW, SFB
- Study conduct: JT, MM, MW, SFB

- Recruitment and follow-up of patients: JT
- Data collection: JT
- Data analysis: FM, LK, MM, MW, SFB, TCE-G
- Data interpretation: AK, DS, FM, JT, MM, MW, SFB, TGN, TCE-G

All authors critically reviewed and edited the manuscript, provided their final approval of the manuscript and are accountable for all aspects of the work**.**

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KEY POINTS:

1) Isolated mesenteric FDG uptake is likely a false-positive finding at the end of induction.

2) Alternative pathology should be considered in the case of new or increased FDG uptake at the end of induction.

3) Quantitative assessment to confirm visual impression of residual uptake in lesions is suggested.

4) These results are important as patients with isolated mesenteric uptake without measurable disease on contrast-enhanced CT can be reassured and managed as other patients with CMR.

Question: What is the outcome of patients from the GALLIUM trial with follicular lymphoma treated with first-line immunochemotherapy who did not achieve CMR?

Pertinent Findings: In the PET sub-study of the GALLIUM trial, CMR on PET-CT was the sole independent predictor of overall survival in patients with follicular lymphoma; here, we investigated the outcome of patients who did not achieve a CMR. We found that isolated mesenteric FDG uptake is likely a false-positive finding at the end of induction and does not warrant changes in clinical management nor disease surveillance unless there is measurable disease on contrast-enhanced CT or clinical suspicion of active disease.

Implications for Patient Care: Our results highlight that isolated mesenteric FDG uptake is a false-positive finding at the end of induction in follicular lymphoma. We suggest contrast-enhanced CT for assessment, if appropriate, as early progression never occurred in the absence of measurable disease; this is important for clinical practice as these patients and their families can be reassured and managed as other patients with CMR.

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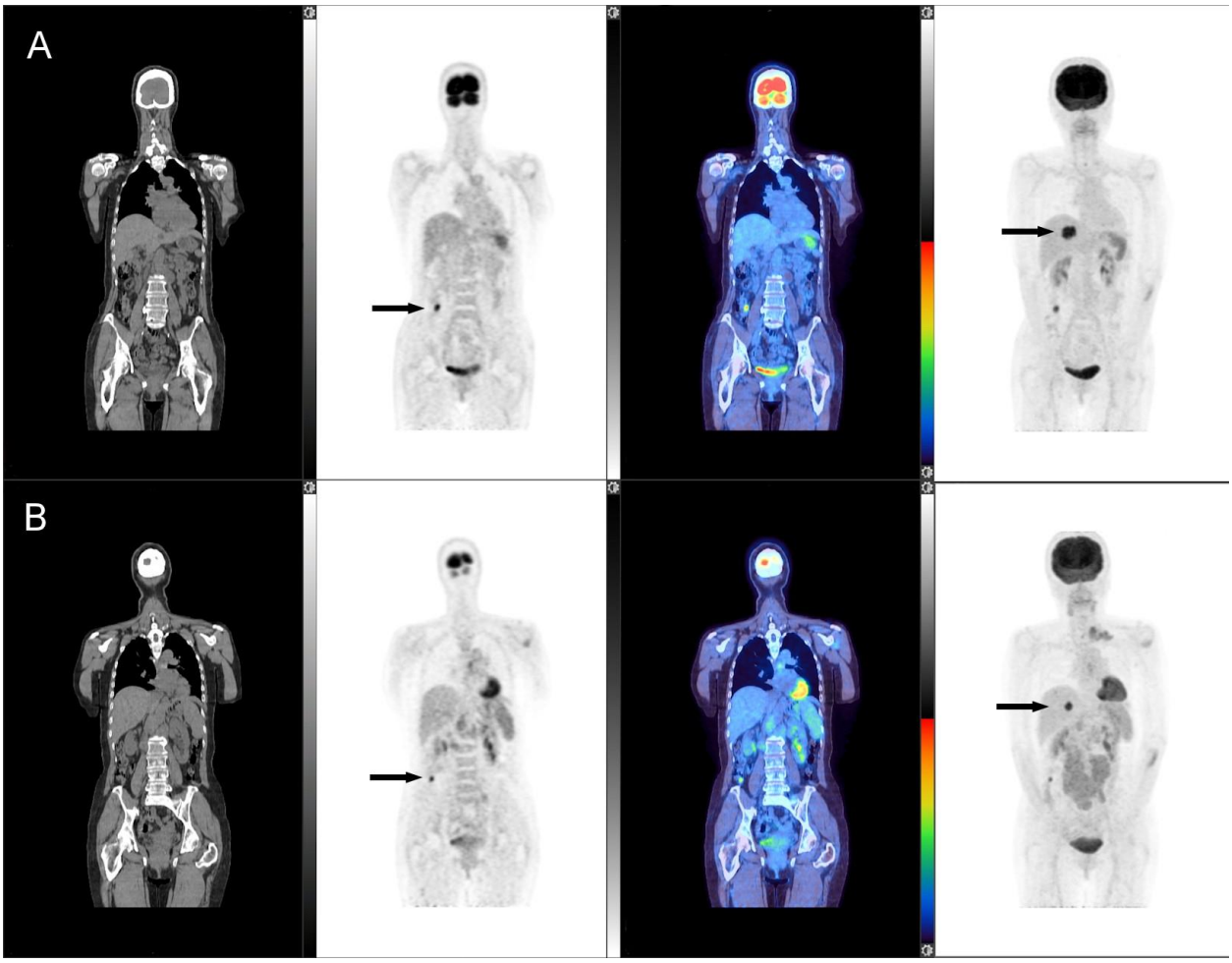
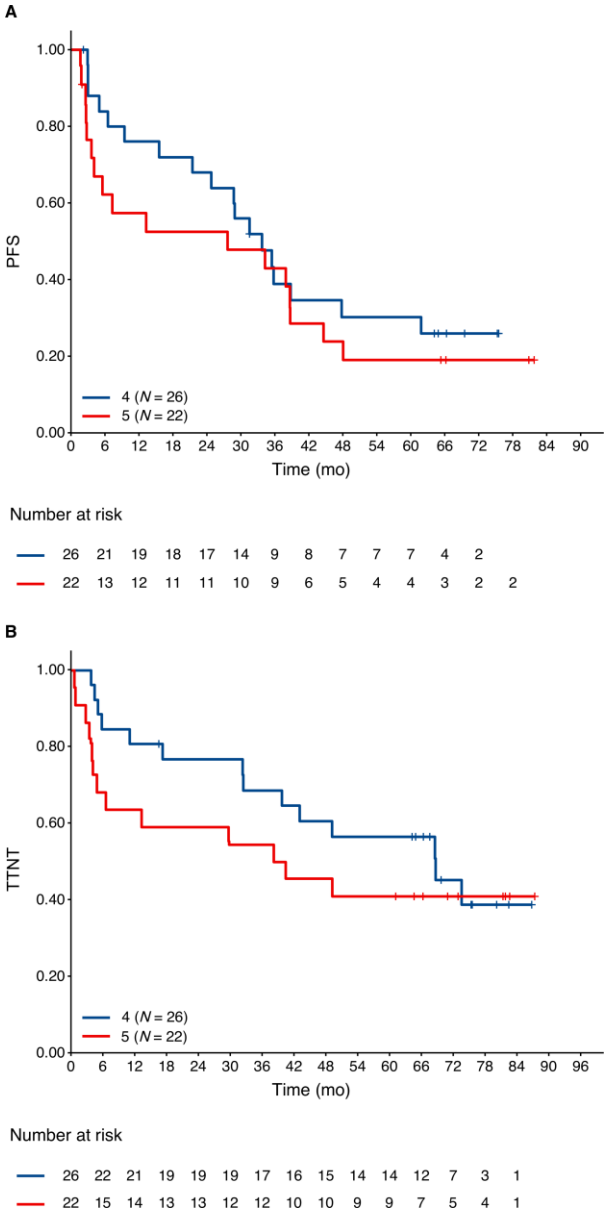
FIGURE 1. Patient scan with CT, PET, fused and maximum intensity projection coronal images. Scans at the end of induction and at baseline are shown in images A and B, respectively. FDG uptake is seen in a focus in the caecum (arrowed in A on the PET image) and in the liver (arrowed in A on the maximum intensity projection image) at the end of induction, which was increased compared with the baseline scan (arrowed in B on PET and maximum intensity projection images). There was CMR at other sites including left supraclavicular and upper abdominal nodes. The patient did not experience progression from follicular lymphoma, but biopsy of the caecum confirmed adenocarcinoma.



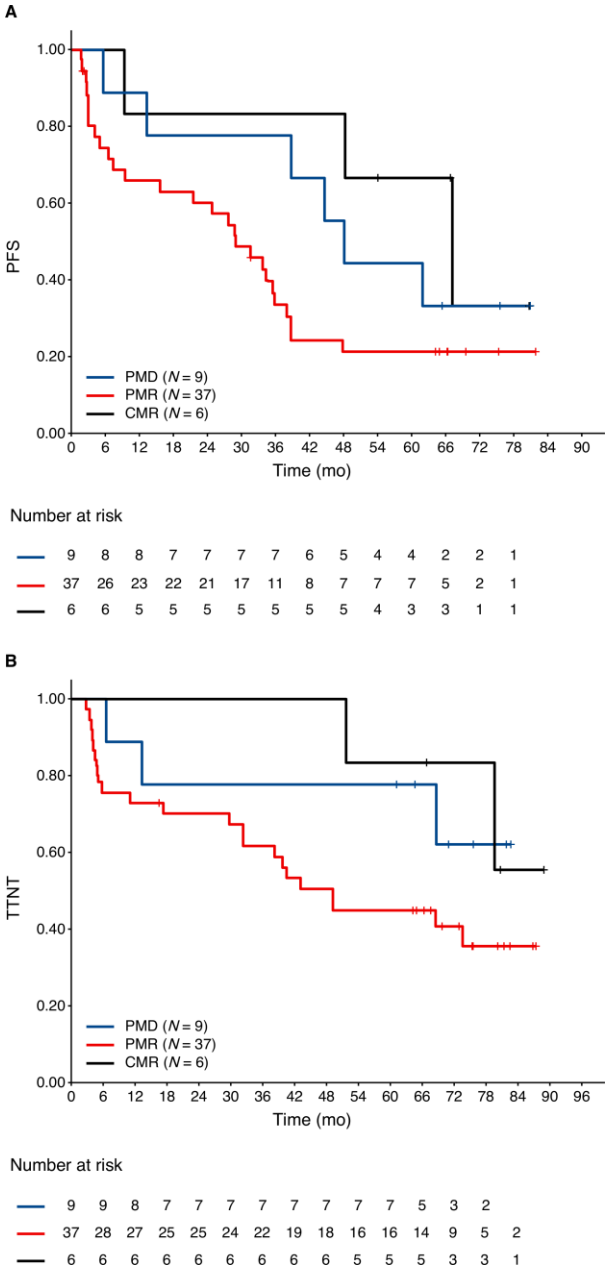
CMR, complete metabolic response; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

FIGURE 2. Landmark Kaplan-Meier plots of PFS (A) and time-to-next anti-lymphoma treatment (B) by Deauville scores 4 and 5 at the end of induction.



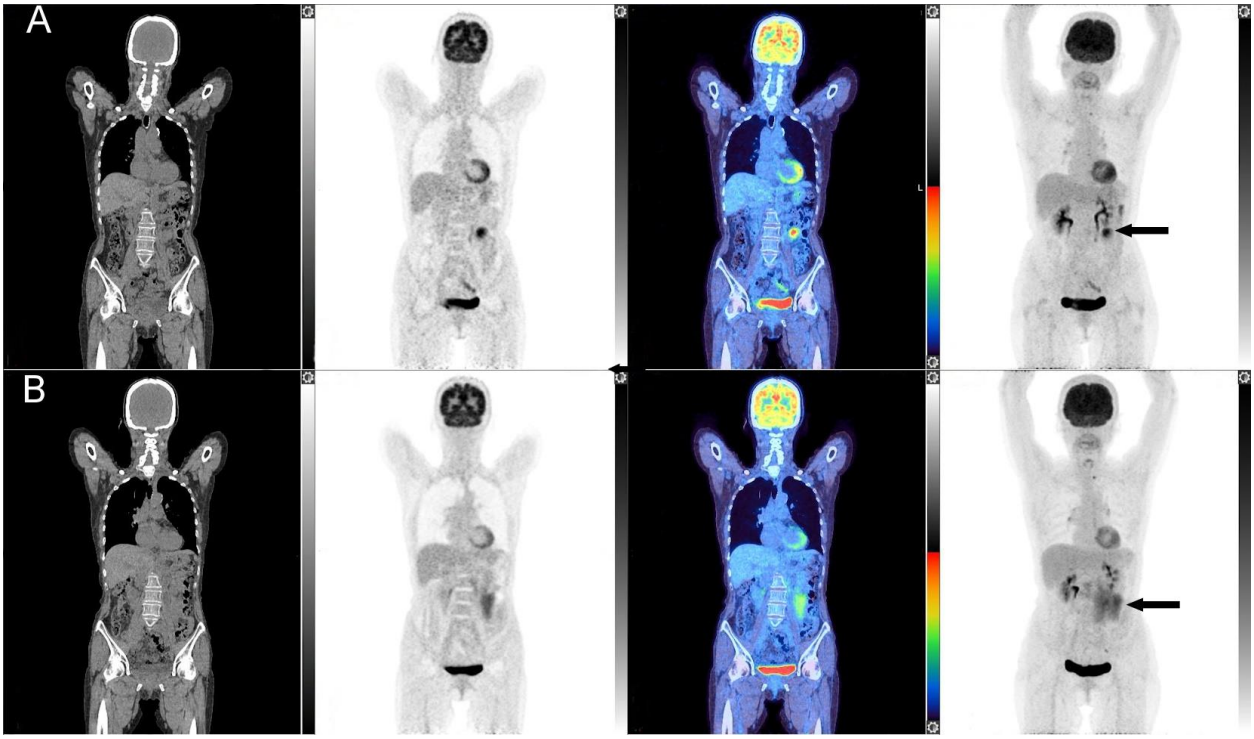
PFS, progression-free survival; TTNT, time-to-next anti-lymphoma treatment.

FIGURE 3. Landmark Kaplan-Meier plots of PFS (A) and time-to-next anti-lymphoma treatment (B) at the end of induction by metabolic response category in patients classified as non-CMR by independent review committee assessment included in this analysis.



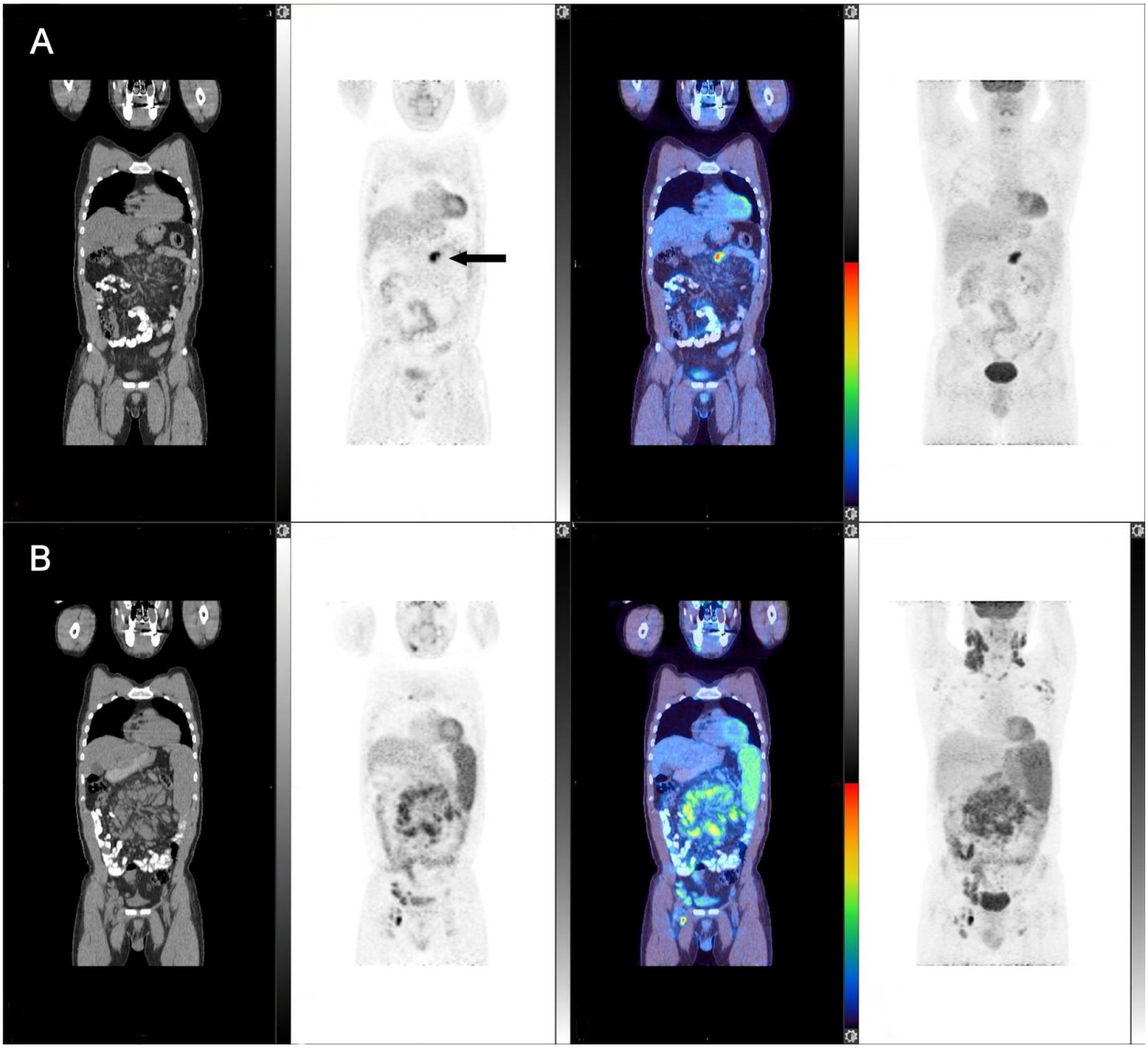
CMR, complete metabolic response; PFS, progression-free survival; PMD, progressive metabolic disease; PMR, partial metabolic response; TTNT, time-to-next anti-lymphoma treatment.

FIGURE 4. Patient scan with CT, PET, fused and maximum intensity projection coronal images. Increased FDG uptake is seen in the mesentery on the end-of-induction PET-CT scan (A) with increased uptake from baseline, SUVmax 11.4 (arrowed in A and B) with CMR at all other sites demonstrated on the baseline scan (B). The lesion measured 42 mm x 24 mm on contrast-enhanced CT and the patient experienced progression of the mesenteric node at 5.5 months on contrast-enhanced CT.



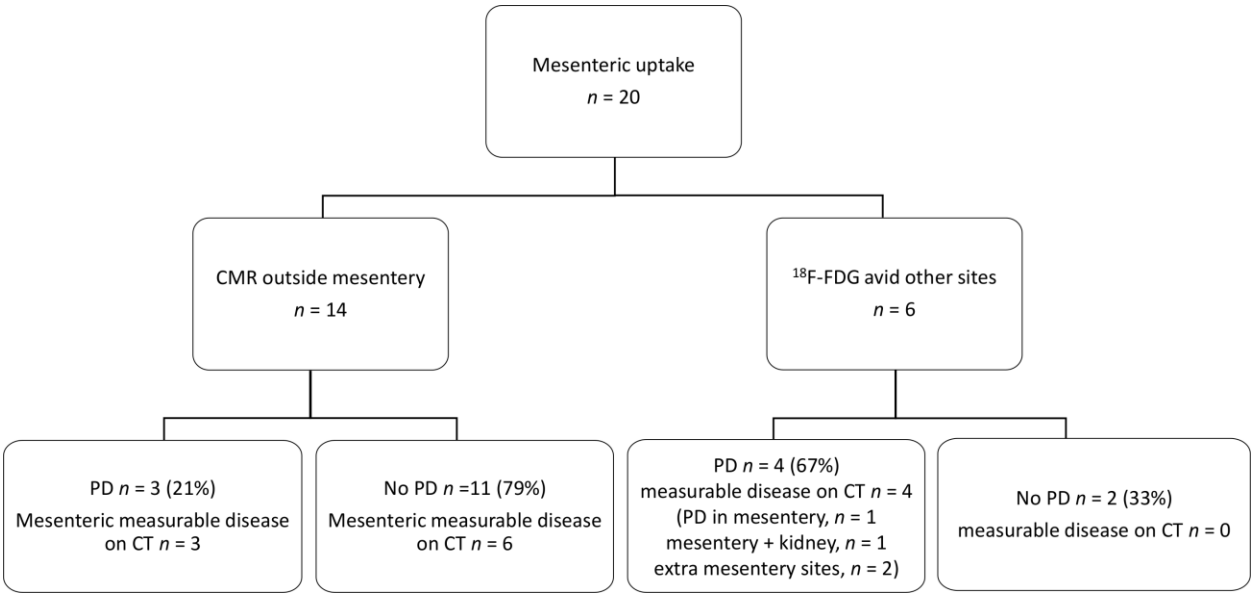
CMR, complete metabolic response; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUVmax, maximum standardised uptake value.

FIGURE 5. Patient scan with CT, PET, fused and maximum intensity projection coronal images. Residual FDG uptake is seen in the mesentery on the end-of-induction PET-CT scan (A) with increased uptake from baseline, SUVmax 11.6 (arrowed in A) with CMR at all other sites demonstrated on the baseline scan (B). The patient did not experience progression.



CMR, complete metabolic response; CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUVmax, maximum standardised uptake value.

FIGURE 6. PFS24 events on follow-up CT in patients with abnormal FDG uptake in the mesentery at the end of induction



CMR, complete metabolic response; CT, computed tomography; FDG, fluorodeoxyglucose; PD, progressive disease; PFS24, progression or death within 24 months.

GRAPHICAL ABSTRACT