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Early ^{18}F-FDG PET/CT response predicts survival in Relapsed/Refractory Hodgkin Lymphoma treated with Nivolumab

RUNNING TITLE
ePET predicts OS after anti-PD1 in HL

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ABSTRACT

Anti-PD-1 monoclonal antibodies (anti PD-1 mAbs) such as nivolumab and pembrolizumab are associated with high response rates in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL). To date, no prognostic factor for overall survival (OS) has been established with these agents in HL. We examined whether the first early response assessment evaluated using 18F-Fluorodeoxyglucose PET/CT ($ePET_1$), may be associated with OS in this setting. **Methods:** This retrospective study included 45 patients from 34 institutions. In a blinded, centralized review, three independent radiologists classified $ePET_1$ obtained at a median of 2.0 months (interquartile range: 1.7-3.7 months) after nivolumab initiation using existing criteria (*i.e.,* Lugano 2014, LYRIC 2016). Patients were classified at $ePET_1$ according to 4 possible response categories: complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD). As the OS of patients with NMR and PMR were similar, they were grouped together. OS was estimated using the Kaplan-Meier method and compared between groups using log-rank testing. **Results:** Eleven patients (24%) died after a median follow-up of 21.2 months. The classification at $ePET_1$ was identical between Lugano and LYRIC since all 16 progression events at $ePET_1$ classified as indeterminate response per LYRIC were confirmed on subsequent evaluations. Both Lugano and LYRIC 2016 classified patients as CMR in 13 pts (29%), PMD in 16 pts (36%), NMR in 4 pts (9%) and PMR in 12 pts (27%). The 2-year OS [95CI] probability was significantly different in patients with PMD (0.53 [0.32-0.87]), NMR or PMR (0.80 [0.63-1.00]), and CMR (1.00 [1.00-1.00]) in the overall population (p=0.02, n=45 pts) as well as according to a landmark analysis at 3 months (p=0.05, n=32 pts). **Conclusion:** In R/R HL patients treated with anti PD-1 mAbs, $ePET_1$ assessment using either Lugano or LYRIC predicts OS and allows early risk-stratification suggesting that $ePET_1$ may be used to develop risk-adapted strategies.

Keywords: anti-PD-1, immunotherapy, nivolumab, hodgkin lymphoma, 18F-FDG PET

INTRODUCTION

Immune checkpoint inhibition with anti-Programmed Death 1 monoclonal antibodies (anti PD-1 mAbs) has shown promising results in patients with relapsed or refractory (R/R) Hodgkin lymphoma (HL), and two agents (nivolumab and pembrolizumab) are approved in this setting.(*1,2*) Although anti PD-1 mAbs provide high overall response rates, the majority of those responses are partial and most patients eventually progress.(*3-7*) Despite this, a subset of patients may experience prolonged remissions even after anti PD-1 discontinuation.(*8*) While a greatest depth of radiographic best response may be associated with duration of response (*9,10*), no clear prognostic factor for OS, radiographic or otherwise, has yet emerged(*3,4*). In addition, a prior study of PET/CT described that new imaging patterns of response and progression, such as transient progressions and indeterminate responses, were observed in up to one-third of R/R HL patients treated with anti PD-1 mAbs(*11,12*), further calling into question the relevance of conventional radiographic response categories.

There are controversies regarding the accuracy of PET/CT in assessing response when immunological agents are used, and some authors suggest that PET/CT should not be used in HL outside of a clinical trial. A core concept of response evaluation using PET/CT is that patients with HL and a complete metabolic response (CMR) on PET/CT to chemotherapy are likely to have a durable remission and potentially be cured. Even the ability of CMR to measure response and predict clinical benefit is currently contested.(*13*) In an analysis of patients with HL treated with nivolumab, the progression free survival (PFS) and overall survival (OS) of patients with partial metabolic response (PMR) was only slightly inferior to those with CMR. This would suggest that attainment of a CMR is not a critical parameter in the new era of immunotherapy.(*3*)

In HL patients, interim PET/CT closely correlates with the outcome of patients treated with cytotoxic chemotherapies and is commonly used to guide response-adapted treatment strategies. These strategies may benefit patients either by improving the efficacy (through early treatment escalation) or by decreasing the toxicity of the treatments (through treatment de-escalation).(*14-16*) Whether early PET/CT also predicts outcome in HL patients treated with anti PD-1 mAbs remains to be determined.(*17-21*) If it were, early PET/CT could be used to define treatment duration or to change the therapeutic regimen, for example by identifying patients requiring consolidation or by reinforcing the treatment with other agent(s) to try to deepen responses and ultimately convert partial response to complete response(*3,4*). Consequently, we evaluated the prognostic value of early response evaluation ($ePET/CT_1$) in R/R HL patients treated with anti PD-1 mAbs using the 2014 Lugano and the 2016 LYRIC (Lymphoma Response to Immunomodulatory therapy criteria) classifications. To this end, three experienced radiologists, in a centralized consensus review, retrospectively analyzed 45 consecutive patients with R/R HL treated with nivolumab in 34 French centers between 2013 and 2017.

Our primary endpoint was to evaluate if early response using 18F-Fluorodeoxyglucose PET/CT (ePET) predicts overall survival in R/R HL patients treated with anti PD-1 mAb.

MATERIALS AND METHODS

Participants

To be eligible for inclusion in this retrospective multicenter study, patients had to meet with the following criteria: 1) be at least 18 years of age, 2) have confirmed evidence of relapsed or refractory HL 3) with at least one lesion measuring greater than 1.5 cm, 4) have been treated with Nivolumab anti PD-1 mAb, 5) undergo concomitant 18F-FDG PET/CT and CT scans at baseline, and 6) have at least one "early" response monitoring evaluation. Early response evaluations were scheduled according to clinicians' choice during anti PD-1 mAb therapies. From 2013 to 2017, a total of 81 eligible patients were registered in French participating centers; 45 patients were included. Thirty six patients were excluded owing to deviations from inclusion criteria (Fig. 1). Nivolumab was continued until disease progression, unacceptable toxicity, physician decision, or other reason. The decision to continue/discontinue treatment was decided onsite by clinicians during anti PD-1 mAb therapies based upon their expert assessment. This study was HIPAA compliant and approved by the institutional review board of each participating institution (IRB approval number AAAS0104, ATU NIVO number CA209-563). The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice.

Data Collection

De-identified and anonymized PET/CT images were transferred to a core imaging laboratory for image analysis. Whole-body CT scan acquisitions – head, neck, thorax, abdomen, and pelvis – were performed using multislice CT. 18F-FDG PET/CT acquisitions and reconstructions were performed according to the European Association of Nuclear Medicine guidelines(*22*).

Study Design

Study flowchart is presented in Fig. 1. A blinded and independent analysis of the CT-scan and PET/CT of each patient was performed by three radiologists (AC, FZM, LD). Radiologists were blinded to outcome, clinical data, and clinico-pathological features. Following the 2014 Lugano Classification and the LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (2016 revised criteria)(*23,24*), response categories were assigned as complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD) for PET/CT. LyRIC only adds the indeterminate response (IR) as new category at the time of first PMD. Otherwise the CMR/PMR/NMR definitions are the same. Therefore, we classified PMD at $ePET_1$ as IR1, IR2 or IR3.

Study Endpoint

The primary endpoint was overall survival (OS). The failure event for OS was defined as death due to any cause. Survival time was measured from the date of anti PD-1 mAb treatment initiation to the date of death or last follow-up. Progression-free survival (PFS) was a secondary endpoint. PFS was defined as the time from anti PD-1 mAb treatment initiation to disease progression or death from any cause. According to the LYRIC criteria, the disease progression was the last unconfirmed PMD occurring before either a subsequently confirmed PMD or the

end of the follow-up. As an alternative metrics, we used modified PFS (mPFS) defined as the time to progression, death or receipt of additional anticancer therapy for patients who are not in complete response after completion of nivolumab therapy per independent review.

Best overall response (BOR), PFS, and mPFS in this cohort were derived from the evaluation of all available on-treatment imaging timepoints (performed at ~3 month intervals) using the 2016 LYRIC modifications (average of 4.5 PET/CT examinations per patients).

Treatment duration was defined as the time from anti PD-1 mAb treatment initiation to the last cycle of therapy recorded by the investigators at the time of data collection.

Statistical Analysis

Patients were classified in four response categories at $ePET_1$: complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR), or progressive metabolic disease (PMD). The difference in OS, PFS and mPFS between those groups was assessed using log-rank testing (Kaplan-Meier analysis). Landmark analysis was performed to adjust for immortal time bias. Landmark analysis split the follow-up time at a prespecified 3-month time point. Groups are then defined by response categories at $ePET_1$ having occurred before the landmark, and outcome events are only considered if occurring after the landmark. The goal of the landmark method is to estimate in an unbiased way the time-to-event probabilities in each group conditional on the group membership of patients at a specific time point, the landmark time. All analyses were conducted using Microsoft Excel (v2019, Microsoft, USA, 2019), SPSS (v25.0, IBM, USA, 2017), and R (Version 1.2.1335).

RESULTS

Patients' Characteristics

Patients' characteristics are described in Supplemental Table 1 in the overall population as well as per early response according to ePET/CT_1. Among the 45 included patients, the median age in the study population was 39 years (range: 18 to 77 years), and 56% of patients were men. Four percent had Ann Arbor stage I disease, 18% stage II, 20% stage III, and 49% stage IV disease. Patients had received a median number of 6 (range: 3-13) prior lines of therapy. Brentuximab Vedotin was received in 42 pts (93%). Fifty-eight percent of patients had previously received an autologous stem cell transplantation and 53% prior radiation therapy. Median treatment duration with anti PD-1 mAb was 7.3 months (range, 0.5 to 24.2 months).

Early Response Evaluation

Early response evaluation was performed at a mean time of 3 months (standard deviation = 2.3 months) after anti PD-1 mAb initiation (ePET/CT_1). The median time was 2.0 months (interquartile range: 1.7-3.7 months). The distribution of the delay between treatment initiation and $ePET_1$ was similar in all response categories (Supplemental Fig. 1). The response at ePET/CT_1 was CMR in 13 pts (29%), PMD in 16 pts (36%), and NMR or PMR in 16 patients (36%) (Supplemental Figs. 1-3).

Overall Survival

Eleven R/R HL patients (24%) died during the follow-up after anti PD-1 mAb initiation. Median OS was not reached (Table 1 and Fig. 2). Early response evaluation using ePET/CT_1 stratified patients into three risk groups for OS (P=0.02): high risk (PMD patients) with 2-year OS: 0.53 (95CI: 0.32-0.87), intermediate risk (NMD and PMR patients) with 2-year OS: 0.80 (95CI: 0.63-1.00), and low risk (1.00 (95CI: 1.00-1.00) (Fig. 2).
We grouped NMR and PMR because their OS was similar and this facilitated the interpretation of results since NMR were observed in only 4 pts (9%) as compared to PMR in 12 pts (27%).

Landmark Analysis For Overall Survival Analysis

In the subgroup of patients included in the landmark analysis at 3 months, all patients received an $ePET_1$ evaluation within 3 months. Thirty-two patients were included and the response at $ePET_1$ was CMR in 9 pts (28%), PMD in 12 pts (38%), and NMR or PMR in 11 patients (34%). The results observed in the overall population (n=45 pts) were confirmed by the landmark analysis (n=32 pts): early response evaluation using ePET/CT_1 was associated with OS (P=0.05) (Supplemental Table 2, Supplemental Fig. 3).

Progression Free Survival

Median PFS was 8.4 months (95CI: 3.7-13.6) (Table 1 and Supplemental Fig. 4). Early response evaluation using ePET/CT_1 was associated with PFS ($P<10^{-3}$) and stratified patients into three risk groups: high risk (PMD patients) with median PFS: 2.5 months (95CI: 1.8-7.9), intermediate risk (NMD and PMR patients) with median

PFS of 11.7 months (95CI: 3.7-NA), and low risk (CMR patients) with median PFS of 26.3 months (95CI: 11.2-NA).

Modified Progression Free Survival

Median mPFS was 11.2 months (95CI: 7.2-26.2) (Table 1 and Supplemental Fig. 5). Early response evaluation using ePET/CT_1 stratified patients into three risk groups for mPFS ($P<10^{-3}$): high risk (PMD patients) with median mPFS: 5.4 months (95CI: 1.9-19.8), intermediate risk (NMD and PMR patients) with median PFS of 11.1 months (95CI: 5.7-NA), and low risk (CMR patients) with a median PFS not reached (lower estimated 95CI: 23.4 months).

Outcome of Patients with PMD at ePET/CT_1

Using ePET/CT_1, 16 out of 45 pts had PMD according to the Lugano classification.

Using LYRIC criteria, these 16 patients with early progression were differently categorized as follows. Four patients (25%) had indeterminate responses (IR)s type 1 (≥50% increase in the sum of the product of the diameters in the first 12 weeks of therapy). Eight patients (50%) had IR2 (new lesions or existing lesion(s) with growth ≥ 50% in the context of lack of overall progression (< 50% increase) at any time during treatment). Four patients (25%) had IR3 (increase in ^{18}F-FDG uptake without an increase in lesion size or number).

We compared the rate of pseudoprogression and the OS of these 16 pts classified as IR1, IR2 and IR3. All 16 patients (4/4 IR1, 8/8 IR2, 4/4 IR3) were confirmed subsequently to have PMD on their next scan..The overall survival of patients classified as IR1, IR2 and IR3 were not statistically different (Log Rank, P=0.25) although there was a trend showing a worse OS in patients with IR2.

Although all PMD at ePET/CT_1 were subsequently confirmed on a per-patient analysis, we did observed pseudoprogressive lesions on a per-lesion analysis. In two out of these 16 progressive patients (Fig. 3), some individual lesions experienced transient progression in lesions size and metabolism (i.e., lesions were progressive then regressed) while the patients were continuing anti PD-1 mAb although it did not alter patients' response evaluation since other lesions were unequivocally progressive. Therefore, the rate of patients with pseudoprogressive lesions was 12.5% of early progressive patients (2/16) and 4.4% of the overall cohort (2/45).

DISCUSSION

The paradigm of early response assessment in Hodgkin lymphoma (HL) was developed for cytotoxic chemotherapies and its use as a model for immune-modulatory regimens has not yet been studied.(*25-27*) In a centralized review, we retrospectively analyzed 45 consecutive patients with relapsed or refractory (R/R) HL treated with nivolumab. Though early response evaluation using PET/CT guides treatment decisions, including potential treatment discontinuation, the accuracy of ePET/CT_1 for disease monitoring in patients with HL treated with immunotherapy had not been evaluated yet. Our results suggest that early response assessment in R/R HL patients treated with nivolumab predicts outcome including OS. If confirmed, this would support the use of ePET/CT to guide the management of anti-PD1 mAb treated patients, and could serve as a basis for future prospective studies to evaluate PET-guided risk-adapted strategies in HL patients treated with anti-PD1 mAb.

While pseudo-progression represents the most described atypical immune-related pattern of response in solid tumors, along with abscopal effect and hyperprogression (*11,28*), this phenomenon did not significantly alter response evaluation in our cohort. Progressive disease, based upon standard criteria, at an early time-point in patients with R/R HL treated with anti PD-1 mAb may, therefore, be considered to carry a high risk of being 'true' progression rather than pseudo-progression. The size of the cohort has allowed for comparing immune-related LyRIC criteria to conventional response criteria designed in the era of conventional cytotoxic chemotherapy in 16 patients with PMD at ePET/CT_1. All 16 early PMD, classified as indeterminate response per LyRIC criteria, were subsequently confirmed as true PMD. Nonetheless, the use of LyRIC criteria provided interesting insights. First, the rate of patients with at least one pseudoprogressive lesion at ePET/CT_1 was 12.5% of early progressive patients (2/16 pts) and 4.4% of the overall cohort (2/45 pts). Second, the incidence of the pseudoprogression phenomenon might be underestimated since imaging occurred every 3 months and might not capture pseudoprogression occurring either at earlier time points (Supplemental Fig. 1) or between two time points. Third, we observed a trend showing a worse OS in patients with indeterminate response type 2 per LyRIC criteria. Prospective or larger cohorts should confirm this but it might suggest that in R/R HL, the appearance of a new lesion could be a worse progression phenotype.

The use of modified progression-free survival (the time to progression, death, or noncomplete response and use of subsequent anticancer therapy) has gained traction after the publication of the phase III international ECHELON-1 study(*29*), which was designed to evaluate brentuximab vedotin (Adcetris) as part of a front-line chemotherapy regimen for previously untreated advanced classic Hodgkin lymphoma. Interestingly, we demonstrated that early response using ePET/CT_1 predicts mPFS. Nonetheless, there have been debates over why and when mPFS should be used as a primary endpoint. The issue that mPFS brings up is that PFS is a robust endpoint (progression or death) while when using mPFS, if a patient fails to reach CMR and then have subsequent treatment at the discretion of the investigator, that also counts as an event. The problem of mPFS is that in our series,

investigators were not blinded and independent review facility readings were not available to investigators at the time of treatment decision. Consequently, the results of mPFS presented in this study could be inherently biased.

On a wider perspective, the absence of pseudoprogression at 3 months observed in our cohort does not preclude the occurrence of unconventional patterns of response and progression. This is beyond the scope of this study but the clinical decision and PET reporting can be challenging for a radiologist with limited experience for response assessment in patients treated with anti PD-1. Therefore, radiologists should be aware that mixed responses and immune-related adverse events (iRAE) can be detected by ePET/CT_1. Medical imaging detects 74% of irAE in solid tumors and PET is known to be a highly sensitive modality.(*30*) The most frequent sites reported in solid tumors are lung, mediastinal lymph nodes (sarcoidosis-like), enterocolitis, hypophysitis, thyroiditis, hepatitis, arthritis, and pancreatitis. While we identified such irAE in our cohort, we also identified imaging findings suggestive of gastritis and hemolytic anemia.(*27*) A key message is that iRAE should not be misclassified as PMD.

Our study demonstrates that ePET/CT_1 could guide the management of HL patients treated with anti PD-1 mAb. These results can be added to the recent advances in knowledge regarding precision medicine approaches guided by medical imaging. First, we demonstrated that patients with PMD on ePET/CT_1 are associated with the shortest OS in our series. In these patients, the rate of elimination of tumor cells by immunosurveillance is lower than the rate of tumor cells escaping immunosurveillance wherein the immunologically sculpted tumor expands in an uncontrolled manner. However, it does not mean that anti PD-1 mAb do not have any antitumor activity in these patients. Some data have suggested that anti PD-1 treatment past progression could be beneficial(*3*) and that the tumor growth rate observed in PMD patients treated with anti PD-1 mAb is lower than the tumor growth rate observed during the period before anti PD-1 mAb initiation.(*11*) Second, recent reports suggested that anti PD-1 mAb could be discontinued in patients achieving complete metabolic response(*31*) and that more aggressive strategies (i.e., addition of chemotherapy, consolidation with allograft) may be required for patients who are unable to achieve a complete response.(*32*)

The limitations of this study are the retrospective analysis of a multicenter population of patients with moderate sample size. First, the sample size is small compared to datasets evaluating standard of care drugs. However, 45 patients is a large population in the new field of response assessment to immunotherapy. Second, PET acquisitions were performed in different institutions but since baseline and first response assessment were performed in the same center it did not alter response assessment. Additionally, all participating centers followed international guidelines for PET acquisition and reconstruction. Third, the patients were scanned at a median time of 2 months and the absence of coordination in-between centers had to be taken into account by performing a landmark analysis at 3 months. Fourth, this study exploring patterns of response to nivolumab confirm that ePET is an accurate tool for response assessment and constitute a validation set for previously published data by our group using pembrolizumab. Fifth, there was no biopsy available at ePET/CT_1 to correlate imaging phenotype with immune infiltration and persistence of Reed Sternberg cells. Therefore, indeterminate responses (IR) at ePET/CT_1 were

reclassified as true PMD using ePET/CT_2 (performed on average 3 months later) as the reference standard. This is in line with LYRIC guidelines and seem clinically relevant since all patients with IR at ePET/CT_1 experienced a non-equivocal metabolic and anatomical progression at ePET/CT_2 as well as a high mortality rate. Additionally, previous studies in R/R HL patients treated with pembrolizumab demonstrated the persistence of Reed Sternberg cells in all biopsied FDG-positive lesions.(*11,33*) Landmark analysis at 3 months was performed to adjust for immortal time bias. The threshold was 3 months since prior studies have shown that response assessed at an interval of 3 months after treatment initiation is usually consistent with long-term response.(*2,34*) Early PET/CT was used as the reference since a single-center pilot study suggested that PET can detect most responding patients at 3 months, although the anatomical nadir of lesions on CT-scan was not observed until 1 year after treatment initiation(*33*). Additionally, early response evaluation using PET/CT has been demonstrated to change the best overall response category in 31% of patients compared with CT scan alone.(*11*) Finally, the landmark analysis - in a subset of 32 out of 45 patients - reduces the impact that the variation in the number of cycles of therapy given before the early follow-up by $ePET_1$ could have on the study results.

CONCLUSION

In conclusion, our study demonstrates that early metabolic response predicts survival in R/R HL patients treated by anti PD-1 mAb and allows early identification of subsets of patients with high, intermediate, and low-risk of progression and death. Our findings suggest that further prospective studies may be able to confirm that ePET may be used to develop risk-adapted strategies in patients with HL treated with anti PD-1 mAb.

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KEY POINTS

QUESTION:

Does first early response assessment evaluated using Lugano 2014 or LYRIC 2016 criteria on 18F-Fluorodeoxyglucose PET/CT ($ePET_1$) predict overall survival in relapsed or refractory classical Hodgkin lymphoma treated with nivolumab immunotherapy which triggers unconventional patterns of response and progression?

PERTINENT FINDINGS:

In a blinded, retrospective, centralized review of 45 patients from 34 institutions, the classification of $ePET_1$ obtained at a median of 2.0 months after nivolumab initiation was identical between Lugano and LYRIC criteria since all 16 progression events at $ePET_1$ were confirmed on subsequent evaluations as true progression (i.e., not pseudoprogression). The 2-year OS probability was significantly different in patients classified by $ePET_1$ as PMD (53%), NMR or PMR (80%), and CMR (100%) in the overall population (n=45 pts) as well as according to a landmark analysis at 3 months (n=32 pts).

IMPLICATIONS FOR PATIENT CARE:

In relapsed or refractory classical Hodgkin lymphoma treated with nivolumab immunotherapy, $ePET_1$ assessment using either Lugano or LYRIC predicts overall survival and allows early risk-stratification suggesting that $ePET_1$ may be used to develop risk-adapted strategies.

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Fig. 1. Flow chart

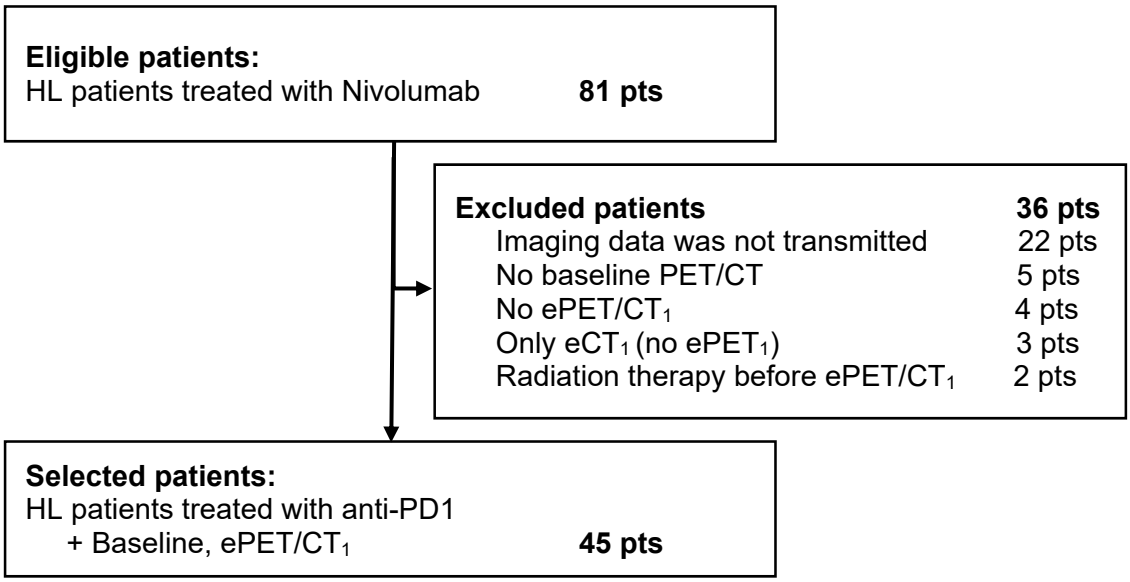


Fig. 2. Kaplan-Meier estimate of OS according to ePET1 response

In the overall population (n=45 pts), Kaplan-Meier estimate of OS from anti PD-1 mAb initiation based on ePET/CT_1 response classification, stratifying patients in three OS risk groups: high (PMD), low (CMR) and intermediate (NMR and PMR). Patients with CMR at ePET1 have a prolonged OS.

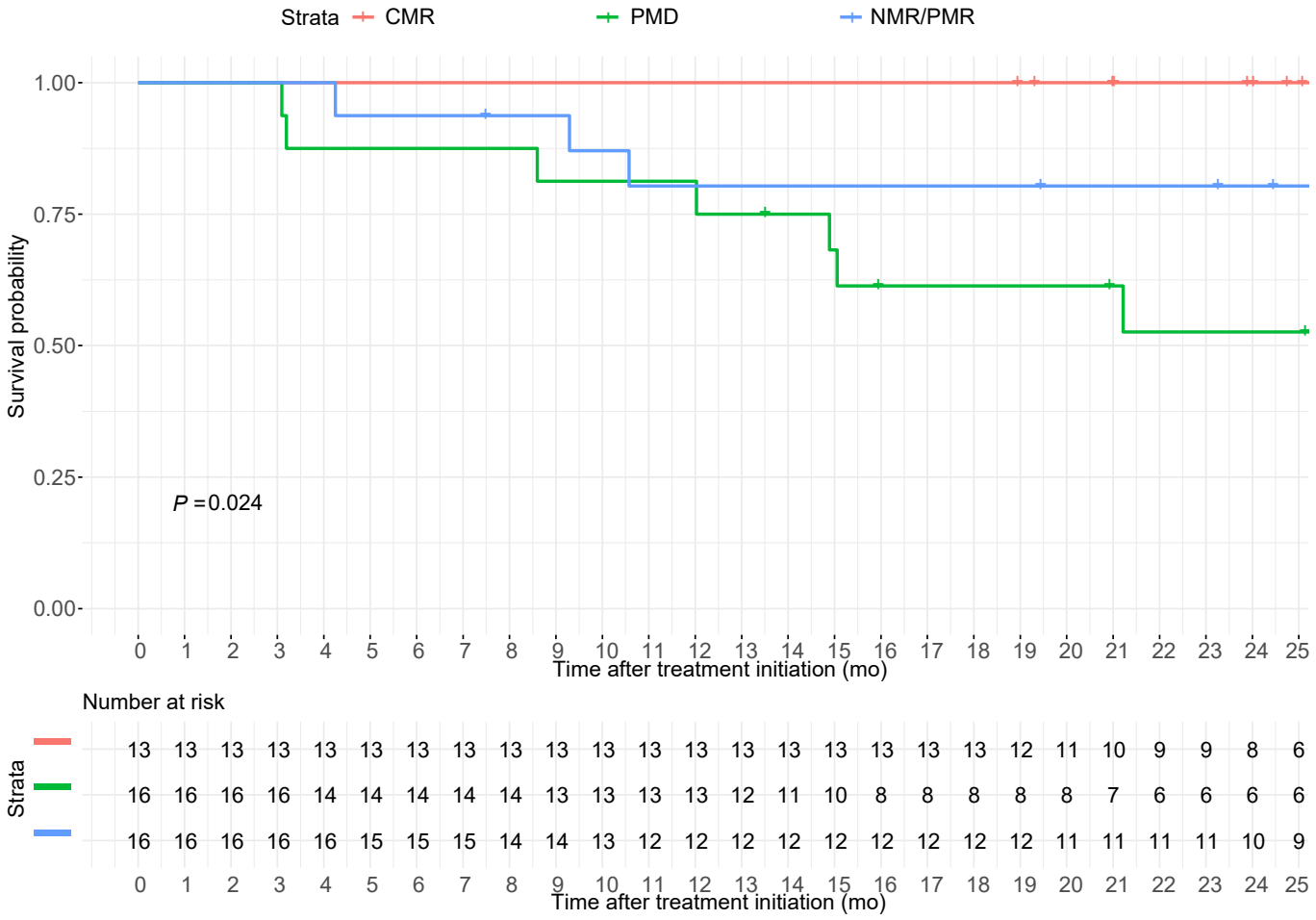


Fig. 3. Pseudoprogressive lesions at $ePET_1$ in unequivocally progressive patients

In these two patients, 18F-FDG PET/CTs were performed at baseline, month-3, and month-8. 18F-FDG PET/CTs showed unconventional immune-related phenomena regarding tumor response or progression.
A. An immune-related adverse event (hemolytic anemia) translated into an increased spleen metabolism. Transient progression in lesions size and metabolism was observed while the patient was treated with nivolumab. These pseudo-progressive lesions did not significantly alter response evaluation since they were observed in an unequivocally progressive patient. On CT-scan, the percentage of the sum of the product of the greatest diameters increased as compared to baseline by +24% at $ePET_1$ and +6% at $ePET_3$. New lesions on $ePET_1$ were confirmed on $ePET_3$.
B. This patient experienced a mixed response with true-progressive, pseudo-progressive, and complete-responding lesions. On CT-scan, the percentage of the sum of the product of the greatest diameters decreased as compared to baseline by -18% at $ePET_1$ and -56% at $ePET_2$. However, new lesions on $ePET_1$ were confirmed on $ePET_2$. The Total Lesion Glycolysis (TLG) is displayed to demonstrate the opposite trends observed in supra-diaphragmatic lesions, liver lesions, and infra-diaphragmatic lymph nodes. Quantitative approaches could be useful to guide the decision to continue treatment in unequivocally progressive patients with mixed responses.

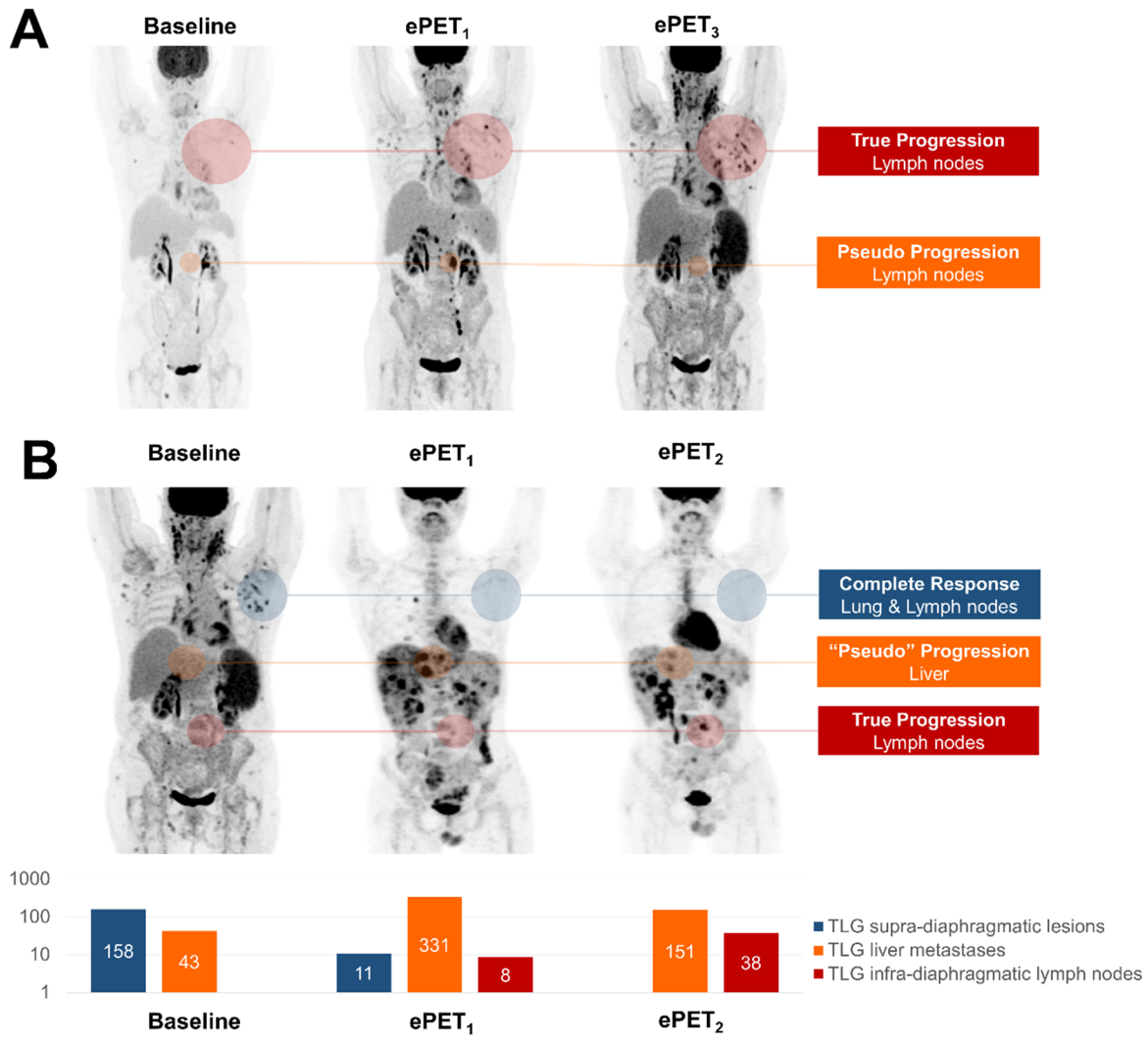


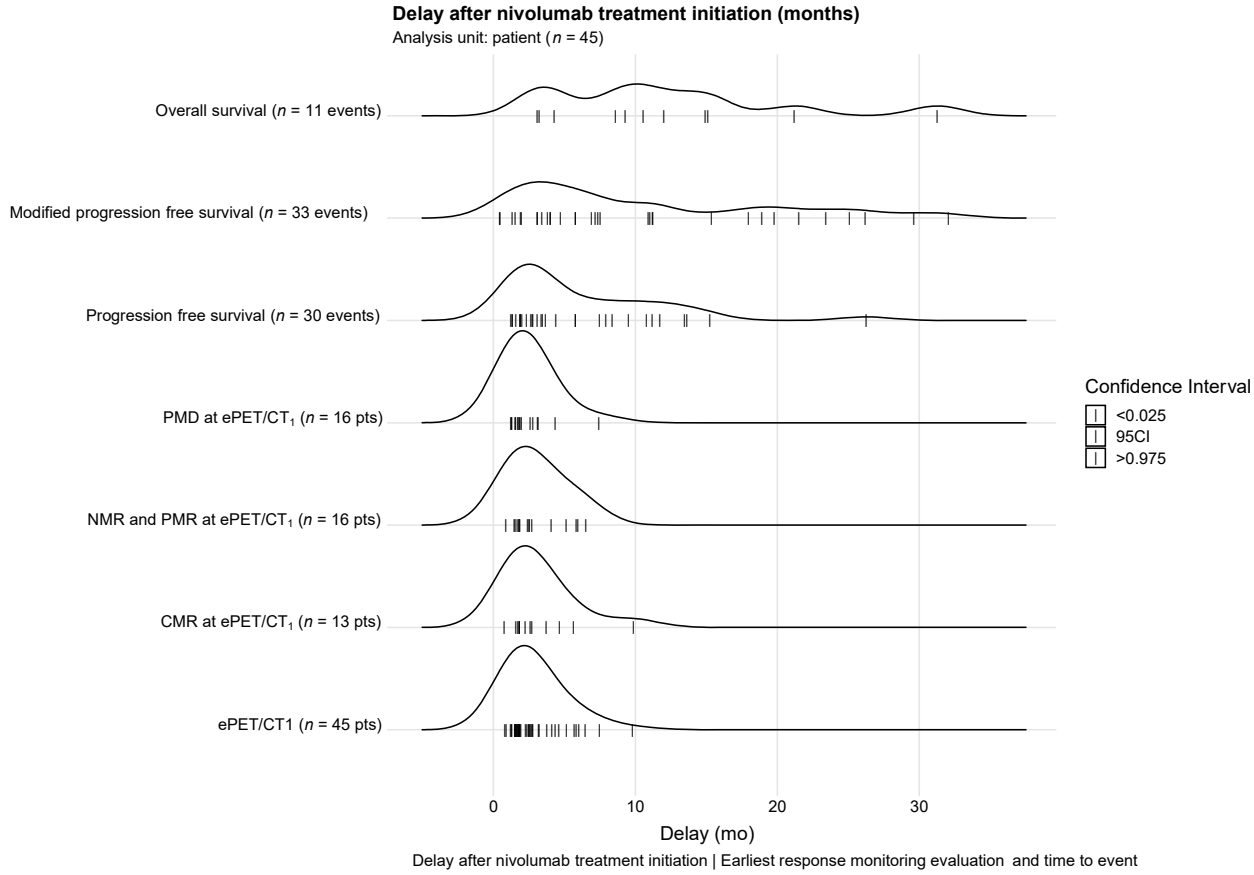
Table 1. Patients' OS, PFS and mPFS per early response on ePET/CT$_1$ (Lugano 2014)

	No. Total	24-month OS estimate (95CI, events)	Median PFS (95CI)	Median mPFS (95CI)
Overall	45 (100%)	0.77 (95CI: 0.65-0.91, n=10)	8.4 months (95CI: 3.7-13.6)	11.2 months (95CI: 7.2-26.2)
ePET/CT$_1$				
PMD	16 (36%)	0.53 (95CI: 0.32-0.87, n=7)	2.5 months (95CI: 1.8-7.9)	5.4 months (95CI: 1.9-19.8)
NMR/PMR	16 (36%)	0.80 (95CI: 0.63-1.00, n=3)	11.7 months (95CI: 3.7-NA)	11.1 months (95CI: 5.7-NA)
CMR	13 (29%)	1.00 (95CI: 1.00-1.00, n=0)	26.3 months (95CI: 11.2-NA)	NA months (95CI: 23.4-NA)
P-value		p=0.02	p<0.0001	p=0.0005

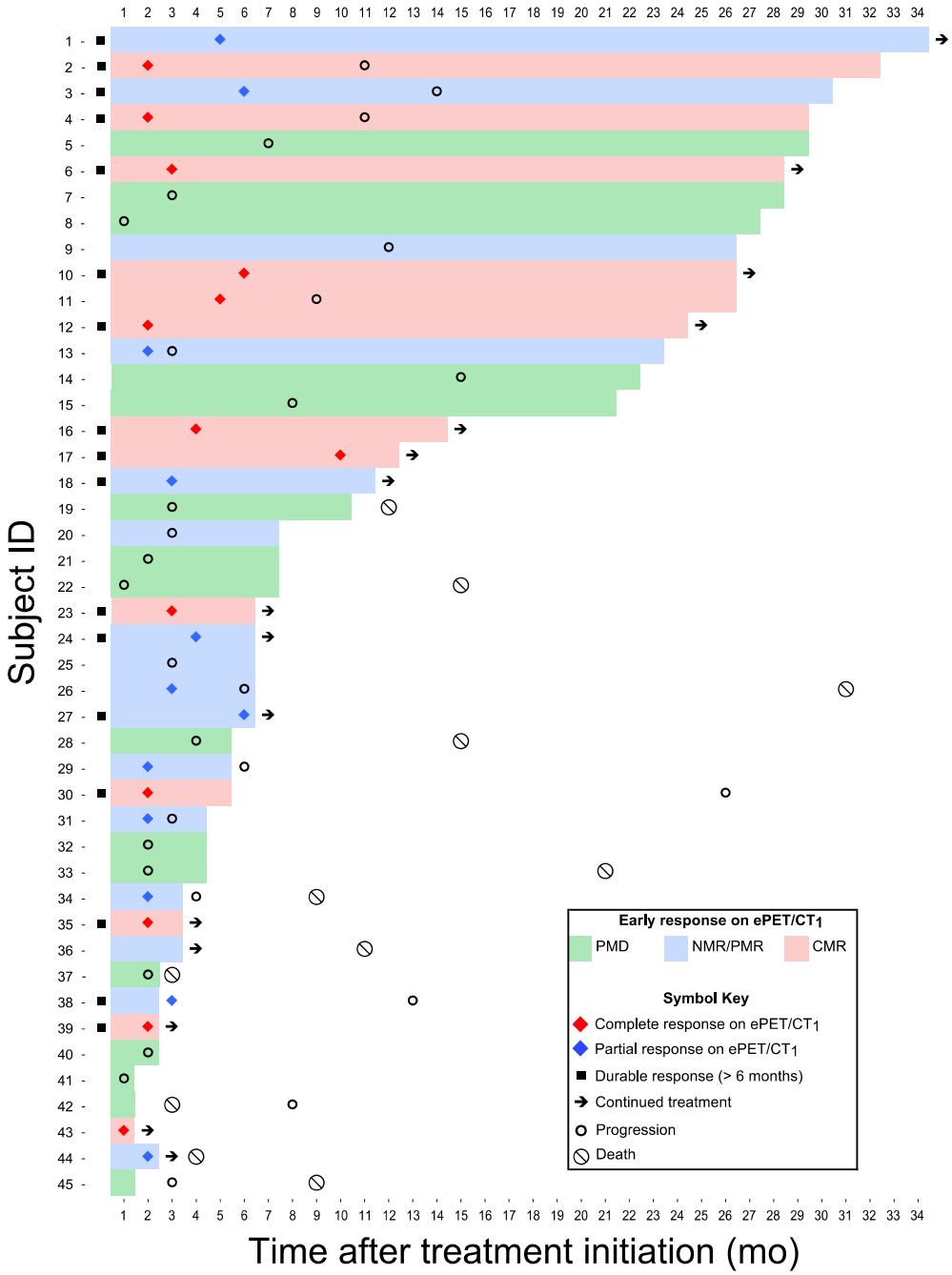
OS: overall survival, *PFS*: progression free survival, *mPFS*: modified progression free survival, *CMR*: complete metabolic response, *PMR*: partial metabolic response, *NMR*: no metabolic response, *PMD*: progressive metabolic disease. *CT*: computed tomography, *PET*: 18F-FDG PET/CT.

Supplemental Fig. 1. Distribution of ePET/CT$_1$ acquisition time, and events (PFS, mPFS, OS)

Partially overlapping line plots visualizing distributions over time in months of ePET/CT$_1$ evaluation, time to progression and time to death. Density curves represent the distribution for each category: PMD, NMR/PMR, CMR, and overall. The tails of the distributions are highlighted to represent the 95% confidence interval. Each time points are shown below each density curve using vertical lines.

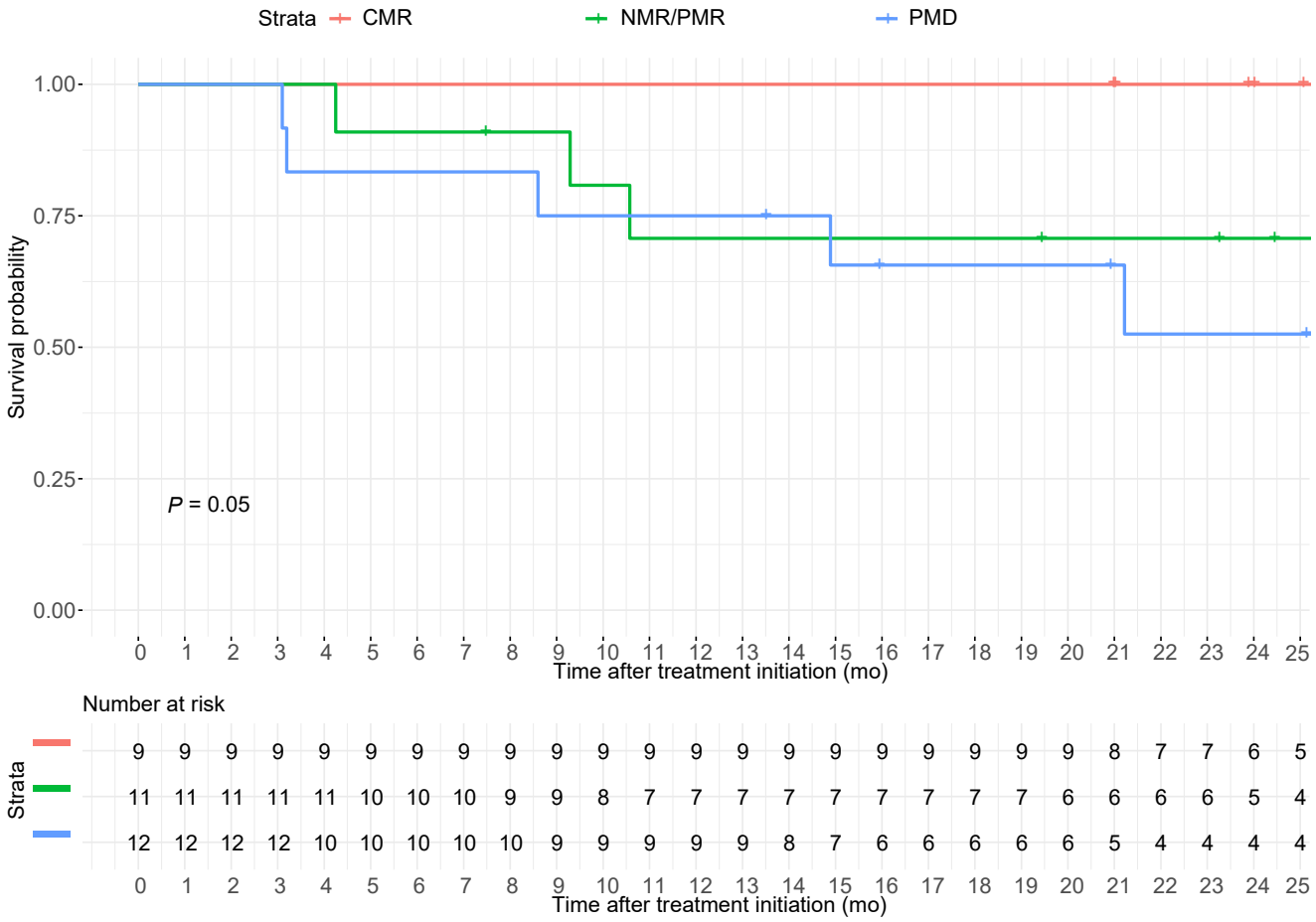


Supplemental Fig. 2. Efficacy and duration of response per ePET/CT$_1$ response categories
The panel shows a swimmer plot of outcomes in all 45 patients. The type of response (Lugano 2014) at ePET/CT$_1$ is displayed. Patients with a partial metabolic response on ePET$_1$ may experience prolonged clinical benefit on nivolumab (i.e., Patients 1 and 18). Patients with a partial metabolic response on ePET$_1$ may experience durable response after nivolumab discontinuation (i.e., patient 38 discontinued therapy at month-3). A durable response was observed after nivolumab treatment discontinuation in patients with a complete metabolic response at ePET$_1$ (i.e., patient 30). The evident clinical benefit led several centers to continue treatment beyond progression (i.e., patients 2-5). The decision to continue/discontinue treatment was decided onsite by clinicians during nivolumab therapies based upon their expert assessment. Nivolumab could be discontinued due to disease progression, unacceptable toxicity, physician decision, or other reason.

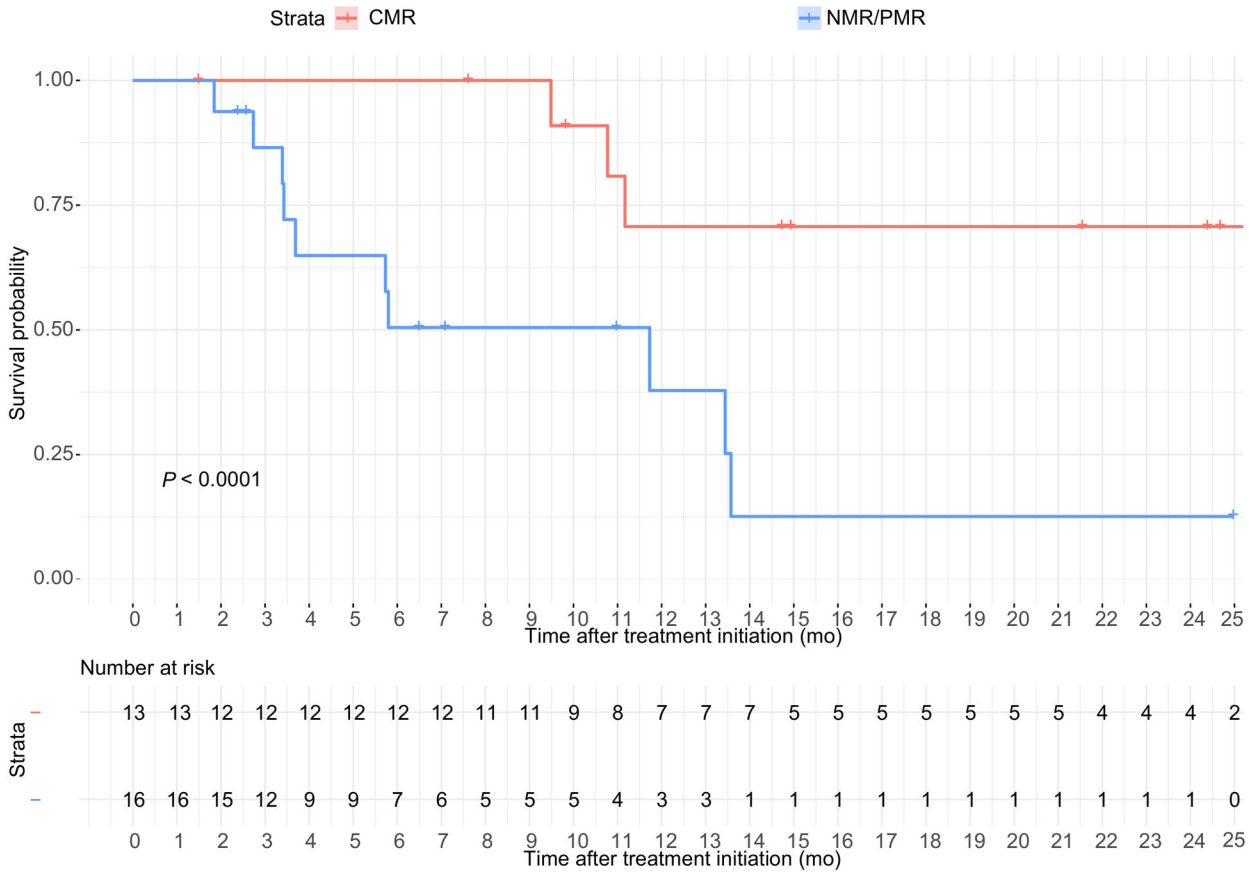


Supplemental Fig. 3. Kaplan-Meier estimate of OS according to ePET1 response

Using the landmark analysis at 3 months (n=32 pts), Kaplan-Meier estimate of OS from anti PD-1 mAb initiation based on ePET/CT_1 response classification, stratifying patients in three OS risk groups: high (PMD), low (CMR) and intermediate (NMR and PMR). Patients with CMR at ePET1 have a prolonged OS.

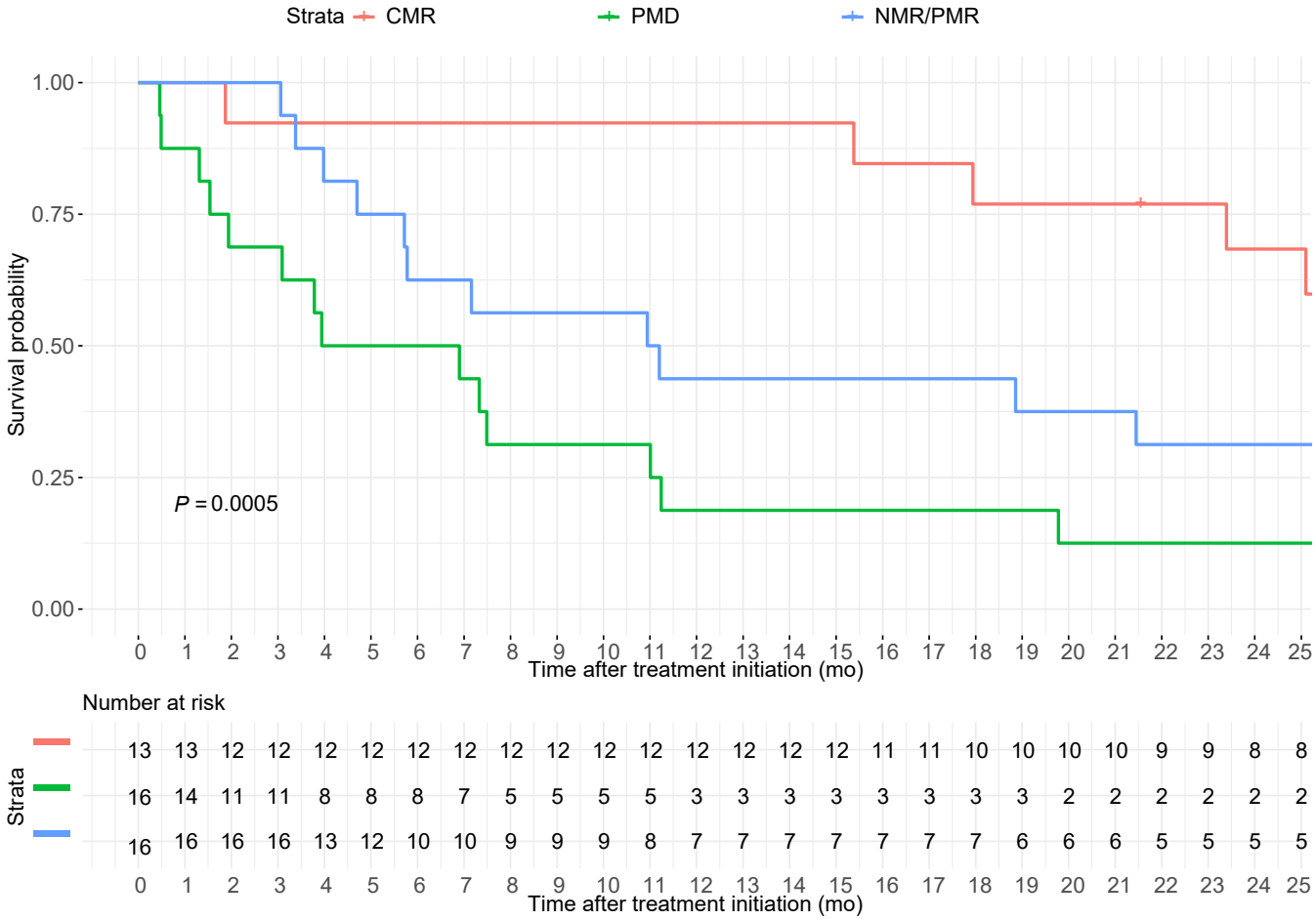


Supplemental Fig. 4. Kaplan-Meier estimate of PFS according to the response classification using ePET1
Kaplan-Meier estimate of Progression Free Survival from anti PD-1 mAb initiation based on ePET/CT_1 response classification, stratifying patients in three PFS risk groups: high (PMD), low (CMR) and intermediate (NMR and PMR). Patients classified as PMD at $ePET_1$ are not displayed in this Fig. since by definition all patients progressed at first evaluation (PET is the reference standard for response evaluation).



Supplemental Fig. 5. Kaplan-Meier estimate of mPFS according to ePET1 response

Kaplan-Meier estimate of mPFS from anti PD-1 mAb initiation based on ePET/CT_1 response classification, stratifying patients in three mPFS risk groups: high (PMD), low (CMR) and intermediate (NMR and PMR).



Supplemental Table 1. Patients' characteristics

Characteristics	Overall	Response at ePET/CT$_1$			
		PMD	NMR/PMR	CMR	p
n	45	16	16	13	
Clinical characteristics					
Male (n (%))	25 (55.6)	8 (50.0)	11 (68.8)	6 (46.2)	0.408
Female (n (%))	20 (44.4)	8 (50.0)	5 (31.2)	7 (53.8)	
Age (mean (SD))	45 (19)	51 (19)	47 (18)	33 (14)	0.025
B symptoms (n (%))	12 (26.7)	6 (37.5)	3 (18.8)	3 (23.1)	0.442
Ann Arbor stage at diagnosis					0.247
Localized	12 (26.7)	4 (25.0)	3 (18.8)	5 (38.4)	
I (n (%))	2 (4.4)	0 (0.0)	1 (6.2)	1 (7.7)	
II (n (%))	10 (22.2)	4 (25.0)	2 (12.5)	4 (30.8)	
Advanced	33 (73.3)	12 (75.0)	13 (28.3)	8 (61.5)	
III (n (%))	10 (22.2)	4 (25.0)	5 (31.2)	1 (7.7)	
IV (n (%))	23 (51.1)	8 (50.0)	8 (50.0)	7 (53.8)	
Prior treatments					
Number of prior lines (mean (SD))	6.4 (2.9)	6.69 (2.80)	5.94 (2.24)	6.46 (3.57)	0.753
ABVD (n (%))	39 (86.7)	16 (100.0)	14 (87.5)	9 (69.2)	0.053
BEACOPP (n (%))	8 (17.8)	1 (6.2)	2 (12.5)	5 (38.5)	0.062
DHAP DHAC DHAO1 (n (%))	24 (53.3)	7 (43.8)	7 (43.8)	10 (76.9)	0.130
IGEV (n (%))	5 (18.8)	3 (18.8)	1 (6.2)	1 (7.7)	0.477
GPD (n (%))	1 (2.2)	0 (0.0)	0 (0.0)	1 (7.7)	0.284
GVD (n (%))	11 (24.4)	2 (12.5)	6 (37.5)	3 (23.1)	0.256
ICE IVO1 (n (%))	15 (33.3)	7 (43.8)	5 (31.2)	3 (23.1)	0.490
IVA (n (%))	3 (6.7)	1 (6.2)	1 (6.2)	1 (7.7)	0.985
MINE (n (%))	8 (17.8)	2 (12.5)	3 (18.8)	3 (23.1)	0.754
Brentuximab Vedotin (n (%))	42 (93.3)	15 (93.8)	14 (87.5)	13 (100.0)	0.405
Radiotherapy (n (%))	24 (53.3)	10 (62.5)	5 (31.2)	9 (69.2)	0.082
Autograft (n (%))	26 (57.8)	8 (50.0)	11 (68.8)	7 (53.8)	0.530
Allograft (n (%))	9 (20.0)	2 (12.5)	4 (25.0)	3 (23.1)	0.641
Nivolumab treatment					
IRAEs (mean (SD))	1.6 (3.7)	0.44 (0.63)	1.38 (1.54)	3.23 (6.64)	0.135
Cycles (mean (SD))	5.7 (5.0)	4.73 (3.69)	7.29 (6.39)	5.00 (4.26)	0.332

Supplemental Table 2. Patients' OS per early response on ePET/CT$_1$ (Lugano 2014) (landmark analysis at 3 months)

	No. Total (%)	12-month OS estimate (95CI)	24-month OS estimate (95CI)
Overall	32 (100%)	0.81 (95CI: 0.68-0.96, n=6)	0.73 (95CI: 0.59-0.91, n=2)
ePET/CT$_1$			
PMD	12 (38%)	0.75 (95CI: 0.54-1.00, n=3)	0.53 (95CI: 0.29-0.96, n=2)
NMR/PMR	11 (34%)	0.71 (95CI: 0.48-1.00, n=3)	0.71 (95CI: 0.48-1.00, n=0)
CMR	9 (28%)	1.00 (95CI: 1.00-1.00, n=0)	1.00 (95CI: 1.00-1.00, n=0)
P-value		p=0.05	

OS: overall survival, *CMR*: complete metabolic response, *PMR*: partial metabolic response, *NMR*: no metabolic response, *PMD*: progressive metabolic disease. *CT*: computed tomography, *PET*: 18F-FDG PET/CT.