Journal of Nuclear Medicine, published on November 27, 2020 as doi:10.2967/jnumed.120.254508

# Response evaluation and survival prediction following PD-1 immunotherapy in patients with non-small-cell lung cancer: comparison of assessment methods.

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**Declarations:**

**Funding:** Not applicable

**Conflicts of interest:** The authors declare that they have no conflict of interest.

All authors have read and approved the submitted manuscript.

**Short Running Title:** Anti-PD-1 response assessment in NSCLC
**Word count:** 4987

## ABSTRACT

Immunotherapy using programmed cell death (PD)-1 blockers is a promising therapeutic modality for non-small-cell lung cancer (NSCLC). Therefore, defining the most accurate response criteria for immunotherapy monitoring is of great importance in patient management. This study aimed to compare the correlation between survival outcome and response assessment assessed by PET Response Criteria in Solid Tumors (PERCIST) 1.0, immunotherapy-modified PERCIST (imPERCIST), Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immunotherapy-modified RECIST (iRECIST) criteria in NSCLC patients.

**Methods:** Seventy-two patients with NSCLC treated with nivolumab or pembrolizumab with baseline and follow-up $^{18}$F-FDG PET/CT data were analyzed. The patients were categorized into responders (complete or partial response) and non-responders (stable or progressive disease) according to PERCIST1 and PERCIST5 (analyzing the SULpeak of one or up to five lesions), imPERCIST1, imPERCIST5, RECIST and iRECIST. The correlation between achieved response and overall survival (OS) was compared.

**Results:** The overall response rate and the overall disease control rate of the study population were 29% and 74% respectively. The OS and progression free survival (PFS) of patients with complete and partial response were statistically comparable. The OS and PFS were significantly different between responders and non-responders (20.3 vs. 10.6 months, p=0.001 for OS and 15.5 vs. 2.2 months p<0.001 for PFS respectively). Twenty-three (32%) patients with progressive disease according to PERCIST5 had controlled disease according to imPERCIST5; follow-up of patients showed that 22% of these patients had pseudoprogression. The overall incidence of pseudoprogression was 7%. The response rate was 25% and 24% according to PERCIST1 and PERCIST5 (p=0.2), and 32% and 29% according to imPERCIST1 and imPERCIST5 (p=0.5), respectively, indicating no significant difference between analyzing the SULpeak of only the most FDG-avid lesion and analyzing up to the 5 most FDG-avid lesions.

**Conclusion:** The achieved response by all conventional and immunotherapy-modified methods was strongly correlated with patients' survival outcome, with significantly longer OS and PFS in responders than in non-responders according to all assessed definitions. The most FDG-avid lesion according to the PERCIST and imPERCIST criteria accurately reflects the overall metabolic response.

**Keywords:** PD-1 inhibitor; non-small-cell lung cancer; PERIST; imPERCIST

## INTRODUCTION

Programmed death (PD)-1 is one of the main tumor-mediated immune resistance pathways preventing the reaction of T cells to tumor cells (*1,2*). The ability of PD-1 inhibitors to block the PD-1 pathway, has resulted in a paradigm shift in the treatment of a variety of solid tumors (*3-7*). The accurate assessment of response to these therapies is of critical importance in making treatment decisions as reported disease progression is equivalent to treatment failure and necessitates that patients discontinue the treatment and switch to an alternative therapeutic modality (*2*). However, because PD-1 inhibitors stimulate the host antitumor response, a favorable response may initially present with not only an increase in the size and metabolic activity of the existing tumoral lesions but also the appearance of new inflammatory lesions that may appear to be due to progressive disease (*1-3,8*). To address this issue, immunotherapy modified Response Evaluation Criteria in Solid Tumors (iRECIST) and immunotherapy modified PET Response Criteria in Solid Tumors (imPERCIST) were introduced, aiming to assist with discrimination between disease progression and pseudoprogression (*3,8-11*). An ongoing clinical challenge is that while the conventional criteria are vulnerable to reporting pseudoprogression as disease progression, the new immunotherapy-modified classifications may have the drawback of missing on-time diagnosis of true disease progression (*2,9*). The clinical benefit of either of these response assessment methods is still under investigation. While some studies have reported improved accuracy of response assessment using modified methods, the results of some clinical trials evaluating immune checkpoint inhibitors challenge the benefit of iRECIST and imPERCIST over RECIST and PERCIST criteria due to the low incidence of immunotherapy-related pseudoprogression observed in these trials (*1,12-15*). Additionally, it is unclear whether the immune-related response to PD-1 inhibitors follows the same pattern in all solid tumors. This reflects the importance of confirming changes in response to immunotherapy in individual cancers.

This study aimed to evaluate the correlation between survival outcome and response assessment achieved by conventional (RECIST1.1 and PERCIST1.0) and immunotherapy-modified (iRECIST and imPERCIST) methods in patients with NSCLC treated with PD-1 inhibitors and comparing the accuracy of using the first or up to five most metabolically active lesions for overall metabolic response assessment.

## MATERIALS AND METHODS

### Patients

We retrospectively assessed the efficacy of anti-PD1 antibodies (nivolumab and pembrolizumab) as monotherapies in consecutively treated patients with NSCLC between January 2014 and August 2019 by conventional (RECIST1.1 and PERCIST1.0) and immunotherapy-modified (iRECIST and imPERCIST) methods. Patients with more than 12-week intervals between either baseline $^{18}$F-FDG PET/CT (B-PET) and first dose of PD-1 or last dose of immunotherapy and follow-up $^{18}$F-FDG PET/CT (F-PET) were excluded from the study. Additionally, patients with no lesion above the liver metabolic activity threshold as defined by PERCIST (1.5 x liver SUL + 2 SDs of liver SUL), simultaneous active second malignancy, no extra-cranial lesion on B-PET, or less than three months of follow-up after F-PET were excluded (FIGURE 1).

Data collected included: baseline demographics, Eastern Cooperative Oncology Group performance status, tumour characteristics and stage of disease, treatment details and $^{18}$F-FDG PET/CT imaging data (TABLE 1). The dosing and treatment duration of pembrolizumab and nivolumab were decided according to standard guidelines and treating physicians' judgement. Endpoints evaluated were response rate, progression free survival (PFS) and overall survival (OS). The study was approved by the Austin Health Human Research Ethics Committee (approval number: Austin-20/94).

### Imaging Protocol

All patients fasted for at least 6 hours before the $^{18}$F-FDG PET studies. Blood glucose levels were checked intravenously prior to FDG injection. If the blood sugar level was less than 9 mmol/L, we proceeded with the study, and for patients with blood sugar levels greater than 10.1 mmol/L, the assessment was rescheduled. The patients with blood sugar between 9.1 and 10 mmol/L were assessed on a case-by-case basis. FDG dose was in the range of 220 to 300 MBq and was determined according to the patient's body mass index.

Patients who had more than a 30-minute difference in uptake time between B-PET and F-PET were not included in the study. Both baseline and follow-up PET/CT studies were obtained from the skull vertex to the upper thighs on a Philips Ingenuity 128 TOF PET/CT scanner. A low-dose CT scan (120 KvP; 30-50 mAs) was performed for attenuation correction and anatomical registration. Emission scans were performed for 2-3 minutes per bed position. An iterative reconstruction algorithm was applied for image reconstruction.

**Image Analysis**

Images were analyzed by two nuclear medicine specialists on a computer display using a dedicated software package (version 12.2.0; MedView Software Inc.). In addition, two radiologists blinded to the PET/CT result assessed the patients diagnostic CT for RECIST and iRECIST response assessment. In rare cases that diagnostic CT was not available, low-dose CT component of PET/CT study was used for the RECIST and iRECIST classification.

The peak standardized uptake value normalized by lean body mass (SULpeak) was determined by the software within the region of interest drawn on the liver and all metabolically active lesions. For the PERCIST and imPERCIST methods, the first and up to five lesions with the highest SULpeak (maximum two lesions per organ) were selected for further analysis. The selection of the lesions on F-PET was based on SULpeak and was independent of the lesions selected on B-PET, and the same lesions were not necessarily identified.

**Response Assessment**

Comparing the baseline and follow-up PET/CT studies, response to immunotherapy was classified into four categories: complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) and progressive metabolic disease (PMD) according to PERCIST1.0 (*13,14,16*) and imPERCIST (*16*) recommendations (TABLE 2). This analysis was subclassified into PERCIST1 and imPERCIST1 (in case one lesion with the highest SULpeak was used) and PERCIST5 and imPERCIST5 (when up to 5 lesions with the highest SULpeak were analyzed). Similarly, using RECIST 1.1 (*9,11,13*) and iRECIST (*9,11,13*) recommendations (TABLE 2), response to PD-1 inhibitor was categorized into complete response (CR), partial response (PR), stable disease (StD) and progressive disease (PD). The differences between the PERCIST and imPERCIST methods and the RECIST and iRECIST methods are shown in Table 2.

Subsequently, the patients were classified into responders (CR/CMR and PR/PMR) and non-responders (StD/SMD and PD/PMD) and controlled (CR/CMR, PR/PMR and StD/SMD) and uncontrolled (PD/PMD) disease in all investigated response assessment methods.

**Statistical Analysis**

Frequency statistics were obtained using frequency tables and descriptive analysis using SPSS software (version 26.0; SPSS Inc.). Comparisons of quantitative variables were performed using

independent t-tests for independent groups and paired t-tests for dependent variables. Chi-square and McNemar tests were used for comparison of nominal variables between independent and dependent groups, respectively. Survival analysis was performed using the Kaplan-Meier method, and log-rank statistics were used for comparison. $P<0.05$ was considered significant in all comparisons.

## RESULTS

A total of 134 patients were identified of which 72 patients were included in this study (Figure 1). Baseline data are detailed in Table 1. The mean age was 65.8 years, the majority were male (63%) and all patients had an Eastern Cooperative Oncology Group performance status of ≥ 2. The median ICI cycles between PET studies was four for both nivolumab and pembrolizumab, time from B-PET/CT to first ICI dose was 21.5 ± 20.7 days and time from last ICI dose to F-PET/CT was 17 ± 8.19 days.

### Correlation of Response Categories with OS and PFS

The mean OS of the study population was 13.7±11.8 months (range: 0.97 to 53.8 months) with PFS of 6.39±11.2 months based on overall staging parameters. The six, 12, 18 and 24-months OS rate were 71%, 46%, 29% and 18%, respectively. Figure 2 demonstrates the OS rates in different response groups according to PERCIST5 and imPERCIST5 (FIGURE 2). The overall response rate and the overall disease control rate were 29% and 74% respectively.

The mean OS and PFS was statistically similar between the complete response and partial response groups according to any of the criteria. Comparing stable disease with progressive disease groups, OS was statistically similar in these two population as well. Therefore, each pair was grouped together, resulting in two categories: responders (CR/CMR and PR/PMR) and non-responders (StD/SMD and PD/PMD). According to imPERCIST, the mean OS was 20.3±14.7 months among responders and 10.6±8.7 months among non-responders ($P=0.006$), and the mean PFS was 15.5±14.2 months among responders and 2.2±6.1 months among non-responders ($P<0.001$). The PFS and OS were also significantly different between responders and non-responders according to the other five evaluated methods. Table 3 compares OS between patients with complete response and partial response, and patients with stable disease and progressive disease according to all assessed criteria (TABLE 3). The difference in OS between responders and non-responders is illustrated in figure 3.

**Comparison of Conventional and Immunotherapy-modified Methods Regarding Metabolic Response Assessment**

In the comparison between PERCIST and imPERCIST, we noted that imPERCIST recategorized five non-responders as responders (P=0.06). This occurred in four patients when comparing PERCIST5 and imPERCIST5 (P=0.12). All responders according to PERCIST were also responders according to imPERCIST regardless of the number of studied lesions. There was no statistical difference between conventional and immunotherapy-modified metabolic response assessment methods regarding the differentiation between responders and non-responders to anti-PD1 therapy. However, when the patients were classified as having controlled (n = 31) or uncontrolled (progressive) disease (n = 41), more than half of the patients (n = 23) with uncontrolled disease according to PERCIST were recategorized as having controlled disease using imPERCIST (P<0.001). Follow-up of these patients showed that among these 23 patients who had PMD according to PERCIST and who were recategorized as having SMD (83%) and PMR (17%) according to imPERCIST, five (22%) had pseudoprogression due to immunotherapy-related inflammatory lesions on follow-up, while in 16 (70%) patients, the new lesions that appeared in the follow-up PET were true metastases. The nature of the new lesions in 2 out of 23 patients remained unknown (TABLE 4). No inflammatory lesion had SULpeak above 8.8. The incidence of pseudoprogression in the overall study population was calculated at 7%.

**Comparison of Metabolic Response Assessment Methods Using One or up to Five Lesions**

Using the SULpeak of the most FDG-avid lesion or up to five of the most FDG-avid lesions in both conventional and immunotherapy-modified criteria, there was no difference between PERCIST1 and PERCIST5 (p=0.3) or imPERCIST1 and imPERCIST5 (p=0.5) in regard to the differentiation between responders and non-responders. Similarly, no statistically significant difference was identified between the evaluation of metabolic activity of one or up to five lesions in the differentiation of patients with controlled disease from those with disease progression.

**Comparison of Anatomical and Metabolic Response Assessment Methods**

When comparing RECIST and iRECIST with PERCIST and imPERCIST, no statistically significant difference was noted between RECIST and PERCIST1 (p=0.22) or iRECIST and imPERCIST1 (p=0.59) regarding response assessment.

## DISCUSSION

Immunotherapy is one of the most promising therapeutic modalities in patients with solid tumors; and the interpretation of response in patients is vital to ensure therapeutic response is accurately assessed (*12,17-19*). The present study showed comparable results using one or up to five lesions with the highest metabolic activity for both PERCIST and imPERCIST criteria, suggesting that interval change in metabolic activity of the most FDG-avid lesion can accurately reflect the overall metabolic response to PD-1 inhibitors. To the extent of our knowledge, this is the first study to evaluate this issue in patients with NSCLC. However, similar observations have been reported previously on patients with metastatic melanoma treated with immune checkpoint inhibitors (*16*).

Our study showed longer OS and PFS in responders compared to non-responders according to all evaluated response assessment methods with no statistically significant difference between conventional and immunotherapy-modified criteria. As PD-1 inhibitors stimulate the host antitumor response, unusual response patterns on both anatomical and metabolic imaging assessments are expected (*20*) and make it increasingly challenging to evaluate the effectiveness of immunotherapy agents using imaging modalities accurately (FIGURE 4).

According to our results, there was no significant difference between conventional and immunotherapy-modified metabolic response assessment methods in differentiating between responders and non-responders. However, when categorizing patients into controlled and progressive disease, the imPERCIST criteria correctly recategorized a fifth of patients with pseudoprogression categorized as having progressive disease into the controlled disease category.

Prior studies have demonstrated no significant improvement in response assessment using immune modified methods (*13,21*). Consistent with these studies, we found that conventional and immunotherapy-modified methods of assessment were not significantly different in categorizing the patients as responders and non-responders, with only 7% and 4% of patients recategorized from non-responders by PERCIST and RECIST to responders by imPERCIST and iRECIST, respectively. The best explanation is that most patients (19 out of 23, 83%) with changes in response category after using immunotherapy modified criteria transferred from PD/PMD into StD/SMD group. As the PD/PMD and StD/SMD groups are both subcategories of non-responders, no statistically significant difference was seen between these two methods.

The mean OS of patients with PD/PMD who remained in the same group after using the immune-modified method was lower than that of patients who were recategorized into StD/SMD or PR/PMR groups, favoring a better response evaluation by using immunotherapy-modified methods in both

anatomical and metabolic assessments. Similarly, Beer et al. evaluated 42 patients with NSCLC who underwent PD-1/PD-L1 inhibitor treatment and reported significantly longer median PFS and OS for responders than for non-responders for both PET-based and CT-based criteria (*18*). On the other hand, Rossi and coworkers evaluated 48 patients with advanced NSCLC who treated with immunotherapy (*17*) and observed low concordance between the $^{18}$F-FDG-PET-based (PERCIST and imPERCIST) and CT-based (RECIST1.1 and irRC) criteria, which disagrees with our results that showed a comparable OS prediction ability of metabolic and anatomical imaging (TABLE 3). Using a dual time point $^{18}$F-FDG-PET/CT scan based on the iPERCIST and PERCIST methods in 28 NSCLC patients, Goldfarb et al. showed a longer OS in responders compared to non-responders (19.9 vs. 3.6 months) and reclassification of 39% of patients using iPERCIST criteria (*22*). These findings were in concordance with our results that showed 20.3 vs. 10.6 months OS in responders vs. non-responders based on imPERCIST and 32% reclassification of patients using immunotherapy-modified criteria.

In our study, the incidence rate of pseudoprogression in patients with NSCLC treated with immunotherapy was 7%, which is comparable to 6.6% incidence of pseudoprogression in melanoma cases after immunotherapy observed by Chiou et al. (*1*) and 8% pseudoprogression incidence reported by Martin-Romano et al. in solid tumors after immunotherapy (*23*).

There are certain limitations of this study. First, this study has a retrospective design, which may result in recruitment bias. For RECIST and iRECIST response assessment, we used a low-dose CT component of 18F-FDG PET/CT when diagnostic CT was not available, which may not be as accurate as diagnostic CT. Additionally, due to limited number of patients treated with pembrolizumab, comparing different response criteria in patients treated with pembrolizumab and nivolumab was not performed. Finally, predictive biomarkers were not used for comparison with results.

## CONCLUSION

Both conventional and immunotherapy-modified anatomical and metabolic response assessment methods have a strong ability to discriminate between responders and non-responders. The most FDG-avid lesion on the PERCIST and imPERCIST criteria accurately represents the overall metabolic response.

**Financial disclosure:** There are no potential conflicts of interest relevant to this article.

**KEY POINTS**

**QUESTION:** What is the correlation between survival outcome and response assessment assessed by PET Response Criteria in Solid Tumors (PERCIST) 1.0, immunotherapy-modified PERCIST (imPERCIST), Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immunotherapy-modified RECIST (iRECIST) criteria in NSCLC patients following PD-1 immunotherapy?

**PERTINENT FINDINGS:** In a retrospective study of seventy-two patients with NSCLC treated with nivolumab or pembrolizumab with baseline and follow-up $^{18}$F-FDG PET/CT data, the overall response rate and the overall disease control rate of patients with complete and partial response were statistically comparable between groups, and there was no significant difference between analyzing the SULpeak of only the most FDG-avid lesion and analyzing up to 5 most FDG-avid lesions.

**IMPLICATIONS FOR PATIENT CARE:** These results indicate that the most FDG-avid lesion according to PERCIST and imPERCIST criteria accurately reflects the overall metabolic response, and could be utilized in assessing response to PD-1 immunotherapy in NSCLC patients.

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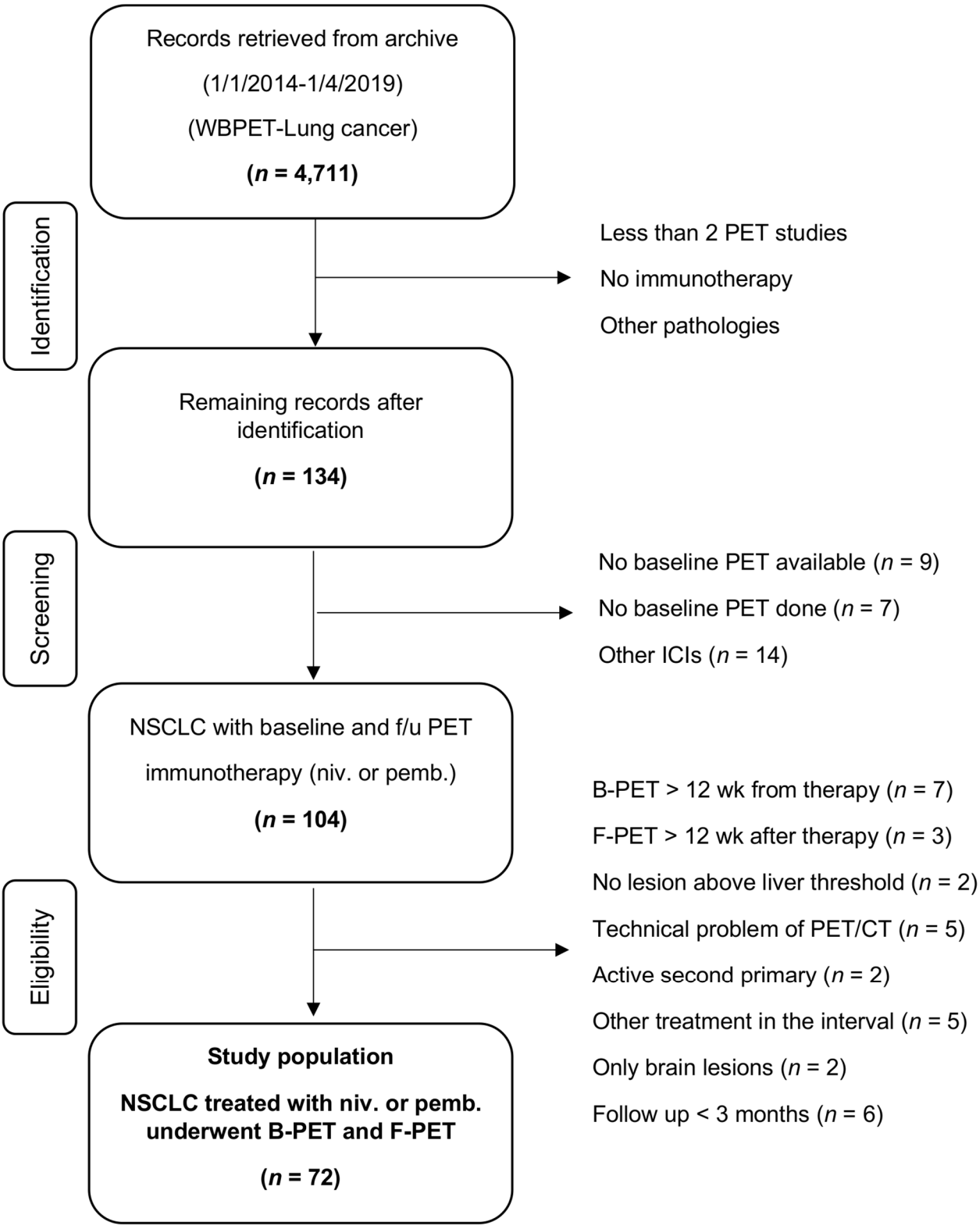



**FIGURE 1:** Flowchart

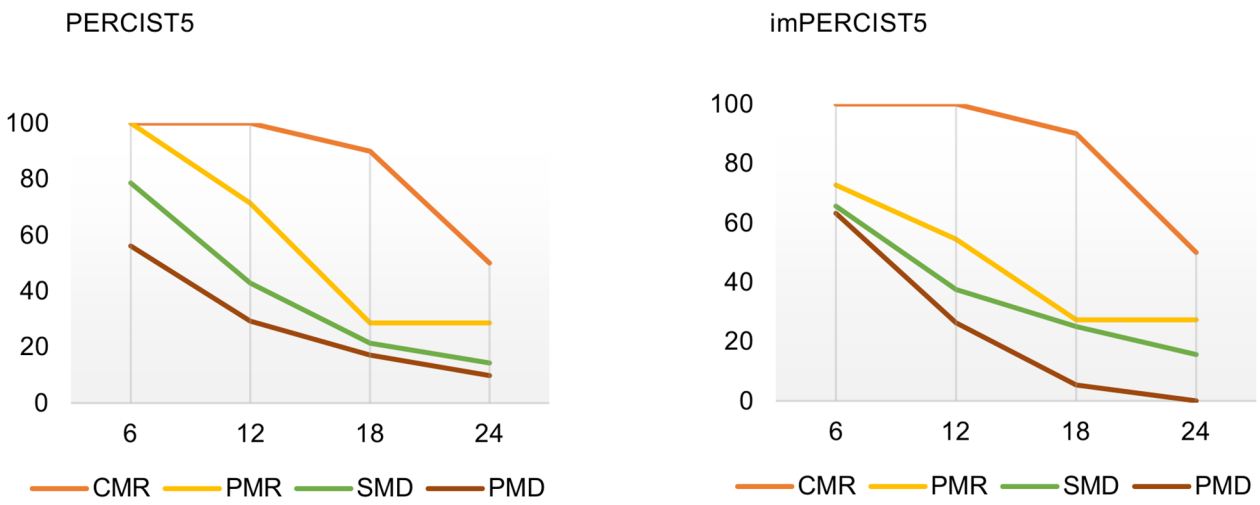



**FIGURE 2:** The overall survival rate in different response groups according to PERCIST5 (A) and imPERCIST5 (B)

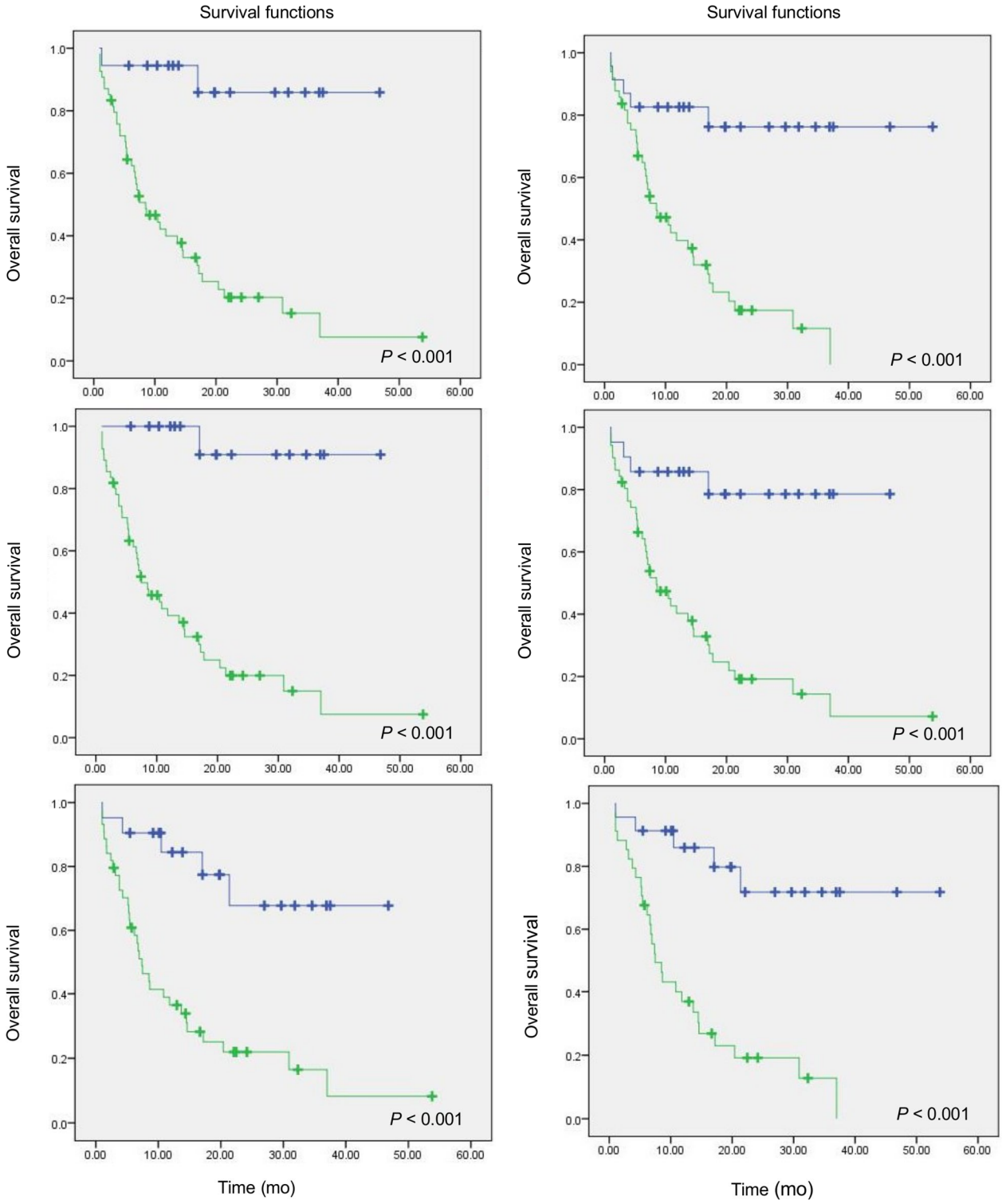
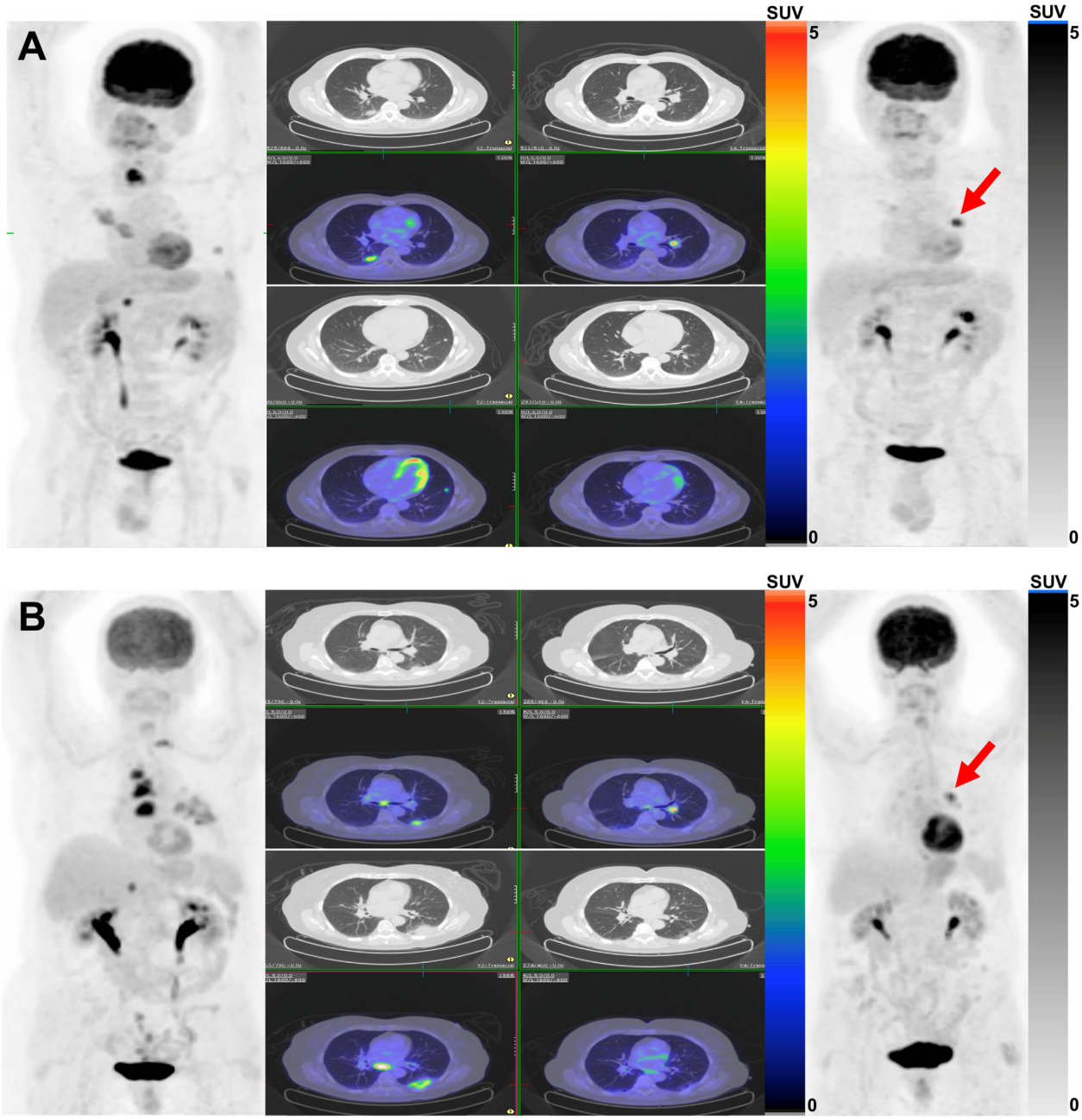



**FIGURE 3:** Survival curve of responders (blue line) versus non-responders (green line) using PERCIST1 (Top Left), imPERCIST1 (Top Right), PERCIST5 (Middle Left), imPERCIST5 (Middle Right), RECIST (Bottom Left) and iRECIST (Bottom Right)

**FIGURE 4:**




A: 54-year-old man with metastatic right lower lobe lung adenocarcinoma. The baseline PET/CT (left) demonstrates multiple pulmonary, thyroid and right adrenal metastatic lesions. The highest SULpeak belongs to the thyroid lesion (SULpeak: 13.0). After 4 cycles of nivolumab, follow-up PET/CT (right) showed excellent metabolic response of previous lesions along with interval development of a new left pulmonary hilar lesion (SULpeak: 7.8) (arrow). The response was assessed as PMD according to PERCIST and, PMR based on imPERCIST (SUL change: 39.9%). This hilar node spontaneously resolved after two months and he is on complete remission since then.

B: 70-year-old man with metastatic left lower lobe lung adenocarcinoma. The baseline PET/CT (left) demonstrates multiple nodal, T2 thoracic vertebral and right adrenal metastatic lesions. The highest SULpeak belongs to a paratracheal nodal metastasis (SULpeak: 10.7). After 6 cycles of nivolumab, follow-up PET/CT (right) showed excellent metabolic response of the previous lesions along with interval development of a new left pulmonary hilar lesion (SULpeak: 6.1) (arrow). The response was assessed as PMD according to PERCIST and, PMR based on imPERCIST (SUL change: 43.4%). Patient's follow-up confirmed metastatic nature of the hilar lymph node.

**TABLE 1:** General characteristics of the patients, tumour, immunotherapy and $^{18}$F-FDG PET/CT studies

| Characteristic | | Total (%) *n* = 72 |
|---|---|---|
| Age (y) | | 65.8 ± 16.1 |
| Sex* | Male | 45 (63) |
| | Female | 27 (38) |
| Subtype* | Adenocarcinoma | 43 (60) |
| | Squamous cell carcinoma | 21 (29) |
| | Large cell carcinoma | 7 (10) |
| | N/A | 1 (1) |
| Stage* | I | 1 (1) |
| | II | 9 (13) |
| | III | 23 (32) |
| | IV | 29 (40) |
| | N/A | 10 (14) |
| PD-1 Inhibitor* | Nivolumab | 62 (86) |
| | Pembrolizumab | 10 (14) |
| ICI cycles between 2 PET studies | | 2-8 (Median: 4) |
| Time from B-PET/CT to 1st ICI+ (days) | | 21.5 ± 20.7 |
| Time from last ICI to F-PET/CT+ (days) | | 17 ± 8.19 |
| $^{18}$F-FDG Dose+ (MBq) | B-PET/CT | 273.8 ± 32.9 |
| | F-PET/CT | 266.1 ± 36.2 |
| | | *P = 0.01* |
| Uptake Time+ (minute) | B-PET/CT | 68.0 ± 9.2 |
| | F-PET/CT | 68.1 ± 10.0 |
| | | *P = 0.96* |
| Blood Sugar+ (mmol/L) | B-PET/CT | 6.2 ± 1.4 |
| | F-PET/CT | 6.3 ± 1.5 |
| | | *P = 0.43* |
| Liver SUL+ (mean) | B-PET/CT | 1.7 ± 0.2 |
| | F-PET/CT | 1.7 ± 0.2 |
| | | *P = 0.25* |

N/A = not available

* Data are number followed by percentage

+ Date are mean ± standard deviation

**TABLE 2:** Summary of PET-based and CT-based response assessment criteria for immunotherapy response evaluation

| Responses | $^{18}$F-FDG PET/CT-based criteria | | Responses | CT-based criteria | |
|---|---|---|---|---|---|
| | **PERCIST 1.0** | **imPERCIST** | | **RECIST 1.1** | **iRECIST** |
| Progressive metabolic disease (PMD) | >30% relative increase and >0.8 absolute increase in SULpeak of hottest lesion or unequivocal progression of $^{18}$F-FDG-avid non-target lesion or appearance of new FDG –avid. | defined only by an increase of the sum of SULpeaks of the 5 lesions by 30% | **Progressive disease (PD)** | ≥20% increase in sum of diameters of TLs or unequivocal progression of NL or appearance of new lesion. | iUPD: ≥20% of the sum of longest diameters compared with nadir (minimum 5mm) or progression of non-target lesions or new lesion Confirmation of progression recommended minimum 4 weeks after the first iUPD assessment<br>iCPD: Increased size of target or non-target lesions Increase in the sum of new target lesions > 5mm Progression of new non-target lesions Appearance of another new lesion |
| Stable metabolic disease (SMD) | Not meeting criteria for CMR, PMR or PMD. | Not meeting the definitions for CMR, PMR, or PMD | **Stable disease (StD)** | Neither sufficient TR or TG to quality for PR or PD | Neither sufficient TR or TG to quality for PR or PD |
| Partial metabolic response (PMR) | >30% relative decrease and >0.8 absolute decrease in SULpeak of hottest lesion. | If the sum of SULpeak decreased by at least 30% | **Partial response (PR)** | ≥ 30% decrease in SoDs of TLs; NLs may persist but not unequivocally progress | ≥ 30% decrease in SoDs of TLs; NLs may persist but not unequivocally progress |
| Complete metabolic response (CMR) | Complete resolution of FDG uptake within measurable target lesion and disappearance of all other lesions to background blood pool levels. | defined as the resolution of all malignant lesions and was nominally assigned an SULpeak of zero for quantitative analysis | **Complete response (CR)** | Disappearance of all TLs and NLs ; all LNs < 10mm short axis | Disappearance of all TLs and NLs; all LNs < 10mm short axis |

iUPD: unconfirmed progressive disease

iCPD: confirmed progressive disease

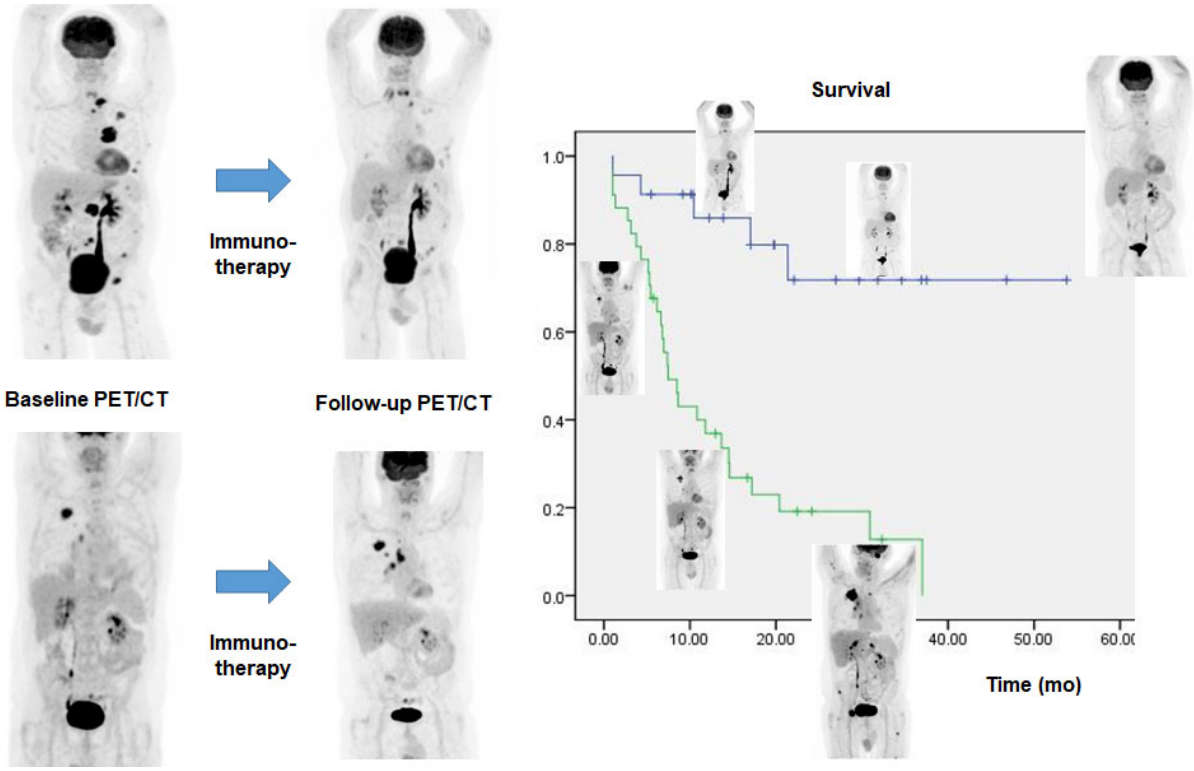
**TABLE 3:** Compares mean survival (months) between patients with CR/CMR and PR/PMR, patients with StD/SMD and PD/PMD and, between responders and non-responders according to different response assessment methods.

| | CR/CMR | PR/PMR | *P* value | StD/SMD | PD/PMD | *P* value |
|---|---|---|---|---|---|---|
| **PERCIST1** | 23.7 [14.0-33.4] | 17.6 [2.2-33.0] | 0.31 | 14.1 [3.1-25.1] | 10.4 [1.0-19.8] | 0.26 |
| **PERCIST5** | 23.7 [14.0-33.4] | 19.9 [4.9-34.9] | 0.53 | 13.2 [2.1-24.3] | 10.4 [0.3-20.5] | 0.30 |
| **imPERCIST1** | 23.7 [14.0-33.4] | 17.7 [0.1-35.3] | 0.34 | 11.1 [1.4-20.8] | 9.6 [3.0-16.2] | 0.55 |
| **imPERCIST5** | 23.7 [14.0-33.4] | 15.9 [1.4-30.4] | 0.16 | 12.9 [0.6-25.2] | 8.5 [2.7-14.3] | 0.16 |
| **RECIST** | 25.5 [14.9-36.1] | 17.5 [4.7-30.3] | 0.19 | 14.4 [12.5-16.3] | 9.6 [0.9-18.3] | 0.19 |
| **iRECIST** | 25.5 [14.9-36.1] | 19.9 [5.1-34.7] | 0.40 | 13.8 [1.7-25.9] | 9.4 [0.5-18.3] | 0.18 |
| | **Responders** | | | **Non-Responders** | | |
| **PERCIST1** | 21.0 [8.5-33.5] | | | 11.3 [0.8-21.8] | | 0.002 |
| **PERCIST5** | 22.2 [10.3-34.1] | | | 11.0 [0.4-21.6] | | < 0.001 |
| **imPERCIST1** | 20.3 [5.6-35.0] | | | 10.6 [1.9-19.3] | | 0.006 |
| **imPERCIST5** | 19.6 [6.8-32.4] | | | 11.3 [0.8-21.8] | | 0.005 |
| **RECIST** | 19.8 [7.3-32.3] | | | 11.2 [0.6-21.8] | | 0.004 |
| **iRECIST** | 21.4 [7.5-35.3] | | | 10.1 [1.4-18.8] | | 0.001 |

Data in brackets are 95%CIs.

**TABLE 4:** Patients with progressive disease according to PERCIST1 which re-categorized to other response categories by imPERCIST1

| Patient no. | Response in imPERCIST1 | % SUL change | New lesion site | SUL peak | Final diagnosis |
|---|---|---|---|---|---|
| 1 | SMD | -24.9 | Cervical node | 7.08 | Metastasis |
| 2 | SMD | -7.1 | Temporal cortex | 18.3 | Metastasis |
| 3 | SMD | 15.9 | Spleen | 5.8 | Inflammatory |
| 4 | SMD | 11.1 | Bone | 8.87 | Metastasis |
| 5 | SMD | 1.25 | Axillary lymph node | 5.55 | Unknown |
| 6 | PMR | 35.5 | Pulmonary nodule | 5.13 | Inflammatory |
| 7 | SMD | -29.9 | Frontal cortex | 18.9 | Metastasis |
| 8 | SMD | -25 | Subcutaneous | 11 | Metastasis |
| 9 | SMD | -24.1 | Supraclavicular fossa | 8.68 | Metastasis |
| 10 | SMD | -11.5 | Mediastinal lymph node | 12 | Metastasis |
| 11 | SMD | -6.8 | Adrenal | 7.78 | Metastasis |
| 12 | SMD | -22.5 | Pulmonary | 14.5 | Metastasis |
| 13 | SMD | -22 | Coeliac trunk | 6.85 | Metastasis |
| 14 | SMD | -13.9 | Pulmonary | 8.48 | Inflammatory |
| 15 | SMD | -24.1 | Sub-carinal lymph node | 7.25 | Unknown |
| 16 | PMR | 43.4 | Hilar lymph node | 6.06 | Metastasis |
| 17 | PMR | 39.9 | Hilar lymph node | 7.81 | Inflammatory |
| 18 | SMD | -7.6 | Bone | 14.6 | Metastasis |
| 19 | SMD | 23.6 | Cerebellar | 7.2 | Metastasis |
| 20 | SMD | -22 | Pulmonary | 8.8 | Inflammatory |
| 21 | SMD | -19.5 | Thyroid | 8.1 | Metastasis |
| 22 | SMD | 19.3 | Bone | 5.8 | Metastasis |
| 23 | PMR | 33.5 | Adrenal | 5.4 | Metastasis |




**Graphical Abstract**