

The predictive value of early in-treatment FDG-PET/CT response to chemotherapy in combination with bevacizumab in advanced non-squamous non-small cell lung cancer

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ABSTRACT

¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) is potentially applicable to predict response to chemotherapy in combination with bevacizumab in patients with advanced non-small cell lung cancer (NSCLC).

Methods:

In 25 patients with advanced non-squamous NSCLC, ¹⁸F-FDG-PET/CT was performed before treatment and after two-weeks, at the end of the second week of first cycle carboplatin – paclitaxel and bevacizumab (CPB) treatment. Patients received up to a total of 4 cycles of CPB treatment. Maintenance treatment with bevacizumab monotherapy was continued until progressive disease without significant treatment related toxicities of first line treatment. In case of progressive disease bevacizumab was combined with erlotinib. Standardized uptake value (SUV) corrected for lean body mass (SUL and SUL_{peak}) were obtained. PET response criteria in solid tumors (PERCIST) were used for response evaluation. These semi-quantitative parameters were correlated with progression free survival (PFS) and overall survival (OS).

Results:

Metabolic response, defined by a significant reduction in SUL_{peak} ≥30% after two weeks of CPB, was predictive of PFS and OS. For partial metabolic responders (*n* = 19) median OS was 22.8 mo. One year and 2-y OS were 79% and 47%, respectively. Non-metabolic responders (*n* = 6) (stable metabolic disease or progressive disease) showed a median OS of 4.4 mo (1-y, and 2-y OS was 33% and 0% respectively) (*P* < 0.001).

Conclusion:

¹⁸F-FDG-PET/CT after one treatment cycle is predictive of outcome to first line chemotherapy with bevacizumab in patients with advanced non-squamous NSCLC. This enables identification of patients at risk of treatment failure, permitting treatment alternatives such as early switch to a different therapy.

Key Words:

Early response prediction, advanced non-small cell lung cancer; carboplatin-paclitaxel chemotherapy; bevacizumab, ¹⁸F-FDG PET/CT, PERCIST

Introduction

Lung cancer is the major cause of cancer-related death in the Western World (1). Non-small cell lung cancer (NSCLC) represents about 80% of all lung cancer. In the majority of cases, patients already have locally advanced or metastatic disease at presentation. Vascular endothelial growth factor (VEGF) is an important mediator in tumor angiogenesis, which plays an important role in cancer cell survival in local tumor growth and in the development of distant metastases. A strongly increased expression of VEGF has been found in non-small-cell lung cancers (2) and is associated with an unfavorable impact on survival (3). Bevacizumab, a monoclonal antibody against VEGF-A, interacts with this pathway by blocking the effect of VEGF. A landmark phase 3 trial has shown that the addition of bevacizumab to carboplatin and paclitaxel in NSCLC improved overall survival (4). Recent **American Society of Clinical Oncology** guideline recommends adding bevacizumab to carboplatin plus paclitaxel (5). One explanation is that bevacizumab leads to vascular normalization of tumor vasculature (6), thus increasing delivery and of cytotoxic therapy to the tumor leading to increased treatment efficacy. The evaluation of tumor volume response by conventional imaging techniques using **Response evaluation criteria in solid tumors (RECIST)** criteria has its limitations in detection of early therapy response (7), especially in the case of targeted treatment. FDG-PET/CT provides rapid, non-invasive, in vivo assessment and quantification of glucose metabolism and might be a powerful tool for measurement of treatment response. Changes in tumor glucose metabolism precede changes in tumor size and can possibly reflect drug effects at a cellular level, resulting in a potential advantage over morphological imaging. Molecular imaging using FDG-PET/CT has shown in NSCLC patients to be a valuable tool for early detection of treatment response in chemotherapy (8), chemo-radiotherapy (9-13) and **targeted** treatment (14-19). The prediction of response using FDG-PET/CT may enable a distinction between patients who are going to benefit from treatment. An early detection of non-responders allows for treatment adaptation or earlier switch to other treatment lines. Ultimately, this can lead to a reduction in ineffective and potentially toxic therapy, a reduction in costs and a more personalized tumor-oriented approach. Few FDG-PET/CT response-monitoring studies have been performed to evaluate anti-angiogenic treatment in NSCLC (20,21). To address this issue, **a side-study for early FDG-PET/CT response monitoring study was performed**, alongside a phase 2 trial in patients with newly diagnosed advanced NSCLC treated with first line chemotherapy carboplatin, paclitaxel **and** bevacizumab (CPB).

We explored the value of FDG-PET/CT to predict clinical outcome by using an early in-treatment FDG-PET/CT.

MATERIALS AND METHODS

Patients

From January 2009 to January 2013, patients with newly diagnosed locally advanced or metastatic NSCLC without prior systemic treatment were enrolled in this prospective single centre study. Patients with histologically or cytologically confirmed non-squamous NSCLC (stage IIIB or stage IV) and at least one measurable lesion (based on RECIST 1.1) were eligible. Exclusion criteria were previous chemotherapy or systemic anti-tumor therapy, previous radical radiotherapy, **performance score ≥ 2 (Eastern Co-operative Oncology Group)** or another active malignancy except for non-melanoma skin cancers in the last 5 years. This study was approved by the institutional review Board of the Radboud university medical center Nijmegen. All patients provided written informed consent.

Treatment

Patients were treated with bevacizumab (15 mg/kg every three weeks), paclitaxel (200 mg/m² body surface area on day 1 every three weeks) and carboplatin (**area under concentration time curve** of 6, on day 1 every 3 weeks). Patients received a maximum of 4 cycles of therapy, after which monotherapy of bevacizumab was continued as long as patients had no evidence of progressive disease and no significant treatment related toxicities. In case of progressive disease bevacizumab 15 mg/kg every 3 weeks continued and erlotinib 150mg/day (second line treatment) added. Both **epidermal growth factor receptor (EGFR)** mutated and EGFR wild type genotypes were included in the study.

Study design

Primary objective of this phase II study was to monitor the efficacy of erlotinib plus bevacizumab (BE) subsequent to progressive disease on CPB as determined by the maximum achieved disease control rate. One of the secondary objectives was determination of early response and FDG-PET/CT was performed before treatment and after 1 cycle of treatment (before the second cycle of treatment). Other

secondary objectives were to monitor disease control rate and time to progression of CPB and BE respectively, and overall survival. The study design is shown in Figure 1. Clinicians were blinded to the results of the in-treatment FDG-PET/CT. Standard clinical response evaluation was done using contrast enhanced computed tomography (CT) at every 6 weeks until disease progression. Response was assessed according to RECIST 1.1 (22) every 6 weeks (or every 9 weeks after week 18 in the BE treatment phase), at onset of clinical signs of progression and in case of premature discontinuation of study treatment. Partial response (PR) or complete response, had to be confirmed after a minimum of 4 weeks. In case of stable disease (SD), follow-up measurements must have met the stable disease criteria at least once after study entry at a minimal interval of 6 weeks.

FDG-PET/CT

For each patient baseline and in-treatment FDG-PET/CT were performed with the same hybrid PET/CT scanner (Siemens Biograph Duo or Siemens Biograph 40 mCT, Siemens Medical Solutions USA, Inc.) according to the guidelines of the European Association of Nuclear Medicine (23). At least 6 hours before ^{18}F -FDG injection, the patients fasted, including discontinuation of any tube or PEG-feeding and any glucose-containing i.v. fluids. Immediately before ^{18}F -FDG injection, the blood glucose level was checked. According to protocol FDG-PET/CT scans were performed at mean 66 minutes (range 58 – 73) after ^{18}F -FDG injection and furosemide 10 mg, covering the neck, thorax, abdomen and pelvis. The PET acquisition time was 4 minutes per bed position. PET scans from the Siemens Biograph Duo were processed using iterative reconstruction with the ordered subsets expectation maximization algorithm (image matrix size, 128 x 128, 4 iterations, 16 subsets; and a 5-mm 3-dimensional Gaussian filter). PET images from the Siemens Biograph 40 mCT were reconstructed with the TrueX algorithm (with a spatially varying point spread function and the incorporation of time-of-flight measurements (Ultra-HD PET). Image reconstruction was performed with three iterations, 21 subsets, and a matrix size of 400×400 (pixel spacing of 2.04 mm). Reconstructed images were corrected for injected dose, decay of ^{18}F -FDG, patient body weight, and attenuation using a low-dose CT scan. Correction for breathing motion using a 4D mode was not used.

Analysis of FDG-PET

FDG-PET/CTs were analyzed on Pinnacle³ (version 8.0d; Philips Radiation Oncology Systems). At baseline, FDG-PET/CT was analyzed visually (number and localization of lesions) and quantitatively. SUV was normalized by lean body mass using Janmahasatian formula (24). The SUL_{peak} of target lesions at baseline was at least $1.5 \times \text{mean liver SUL} + 2 \text{ standard deviations}$ of mean SUL. At follow-up, FDG-PET/CT was analyzed visually (number and localization of lesions, new lesions, visual change in uptake and size) and quantitatively (SUV, SUL, SUL_{peak}). A maximum of five target lesions were selected and delineated using a 50% iso-contour threshold, according to PERCIST criteria (up to a maximum of two lesions per organ). New FDG-avid lesions, suspect for metastasis, were considered progressive disease. For evaluation of response predefined response criteria (PERCIST criteria) were used (25): A complete metabolic response (CMR) was defined as a complete resolution of FDG-uptake within the measurable target lesions and other lesions (less than mean liver activity and at the level of surrounding background blood pool activity) without the advent of new suspicious FDG-avid lesions. Partial metabolic response (PMR) was defined as a reduction of $\geq 30\%$ in the target tumor SUL_{peak} (and an absolute drop of at least 0.8 SUL). PMD was a $\geq 30\%$ increase in SUL_{peak} or advent of new FDG-avid lesions typical of cancer. Stable metabolic disease (SMD) (reduction $< 30\%$ and increase $< 30\%$) was disease other than CMR, PMR or PMD. Two independent readers, blinded to the results of the CT-scans, performed reading of the FDG-PET/CTs and vice versa.

Statistical analysis

Patients were considered evaluable for analysis if they underwent both pre-treatment FDG PET/CT and in-treatment FDG PET/CT. OS was measured from the date of treatment start to time to disease related death. PFS was measured from the date of treatment start to time of disease progression on contrast enhanced CT. In-treatment response evaluation on CT was measured at 6-weeks after treatment start. On FDG-PET/CT (measured 2 weeks in-treatment) metabolic response was defined as CMR or PMR and metabolic non-response was defined as SMD or PMD. Concordance between in-treatment PERCIST and RECIST was assessed using Cohen's κ coefficient and Wilcoxon's signed-ranks test. OS and PFS survival analysis was performed using Kaplan-Meier-method. Responders and non-responders were compared using log-rank statistics. Statistical analysis was performed using SPSS 22.0 (SPSS Inc.) for Windows (IBM Corp, Armonk, NY). The level of statistical significance was defined as a $P <$

0.05 based on two sided tests. No time-dependent adjustment was needed, because no progression or death was observed before the RECIST assessment.

RESULTS

Patients Characteristics and Follow-up

Thirty-two patients were enrolled in the phase 2 study, of which 26 patients had a baseline FDG-PET/CT. Patient characteristics are shown in Table 1. One patient did not receive in-treatment FDG-PET/CT after the first treatment cycle and therefore was excluded from further analysis. Of the remaining 25 patients, 22 patients (88%) received 4 cycles (out of 4) CBP, while three patients (12%) received only 2 cycles first line treatment, due to early disease progression. 21 patients (84%) continued monotherapy bevacizumab. 19 patients (76%) received second line treatment of erlotinib plus bevacizumab after they progressed on (CP)B. One patient receiving second line erlotinib and bevacizumab had an EGFR mutation. In the present study an EGFR mutation was found in two patients. Baseline FDG-PET/CT was always performed before treatment; median time of baseline FDG-PET/CT was 13 days (range 2 – 35d) before treatment. **There was no relation between delay on treatment start and outcome (PFS or OS) in Cox proportional hazards analysis (hazard ratio of 0.997 (0.963 – 1.033) (P=0.871) for OS and hazard ratio of 0.987 (0.952 – 1.023) for PFS (P = 0.470).** The in-treatment FDG-PET/CT was performed after 1 cycle of treatment at day 14 (13 – 20 d), always before the second cycle of treatment. Median time to second line treatment was 9.3 months (range 1.4 – 21.9). Kaplan Meier analysis for PFS and OS stratified using RECIST (6-weeks after treatment start) is shown in Figure 2, no significant difference between response groups was found (log-rank P = 1.000 and P = 0.468 for PFS and OS, respectively). During follow-up all 25 patients died due to disease progression.

Predictive value of FDG-PET/CT

Median baseline SUV was 6.8 and after 15 days of CPB treatment median SUV was 5.0 in the target lesions. In all cases SUL versus SUV response categories (using same cut off levels of 30%) were 100% concordant. According to PERCIST no patient had CMR, 2 (8%) patients had PMD, while 4 (16%) patients had stable metabolic disease (SMD). 19 (76%) patients had PMR. For non-responders

(both PMD and SMD) median PFS was 1.7 months (range 1.0 – 6.1 mo). For patients with PMR median PFS was 8.7 months (range 3.7 – 35.7 mo), 1-y and 2-y PFS were 21% and 5%, respectively. For SMD and PMD median OS was 4.4 months (range 1.7 – 14.1 mo); 1-y, and 2-y OS was 33% and 0% respectively. For PMR median OS was 22.8 months (range 4.3 – 54.6 mo), 1-y and 2-y OS were 79% and 47%, respectively. The Kaplan-Meier analysis of PFS and OS stratified using PERCIST is shown in Figure 3. Figure 4 and 5 show two examples of patients with stage IV disease, with their baseline and in-treatment FDG-PET/CT.

Comparison of treatment response between RECIST and PERCIST

Nineteen patients were classified as SD on CT (6-weeks in-treatment), while 4 patients were classified as SMD according to FDG-PET/CT. 15 patients were classified as PMR. RECIST and PERCIST classifications are shown in Table 2. PERCIST and RECIST were discordant in 16 patients (64%). Of the 19 patients having SD according to RECIST, 14 patients were reclassified as having PMR according to PERCIST. One patient was classified as PMD due to the advent of new FDG-avid lesions suspected of bone metastasis, however these lesions were not detected on the 6-week in-treatment CT (this patient died 52 days after treatment start). Cohen's coefficient $\kappa = 0.023$ was indicating minimal agreement between RECIST and PERCIST. Wilcoxon's signed-ranks test was $P \leq 0.01$ indicating significant difference between RECIST and PERCIST.

DISCUSSION

This prospective study showed that early in-treatment FDG-PET/CT in advanced NSCLC after two weeks of first chemotherapy and bevacizumab is predictive of PFS and OS. Compared to CT, PET detected response earlier during treatment and more frequently. Therefore, the predictive potential of an early in-treatment FDG-PET/CT, performed at two weeks after start of treatment, is better than measurement of size changes on CT according to RECIST at 6 weeks after start of treatment. This resulted in discordance between PERCIST and RECIST in 16 patients (64%). These differences can only partially be explained by the difference in timing of the response evaluation of FDG-PET/CT (2 weeks in-treatment) and diagnostic CT (6 weeks in-treatment). Early after treatment initiation, tumor size changes as a result of, both tumor reduction (i.e. mitotic cell death and cell loss) and tumor growth (i.e. cell division). As a result, small size changes, i.e. actual response or actual tumor growth or

progression are underestimated when tumor size is used as an early predictive marker. According to PERCIST, a significant reduction in FDG-uptake after one treatment cycle was associated with favourable outcome in terms of both PFS and OS. In this study, 6 out of 25 patients (24%) were classified as non-responder (SMD or PMD), showing significantly lower median OS and PFS when compared to patients with a PMR ($P < 0.001$). Of the 19 patients having SD according to RECIST, 14 patients were reclassified as having PMR according to PERCIST, showing that metabolic changes exceeded the threshold criteria earlier than morphological changes. A prospective study by Shang et al. (26) comparing RECIST, EORTC and PERCIST criteria for evaluation of early response (after two weeks) to chemotherapy in NSCLC patients showed that both EORTC and PERCIST criteria were more accurate in predicting an early response to treatment.

Studies addressing response prediction in advanced NSCLC treated with first line chemotherapy and bevacizumab are limited. De Langen et al. (21) demonstrated in (locally) advanced NSCLC patients treated with erlotinib and bevacizumab that a decrease in SUV of more than 20% after three weeks was associated with increased progression free survival. In oncology practice it is important to identify effective biomarkers for prediction of failure or success of treatment. In contrast to our study, other response-monitoring studies (9-14) did not use PERCIST criteria for response evaluation (25).

Predefined response criteria, are not only important tools to assess an objective early response, but are also important in harmonization of FDG-PET/CT studies and facilitate reproducibility across response assessment trials.

Major concern during anti-VEGF treatment is tumor evasion and resistance from VEGF blockage, involving several possible escapes mechanisms (27). An apparent increase in FDG-uptake during treatment might suggest resistance mechanisms resulting in an increase in anaerobic metabolism and an increase in glycolysis. Alternatively, the decrease of tumor vascularity due to anti-angiogenic agents could also lead to an increase in hypoxia and glycolysis. However, ^{18}F -FDG alone is not capable of discriminating between hypoxic and non-hypoxic regions. Tumor hypoxia and metabolism are independent events, which was shown in a study comparing ^{18}F -FAZA and ^{18}F -FDG in NSCLC (28).

The effects of anti-angiogenic treatment could negatively affect the efficacy of FDG-PET/CT early response monitoring in NSCLC. However, in our report we show that early response monitoring in

NSCLC patients treated with chemotherapy the addition of bevacizumab seems feasible. Another entirely different approach is ^{89}Zr -bevacizumab to visualise targeting of VEGFR for prediction of treatment efficacy (29), however further studies are needed to establish a potential role for ^{89}Zr -bevacizumab in NSCLC.

A limitation of our study is the **relative small** number of patients. For development of a clinical application of metabolic treatment response studies, larger series are necessary. **In our analysis PMD and SMD patients were defined as non-metabolic responders. These two categories may have outcome differences can only be detected by a much larger study population.** When effective surrogates for early prediction are established, treatment decision-making based on the early in-treatment FDG-PET/CT seems feasible. In our study we showed that as early as 2 weeks into first line treatment, early metabolic changes predict clinical outcome. The majority of other FDG-PET/CT response assessments studies were performed at relative late time-point during treatment, not allowing any treatment adaptation based on the response assessment (30-32). Early discontinuation of ineffective treatment regimen can possibly prevent unnecessary treatment toxicity. Moreover, earlier switch to a potentially beneficial different therapy could result in early tumour consolidation, better outcomes and better cost-effectiveness.

Another limitation of our study is the second line bevacizumab and erlotinib therapy started after progression on CPB or on bevacizumab maintenance. This investigational second line approach (given in 76% of the patients) showed only modest clinical benefit (33), where OS and PFS on first line CPB were in line with published data (4). However, the optimal strategy of anti-angiogenic therapy in the treatment of advanced NSCLC is still subject to randomized trials and large observational studies. Continuation of bevacizumab treatment in the absence of disease progression is a new treatment strategy in NSCLC, which is less toxic than traditional chemotherapy agents (34) and well tolerated (35). The concept of continuing bevacizumab treatment beyond progression is under investigation (36). More recently, the role of erlotinib with bevacizumab as first-line therapy is being explored (37).

CONCLUSION

The current study in advanced non-squamous NSCLC patients treated with first line chemotherapy and bevacizumab showed that early in-treatment FDG-PET/CT is predictive of response to treatment and overall survival, already after two weeks of therapy. This enables identification of patients at risk of treatment failure, permitting an early and more individualized treatment modification.

DISCLOSURE

A. Timmer-Bonte, M. van der Drift: Roche paid a fee to the pulmonology ward where this author worked at the time of this study. All other authors have declared no conflicts of interest.

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FIGURE 1. Study design.

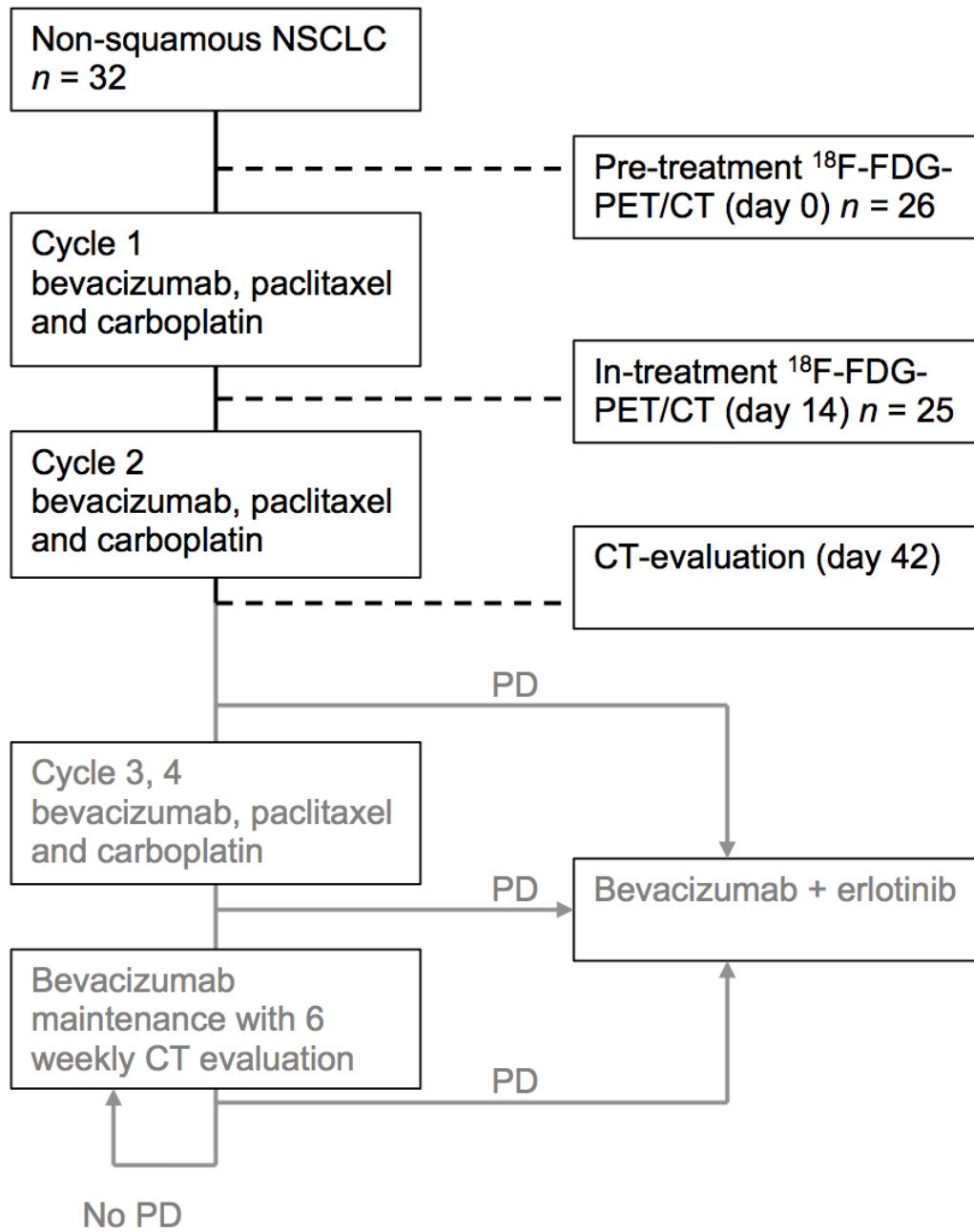


TABLE 1
Patient Characteristics

Characteristics	Value
Median age (y) (range)	54 (42 - 81)
Gender	
Male	15 (47%)
Female	17 (53%)
EGFR mutation status	
EGFR mutation	2 (6%)
No EGFR mutation	30 (94%)
TMM-stage (7 th edition)	
IIIB	1 (4%)
IV	31 (96%)
Smoking status	
Current smoker	15 (47%)
Former smoker	17 (53%)
Previous malignancy	
No	6 (19%)
Yes	26 (81%)
CPB treatment cycles	
<4	6 (19%)
4	26 (81%)
Maintenance bevacizumab cycles	
0	6 (19%)
≥ 1	26 (81%)
BE maintenance cycles	
0	11 (34%)
≥ 1	21 (66%)

TABLE 2

Comparison of in-treatment response between PERCIST and RECIST

RECIST				
	CR (<i>n</i> = 0)	PR (<i>n</i> = 6)	SD (<i>n</i> = 19)	PD (<i>n</i> = 0)
PERCIST				
CMR (<i>n</i> = 0)	0	0	0	0
PMR (<i>n</i> = 19)	0	5	14	0
SMD (<i>n</i> = 4)	0	1	3	0
PMD (<i>n</i> = 2)	0	0	2	0

FIGURE 2. Kaplan-Meier analysis of **PFS** and **OS** stratified using RECIST. For SD median PFS was 8.4; median OS was 14.5 months; For PR median PFS was 7.4 months; median OS was survival was 17.6 months. Log-rank test, $P = NS$.

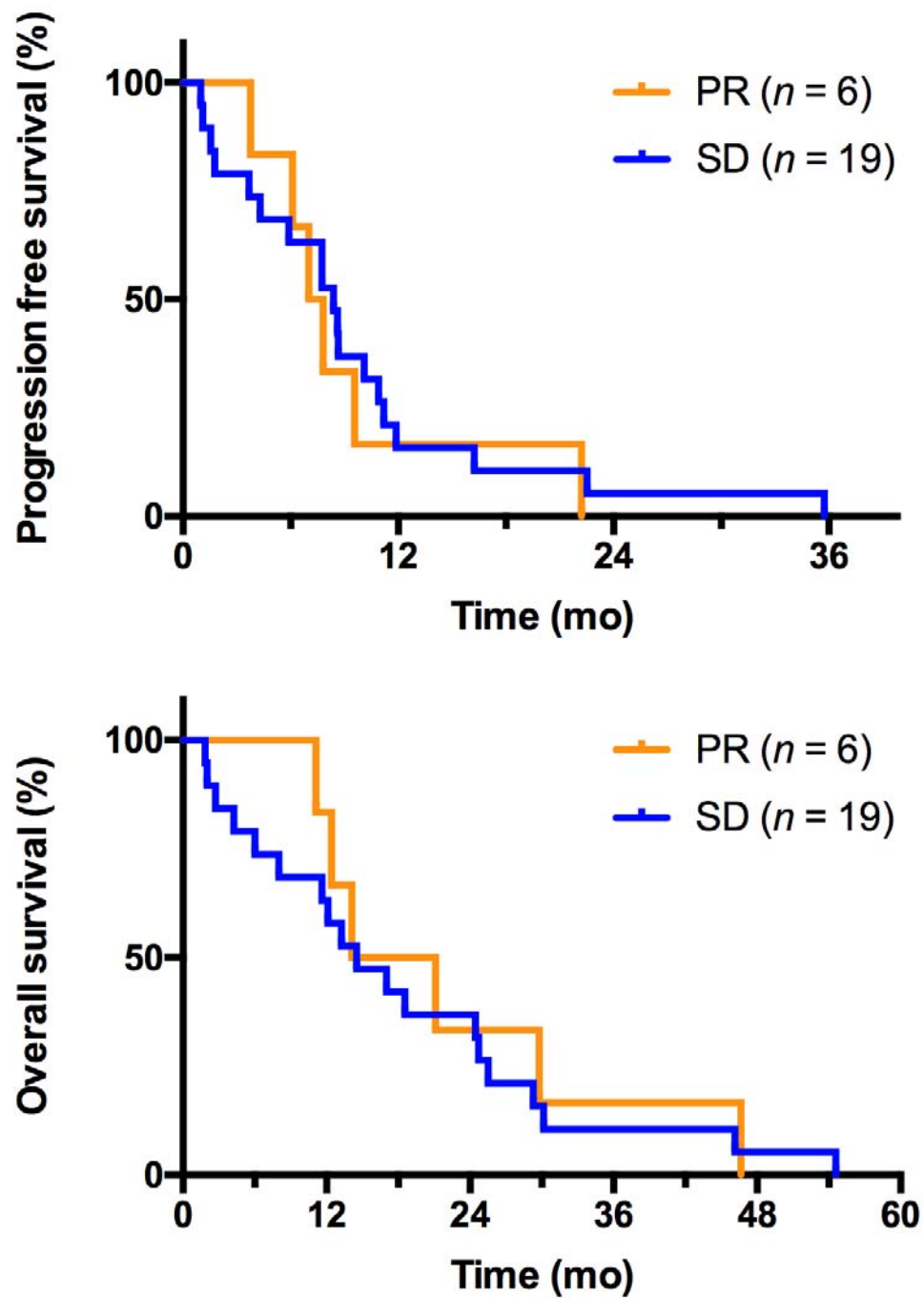


FIGURE 3. Kaplan-Meier analysis of **PFS** and **OS** stratified using PERCIST criteria. For SMD and PMD median PFS was 1.7 months; median OS was 4.4 months; For PMR median PFS was 9.1 months; OS was 22.8 months; Log-rank test, $P < 0.001$.

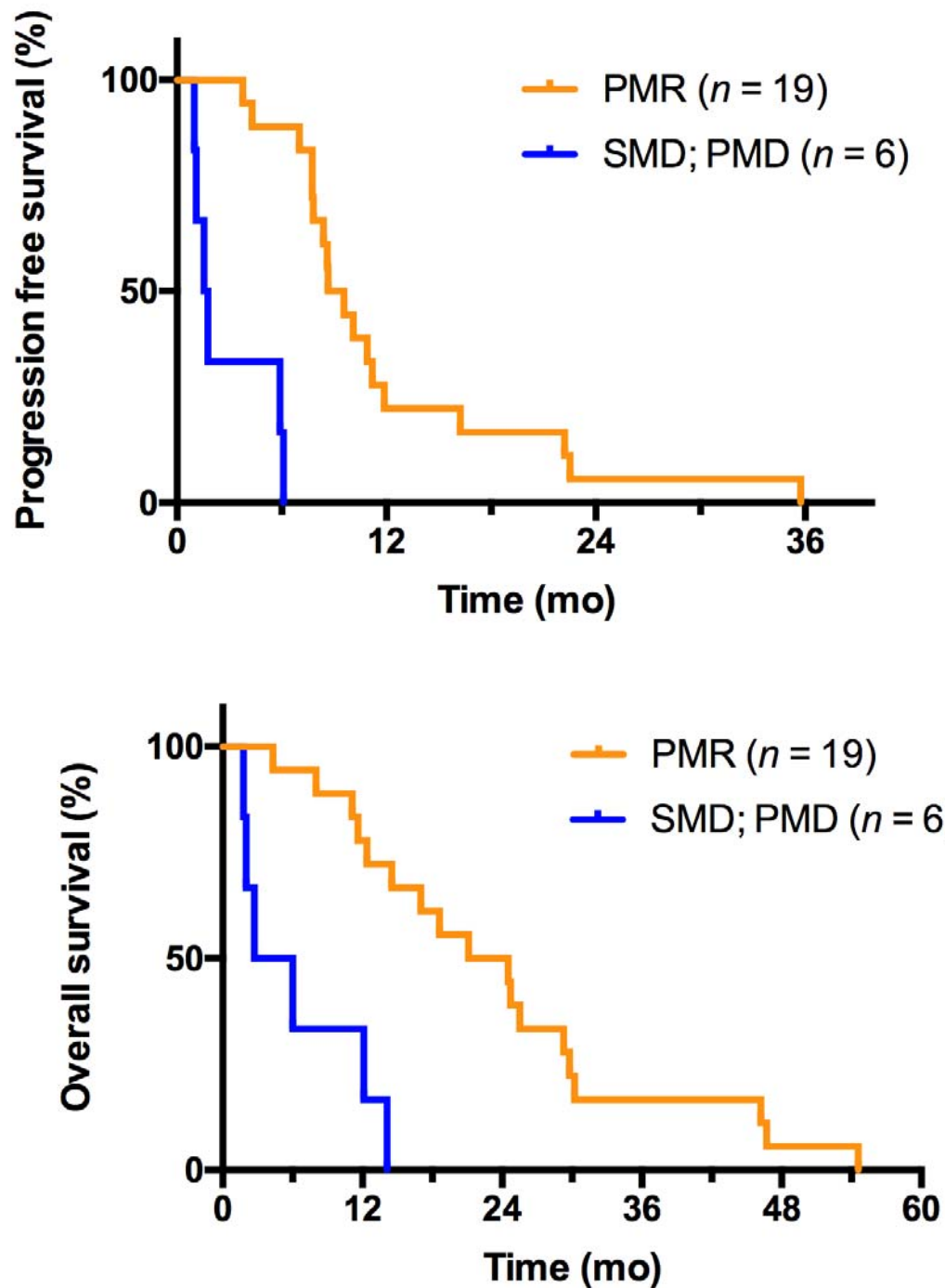


FIGURE 4. Baseline (A) and in-treatment (B) FDG-PET/CT in a 51-year-old female patient with NSCLC, stage IVB, with a Pancoast tumor in the left lung with metastasis in the right adrenal gland (white and black arrows). In-treatment FDG-PET/CT showed apparent decrease in uptake classified as partial metabolic response. Survival was 12.4 months.

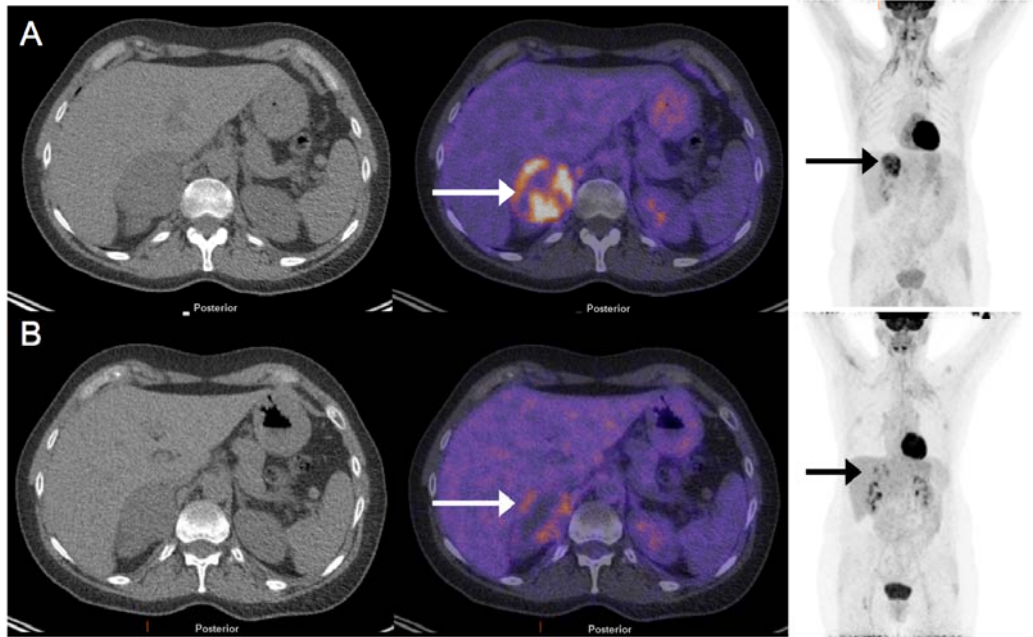
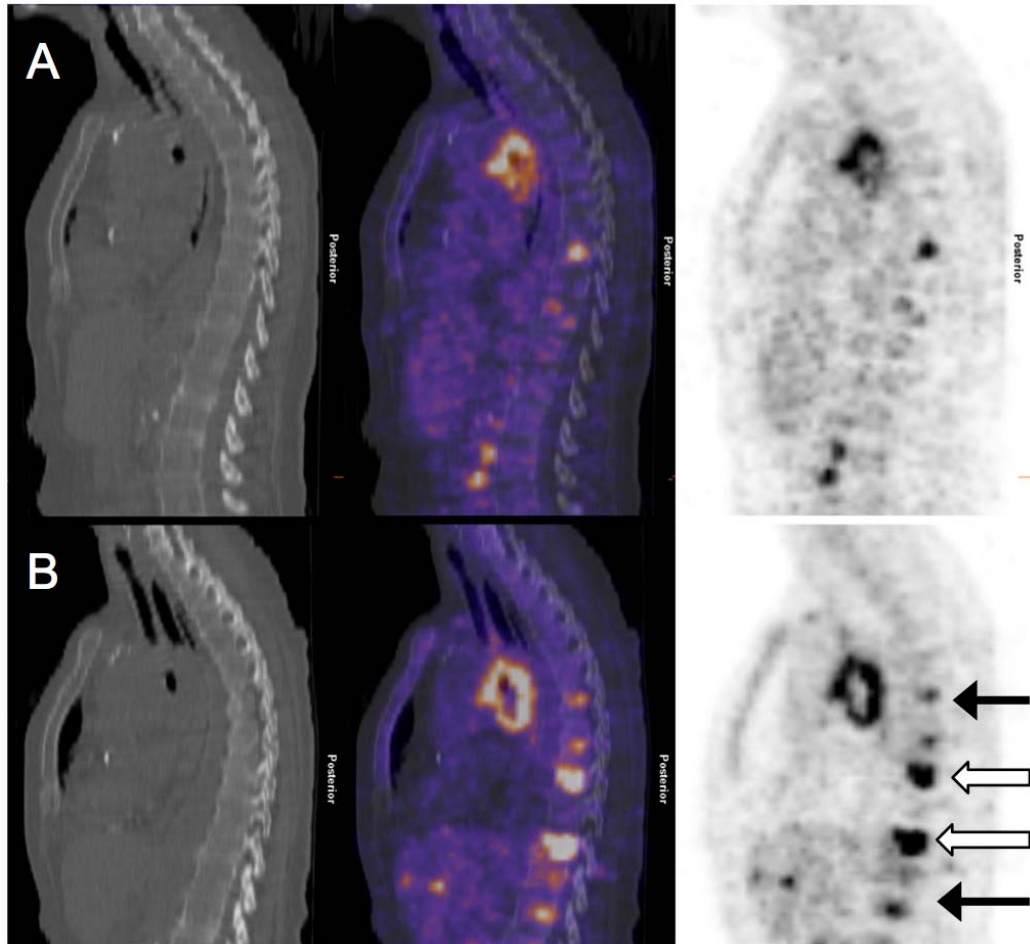
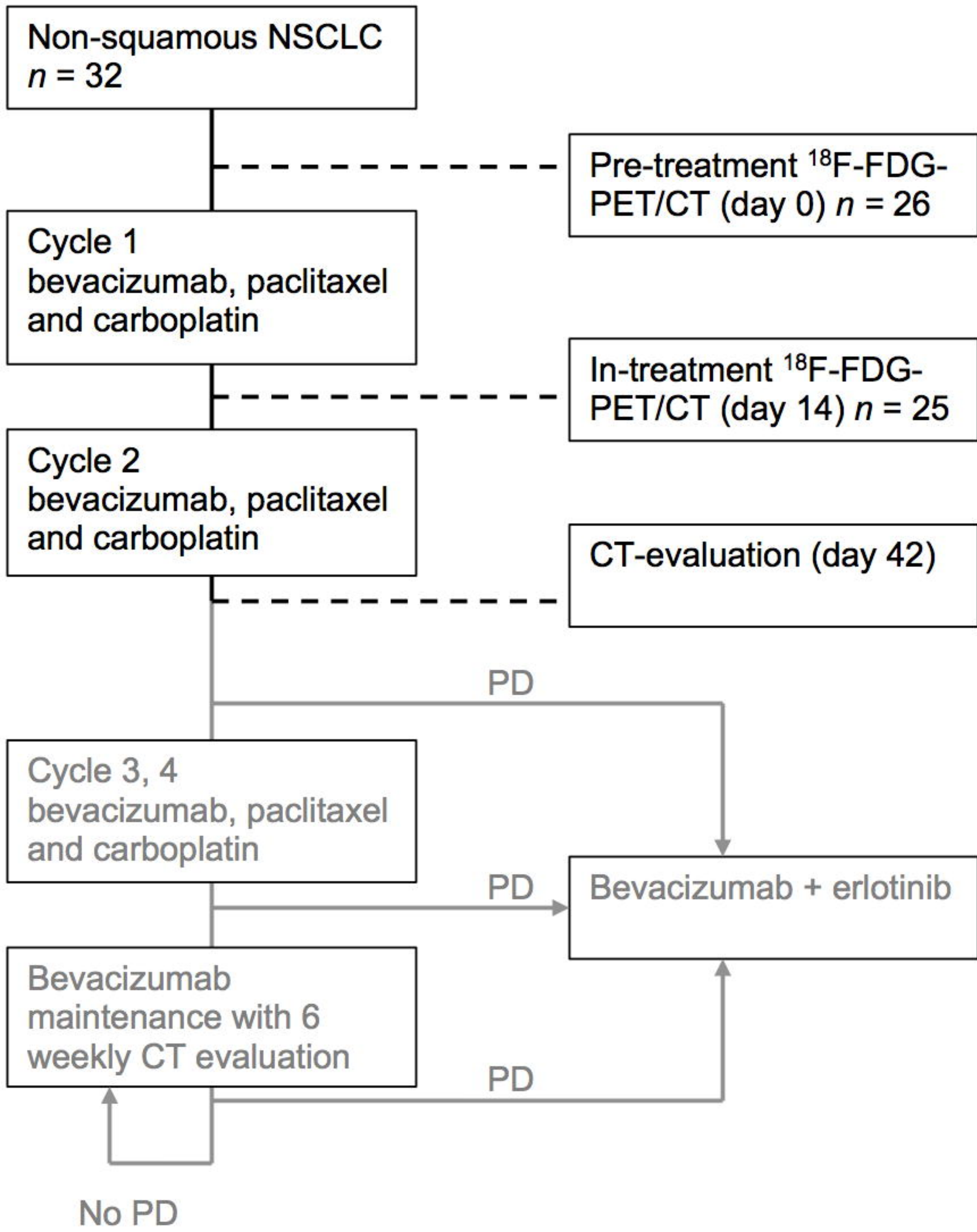
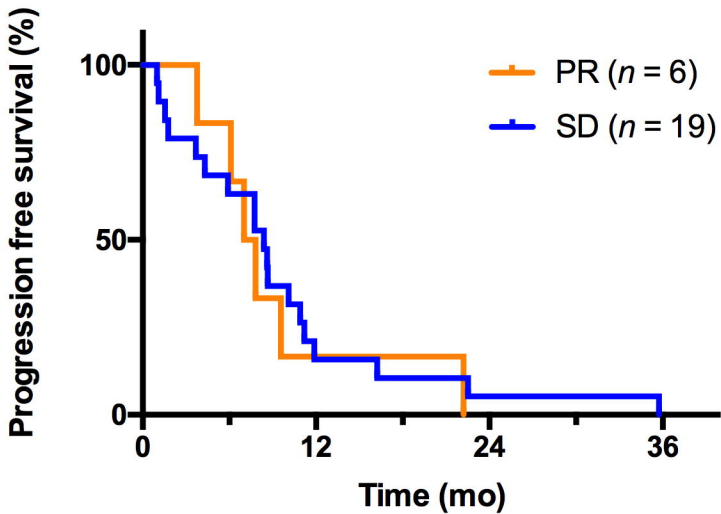
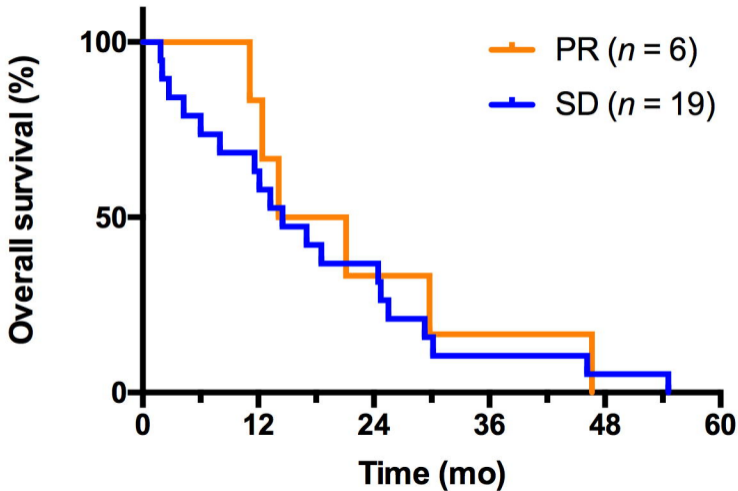


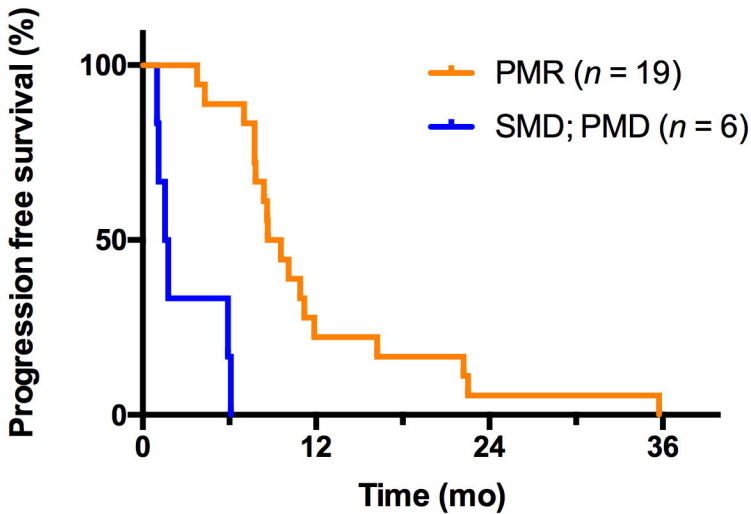
FIGURE 5. Baseline (A) and in-treatment (B) FDG-PET/CT in a 67-year-old female patient with NSCLC, stage IVB, with a tumor in the left lower lobe with metastases in lymph nodes, lung, liver and bones. In-treatment FDG-PET/CT showed apparent increase in uptake (open arrows) and new FDG-avid bone lesions (black arrows), classified as progressive metabolic disease. Survival was 1.7 months.



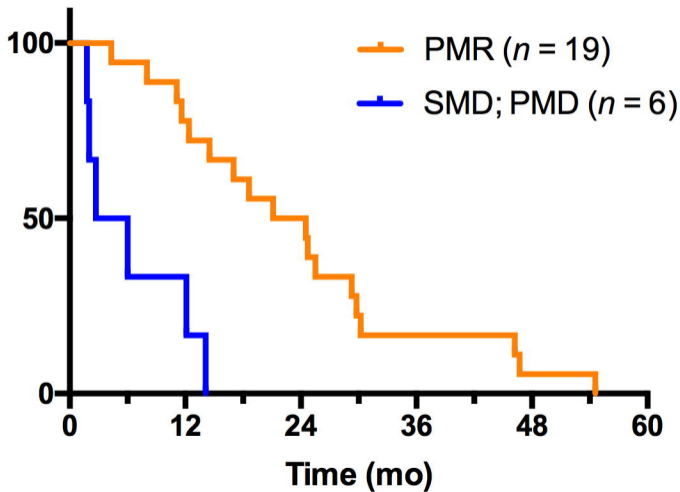


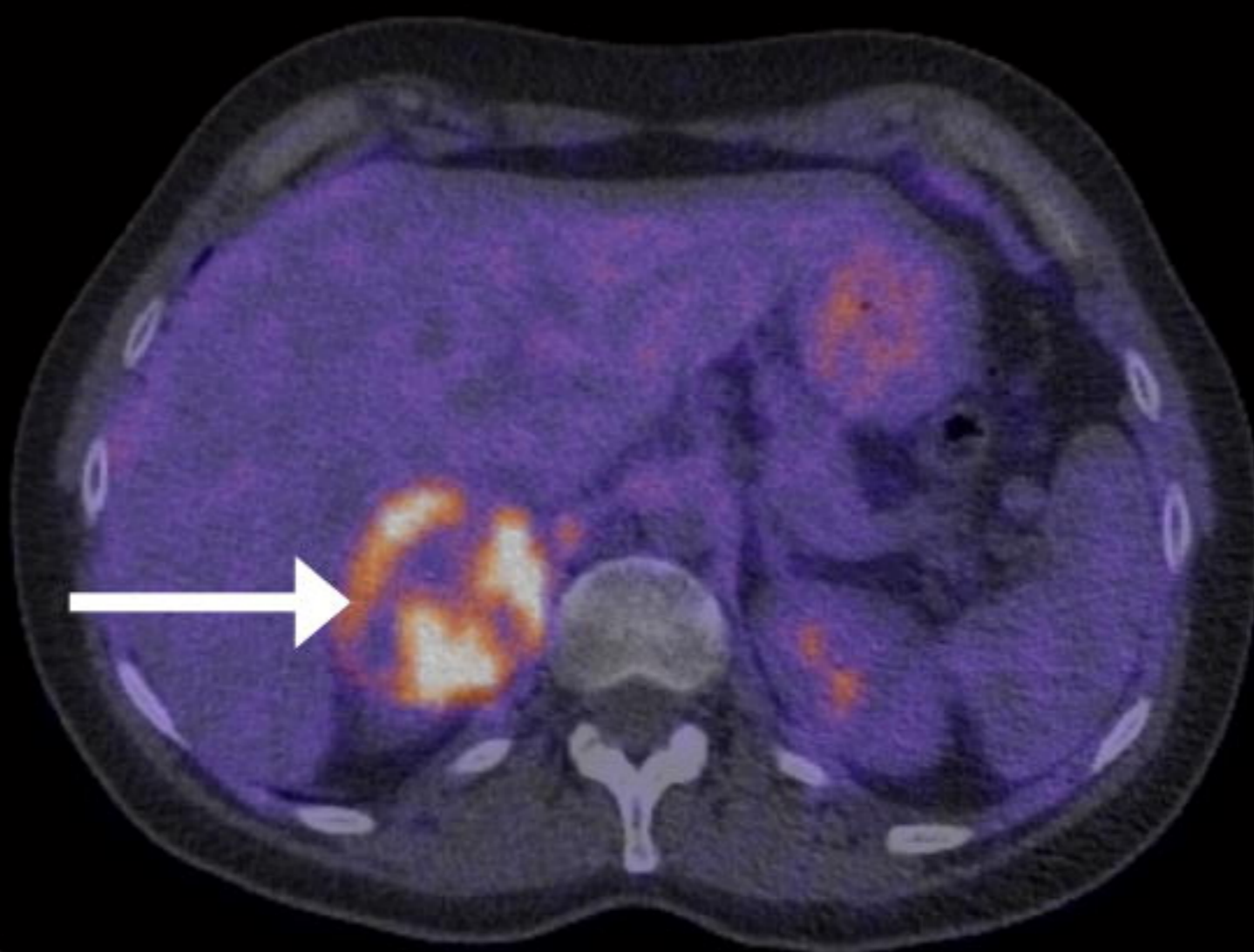






Overall survival (%)



A**B**