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Response assessment in non-small cell lung cancer immunotherapy: initial experiences in utilizing FDG PET/CT and the PD-1 blocker nivolumab

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Summary
Background Most Non-Small-Cell lung cancer (NSCLC) patients need systemic treatment. Immunotherapy is now current standard in first- and second-line treatment. In all pivotal studies, staging was performed using conventional computer tomography (CT) scans. PET/CT-based treatment monitoring is on the contrary recommended in NSCLC guidelines. This investigation aims at describing the benefits, challenges and possible pitfalls of using PET/CT-based monitoring for lung cancer during immunotherapy.
Methods We analyzed 11 NSCLC patients treated with nivolumab at a German tertiary care lung cancer center between 2015 and 2016. All patients received at least two follow-up PET-CTs. Evaluation of response was based on both Response Evaluation Criteria in Solid Tumors (RECIST) and PET Response Criteria in Solid Tumors (PERCIST) criteria.
Results In 7 out of 11 cases, the RECIST and PERCIST results concurred, but two patients with initial stable disease regarding RECIST were reclassified as progressive metabolic disease based on PERCIST criteria. Additionally we identified one case of pseudoprogression using PERCIST criteria in contrast to stable disease using RECIST criteria and one case showing an early and durable response to nivolumab treatment using RECIST, despite a highly hypermetabolic mediastinal lymph node metastasis.
Conclusions The findings indicate that the PERCIST-based evaluation could identify progressive disease earlier. Early identification of nonresponders could lead to prevention of overtreatment and to an early switch to a more effective therapy.

Keywords NSCLC · Immunotherapy · PET-CT · RECIST · PERCIST

Take home message

- PERCIST-based evaluation of response in patients treated with nivolumab might identify progressive disease earlier
- This could lead to prevention of overtreatment and to an early switch of therapy
- The role of PERCIST in patients treated witch checkpoint inhibitors should be evaluated in larger prospective cohorts

Introduction

Non-small cell lung cancer (NSCLC) accounts for about 85% of all diagnosed lung cancers and at initial diagnosis nearly 70% of all patients suffer from locally advanced or metastatic disease [1, 2]. Accordingly, most patients require systemic treatment and especially immunotherapy is of increasing importance in systemic NSCLC treatment. Nivolumab is a fully human IgG4 Programmed Death-1 (PD-1) immune-checkpoint inhibitor that interferes with PD-1 mediated signaling and therefore leads to a regain of antitumor immunity and hence to significant

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and durable improvements for NSCLC patients in the second-line treatment of squamous and non-squamous NSCLC following first-line platinum-based chemotherapy [3, 4]. Moreover, anti-PD-1 therapy with pembrolizumab was recently approved in the first-line treatment of advanced NSCLC with PD-L-1 expression on at least 50% of tumor cells with no Epithelial Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) genomic tumor aberrations [5]. However, with these new treatment options for lung cancer patients, new diagnostic challenges are arising. Especially in the field of radiological diagnostics, several new approaches for monitoring the immune response are under evaluation [6, 7]. In different guidelines FDG-PET/CT is recommended as the diagnostic standard for monitoring response to anticancer treatment in NSCLC [8, 9]. However, the tumor staging in all pivotal immunotherapy studies was performed using conventional CT scans and response evaluation was based on Response Evaluation in Solid Tumors criteria (RECIST 1.1.) [10]. Therefore, the clinical relevance of FDG-PET/CT for the assessment of response to immunotherapy in NSCLC is still unclear. Qualitative and quantitative approaches to assess the metabolic tumor response with ^{18}F-FDG are suggested by the framework for PET Response Criteria in Solid Tumors (PERCIST) [11]. Until now there are only few studies evaluating the benefit of FDG-PET/CT monitoring in NSCLC patients receiving checkpoint inhibition. One study showed that the metabolic response by ^{18}F-FDG could predict efficacy of nivolumab treatment [12]. Further investigations revealed that a high maximum of standardized uptake values (SUVmax) in surgically resected squamous cell carcinomas of the lung correlated with a higher grade of lymph node metastasis and was a risk factor for poor prognosis [13]. Differentiated comparisons between RECIST-based and PERCIST-based treatment monitoring during immunotherapy are still missing. The aim of our investigation was to describe benefits, challenges, and possible pitfalls which we identified when using PET/CT-based treatment monitoring in a cohort of NSCLC patients treated with the PD-1 inhibitor nivolumab.

Table 1 Patients' characteristics and prior therapy, including age, gender, smoking status, lung cancer histology, and the prior therapies of each patient. The last two columns show the response evaluations based on RECIST and PERCIST criteria

Patient ID	Gender	Age	Histology	Smoking status	Prior therapy	RECIST	PERCIST
1	m	71	Squamous NSCLC	50 PY	3 cycles of cisplatin/vinorelbine	PD PD	PMD PMD
2	m	67	Squamous NSCLC	50 PY	6 cycles of cisplatin/vinorelbine; irradiation of the primary tumor site and mediastinum	SD PD	PMD PMD
3	m	63	Adenocarcinoma	Active pipe smoking	6 cycles of cisplatin/pemetrexed; 7 cycles of pemetrexed maintenance	SD PD	PMD PMD
4	f	68	Squamous NSCLC	30 PY	4 cycles of cisplatin/vinorelbine	PD PD	PMD PMD
5	m	69	Squamous NSCLC	40 PY	Pneumonectomy; stereotactic radiation after relapse	SD PR SD in further stagings	PMR PMR SMD in further stagings
6	m	76	Squamous NSCLC	30 PY	Lobectomy; Irradiation of local lymph nodes; 6 cycles of cisplatin/vinorelbine	SD PR SD	SMD PMR PMD
7	m	68	Adenocarcinoma	20 PY	Lobectomy; irradiation of primary tumor site and local lymph nodes; irradiation after local relapse 4 cycles of cisplatin/pemetrexed 2 cycles of pemetrexed maintenance 3 cycles of docetaxel/nintedanib	SD PD	SMD PMD
8	m	51	Adenocarcinoma	80 PY	2 cycles of cisplatin/pemetrexed	PR PD	PMR PMD
9	m	65	Adenocarcinoma	Never	Radiochemotherapy carboplatin/vinorelbine stereotactic radiation of brain metastases	SD PD	PMR PMD
10	m	76	Adenocarcinoma	60 PY	4 cycles of cisplatin/pemetrexed	SD PD	SMD PMD
11	f	68	Adenocarcinoma	30 PY	5 cycles of carboplatin/pemetrexed	PD PR SD in further stagings	PMD PMR SMD in further stagings

PY pack–years, *PD* progressive disease, *SD* stable disease, *PR* partial remission, *PMD* progressive metabolic disease, *SMD* stable metabolic disease, *PMR* partial metabolic remission, *f* female, *m* male

Materials and methods

Patient selection and data extraction

We identified a cohort of 11 stage IV NSCLC patients. The patients received at least two follow-up PET-CT scans during nivolumab treatment at the hospital of the Ludwig Maximilians-University, a German tertiary lung cancer center. The patients received immunotherapy in second- or third-line treatment following systemic therapy. We retrospectively extracted anonymous data sets from the patient record and tumor database including stage at diagnosis, histology, initial treatment, second- and third-line treatment with special focus on the use of PET-CT in the follow-up under nivolumab treatment. We included 9 men and 2 women, with an average age of 69.4 ± 4.4 and 68 ± 0 years, respectively. Five patients had squamous NSCLC and 6 patients an adenocarcinoma. Table 1 shows the patients' characteristics and prior therapies. All patients received a baseline PET-CT scan before initiation of nivolumab treatment. The first follow-up PET-CT scan was performed after 4–12 weeks and the second PET-CT scan after 8–13 weeks. Nivolumab was administered with 3 mg/kg body weight every 2 weeks. No treatment discontinuation due to side effects or other complications was necessary. All patients received continuous treatment with nivolumab.

PET-CT procedure and assessments

A GE (Boston, MA, USA) Discovery 690 PET/CT scanner was used to gain whole body [18F]-FDG PET/CT scans from the proximal femur to the vertex. Following a 6-hour fasting period, blood glucose levels were determined and diuretic medication administered intravenously. Thereafter, [18F]-FDG (mean 228 MBq) was bolus administered. Immediately before the scan was performed, the patients had to void the bladder. Approximately 60 min after intravenous injection of the [18F]-FDG, the emission sequence was started. Diagnostic CT scans (100–190 mAs, depending on the scanned organ region; 120 kV) were acquired with intravenous injection of iodine-containing contrast agent (Imeron 300, Bracco [Milan, Italy]; 2.5 mL/s) at a dose adjusted for body weight. Attenuation map derived from contrast-enhanced diagnostic CT was used for PET correction. PET images were reconstructed with a slice thickness of 5 mm along the Z-axis, as a 256 × 256 matrix, based on the VPFX algorithm.

All PET-CT scans were evaluated analogue to Response Evaluation Criteria in Solid Tumors (RECIST criteria) as well as Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST criteria) [10, 14, 15].

Results

Nonresponders

Patient 1 The first staging under nivolumab treatment after 8 weeks revealed progressive disease under RECIST criteria with an increase of the pulmonary key lesion from 1.2 to 1.8 cm. The patient was in good general condition and developed no side effects of nivolumab. Therefore, the treatment was continued. Ten weeks later, the second staging showed a tumor progression again with further increase of the pulmonary key lesion (2.8 cm) as well as new mediastinal lymph node metastases. Retrospective analysis using PERCIST criteria was in line with the RECIST evaluation and showed a progressive metabolic disease with a change of SUVpeak in the key lesion of 227 and 269% respectively compared to the first staging.

Patient 2 The first staging after 8 weeks revealed stable disease under RECIST criteria with no change of size of the pulmonary key lesion (3.2 cm). Thus, treatment with nivolumab was continued. Ten weeks later, the second staging showed progressive disease with an increase of the pulmonary key lesion (4.3 cm), new brain metastases as well as multiple intrapulmonary metastases. Retrospective analysis using PERCIST criteria revealed already in the first staging a progressive metabolic disease with an increase of SUVpeak in the key lesion of 116% (Fig. 1a).

Patient 3 The first staging after 7 weeks revealed stable disease based on RECIST criteria with no change of size of the pulmonary key lesion (4 to 4.1 cm). Thus nivolumab treatment was continued. Eight weeks later, the second staging showed a stable pulmonary key lesion, but new brain metastases as well as adrenal metastases. Retrospective analysis using PERCIST criteria revealed already in the first staging progressive metabolic disease with an increase of SUVpeak in the key lesion of 131.4%.

Patient 4 The first staging under nivolumab treatment after 5 weeks revealed progressive disease under RECIST criteria with an increase of the hepatic key lesion from 6.9 to 9 cm. Due to the suspicion of a pseudoprogression nivolumab treatment was continued. Twelve weeks later, the second staging again confirmed progressive disease with new mediastinal lymph node and adrenal metastases. Retrospective analysis using PERCIST criteria was in line with the RECIST evaluation and showed progressive metabolic disease with a change of SUVpeak in the key lesion of 56.5 and 96.7% respectively, compared to baseline staging.

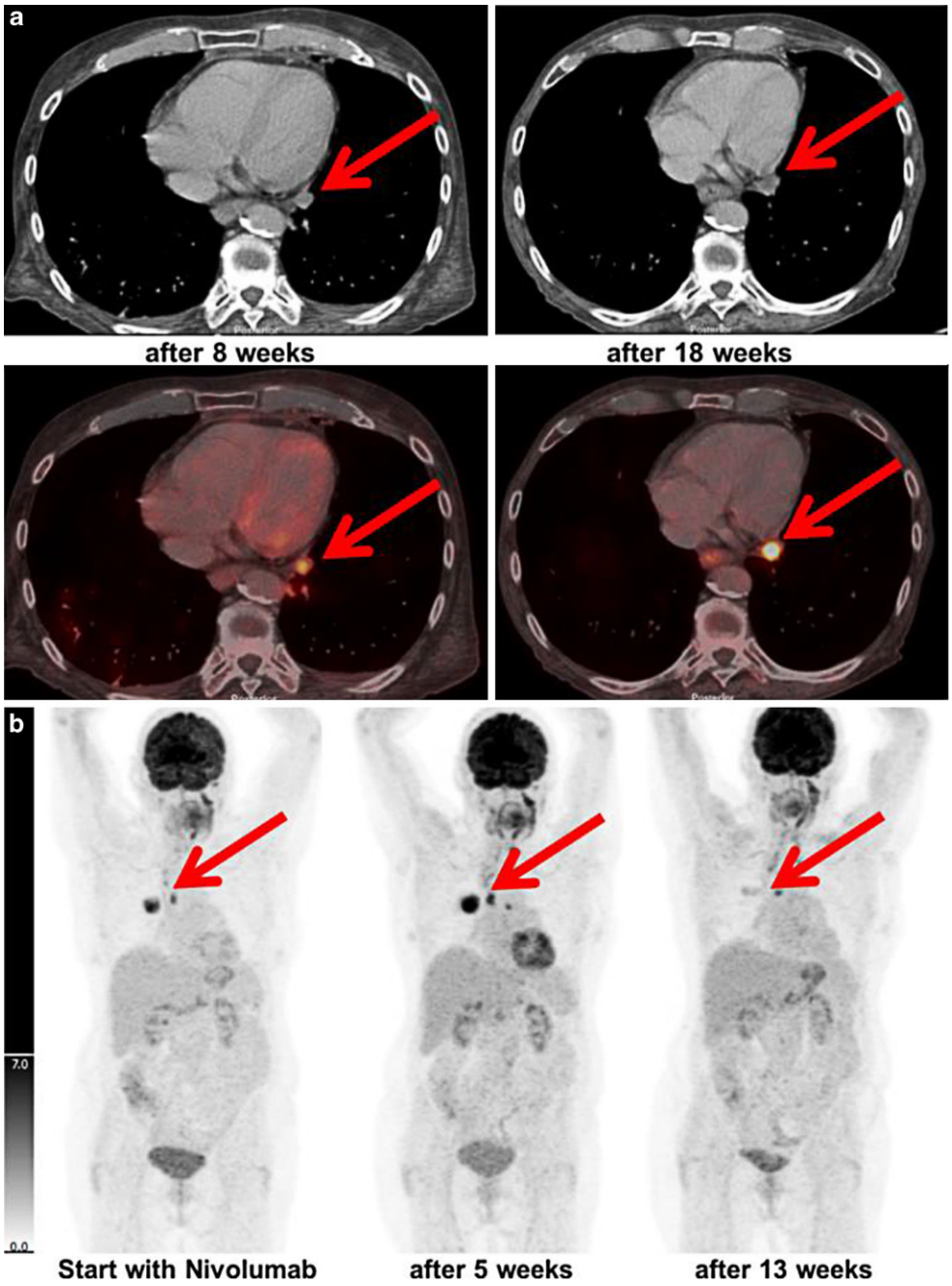

Fig. 1 Exemplary illustration of potential benefits and pitfalls of response evaluation using PERCIST criteria in NSCLC treated with nivolumab. **a** PET-CT scans of patient 2 who showed stable disease regarding RECIST criteria after the first staging, whereas evaluation regarding PERCIST criteria revealed progressive metabolic disease already in the first staging; 10 weeks later sole CT staging also revealed progressive disease. **b** The rare case of a real pseudoprogression in a NSCLC patient

Long-term responder

Patient 5 The first staging under nivolumab treatment after 7 weeks revealed stable disease by RECIST criteria with an increase of the pulmonary key lesion (4.3 to 4.5 cm). Therefore, nivolumab treatment was continued. Ten weeks later, the second staging showed good tumor response with shrinkage of the pulmonary key lesion (1.4 cm). Retrospective analysis using PERCIST criteria were parallel to the RECIST evaluation and showed a partial metabolic response with decrease of SUVpeak in the key lesion of 30.8% compared to the first staging. The patient is still under nivolumab treatment and further stagings revealed stable disease using both RECIST and PERCIST criteria, although the patient still has one FDG-positive mediastinal lymph node.

Progressive disease following initial response

Patient 6 The first staging under nivolumab treatment after 5 weeks revealed stable disease under RECIST criteria without relevant change of the pulmonary key lesion (1.5 to 1.6 cm). Consequently, nivolumab treatment was continued. Nine weeks later, the second staging showed tumor regression of the pulmonary key lesion (0.9 cm). Retrospective analysis using PERCIST criteria confirmed the RECIST

evaluation and showed a formally stable metabolic disease with reduction of SUVpeak in the key lesion of 24.8% compared to the first staging. The assessment of the following RECIST stagings were in line with the PERCIST evaluation showing partial metabolic remissions with a reduction of SUVpeak of 51.9 and 46.5% compared to baseline examination. Even though the patient developed only a slight increase of tumor size (1.1 cm) after 33 weeks, clear progressive metabolic disease with a change of SUVpeak in the key lesion of 367.6% was observed.

Patient 7 After 4 weeks the first staging under nivolumab treatment revealed stable disease under RECIST criteria with no relevant change of the pulmonary key lesion (1.0 to 1.3 cm). Accordingly, treatment with nivolumab was continued. Nine weeks later, the second staging showed a stable pulmonary key lesion (0.9 cm), but new pleural and hepatic metastases. Retrospective analysis using PERCIST criteria was in line with the RECIST evaluation and showed a stable metabolic disease with reduction of SUVpeak in the key lesion of 8.3% compared to the first staging. In the second staging, PERCIST evaluation further showed progressive metabolic disease with a change of SUVpeak in the key lesion of 120.0%, whereas the RECIST results showed tumor progression only in the form of distant metastasis.

Patient 8 The first staging under nivolumab treatment after 7 weeks revealed partial remission under RECIST criteria with a decrease of the pulmonary key lesion (4.2 to 2.9 cm). Therefore, nivolumab treatment was continued. Retrospective analysis using PERCIST criteria confirmed the RECIST evaluation and showed a partial metabolic response with reduction of SUVpeak in the key lesion of 70.1% in the first staging. After 11 weeks the second staging showed stable disease regarding the size of the pulmonary key lesion (2.1 cm), but new mediastinal lymph node metastases. Accordingly, evaluation regarding PERCIST criteria revealed clear progressive metabolic disease with an increase of SUVpeak in the key lesion of 212.8%.

Patient 9 The first staging under nivolumab treatment after 7 weeks showed stable disease under RECIST criteria with a decrease of the pulmonary key lesion (2.2 to 1.8 cm). Nivolumab treatment was therefore continued. Retrospective analysis using PERCIST criteria revealed partial metabolic response with reduction of SUVpeak in the key lesion of 38% in the first staging. After 10 weeks, the second staging showed stable disease regarding the size of the pulmonary key lesion, but new mediastinal lymph node metastases as well as pleural metastases. The response evaluation based on PERCIST criteria also showed progressive metabolic disease with a change of SUVpeak in the key lesion of 204.6%.

Patient 10 The first staging under nivolumab treatment after 12 weeks revealed stable disease under RECIST criteria with a change of the pulmonary key lesion from 0.8 to 1 cm. Treatment with nivolumab was therefore continued. Retrospective analysis using PERCIST criteria also revealed stable metabolic disease. The second staging after 13 weeks showed progressive disease regarding the size of the pulmonary key lesion (2.8 cm) as well as new mediastinal lymph node metastases. Also evaluation using PERCIST criteria revealed a clear progressive metabolic disease with a change of SUVpeak in the key lesion of 278.9%.

Pseudoprogression

Patient 11 The first staging under nivolumab treatment after 5 weeks revealed a stable disease under RECIST criteria with a decrease of the pulmonary key lesion from 3 to 2.7 cm. By contrast, retrospective analysis regarding PERCIST criteria showed clear progressive metabolic disease with a change of SUVpeak in the key lesion of 165.9% compared to baseline staging. Based on the fact that the patient was in good general condition and developed no side effects, nivolumab treatment was continued despite metabolic progression. After 8 weeks the second staging revealed partial remission of the pulmonary key lesion based on both RECIST criteria (2.7 to 0.9 cm) and PERCIST criteria with clear partial metabolic remission with a reduction of SUVpeak in the key lesion of 70% compared to baseline staging (Fig. 1b). The patient has still ongoing response to nivolumab treatment for 80 weeks.

Discussion

This study reports our first experience with response evaluation based on the comparison of RECIST and PERCIST criteria in a series of NSCLC patients treated with the PD-1 inhibitor nivolumab. RECIST criteria monitor the changes in tumor size and are established to assess the response to cytotoxic chemotherapeutic agents [14]. RECIST-based tumor response was also applied in the pivotal study of nivolumab in the second-line treatment in NSCLC patients [3]. Despite RECIST criteria being used extensively, caution must be taken when evaluating the efficacy of newer cancer treatments that may be more cytostatic than cytocidal [11]. Therefore, in the absence of major tumor shrinkage, the lack of tumor progression may also indicate a treatment response [11, 16, 17]. Due to this fact, we additionally used the PERCIST criteria to evaluate the metabolic tumor response of the patients treated with nivolumab in our study cohort. We did not use the immune-related response criteria (irRC) because they do not apply PET criteria [18] and as the RECIST 1.1. response evaluation is still the only tool for response evaluation accepted by the U.S. Food and Drug Administration (FDA).

A total of 11 patients with at least two follow-up PET-CT scans during the treatment with nivolumab were included into the analysis. Evaluation of response was based on both RECIST and PERCIST criteria. In 7 out of 11 cases, the RECIST and PERCIST results concurred, but two patients (patient no. 2 and 3) with initial stable disease regarding RECIST were reclassified as progressive metabolic disease based on PERCIST criteria with an increase of SUVpeak of more than 100%. In the following staging, both patients also showed a progressive disease under the RECIST-based response evaluation. This indicates that the PERCIST-based evaluation could identify progressive disease earlier and therefore prevent overtreatment with immunotherapy. Early identification of nonresponders could lead to prevention of overtreatment, an early switch to a more effective therapy and to reduction of treatment costs.

Beside the possible advantages of PET-CT staging in the group of nonresponders, some potential pitfalls may exist. One patient (patient no. 5) who showed an early and durable response to nivolumab treatment had highly active mediastinal lymph node metastasis in every staging. Under a PERCIST-based response evaluation, this finding would be classified as progressive metabolic disease. Another patient developed the rare circumstance of pseudoprogression during immunotherapy according to both PERCIST and RECIST response evaluations. Pseudoprogression in terms of initial tumor growth or new lesions followed by tumor response is rare in epithelial cancers like lung cancer [18, 19]. Discontinuation of treatment would have to be considered if solely based upon the radiological findings. Therefore, it is important to take into account the clinical status of each individual patient to avoid misinterpretation of tumor progression in scan results.

Until now, there are only few studies evaluating the benefit of FDG-PET/CT monitoring in NSCLC patients receiving checkpoint inhibition. Our study showed a strong correlation between metabolic response by 18F-FDG and efficacy of nivolumab treatment and is therefore in line with previous findings [12].

Tumor size can increase at the beginning of immunotherapeutic treatment by infiltration of immune cells, such as cytotoxic T lymphocytes, surrounding tumors before tumor size decreases significantly [7, 20]. Therefore, immune-related response criteria (irRC) were developed to differentiate atypical responses [19]. On the one hand, they have been shown to be superior in evaluating response of melanoma patients under the treatment with PD-1 inhibitors [7, 18, 21]. On the other hand, there is only one study on NSCLC during immunotherapy evaluated by irRC suggesting an additional benefit especially in the identification of pseudoprogression [19].

To our knowledge differentiated comparisons between RECIST-based and PERCIST-based treatment monitoring during immunotherapy in NSCLC are still missing.

Although our study has limitations, especially the small number of patients, it gives first insights into the potential additional benefits and pitfalls of PET-CT staging in advanced NSCLC patients treated with checkpoint inhibitors. Also time points of first and second PET-CT follow-ups were variable in our cohort. Further investigations should adjust the intervals to 8–12 weeks to improve comparability. Evaluating response to immunotherapy regarding the PERCIST criteria could help to identify nonresponders earlier and thus to reduce overtreatment and costs. This might encourage analyses of larger cohorts, preferably in a prospective setting by the additional information drawn from PET-CT staging.

Author Contributions DK, AS, AT, ZS, TP, RMH, FB and KK designed the study, performed the literature search, and wrote and revised the manuscript. DK, AS, AT, FB and KK reviewed the patient charts and documented clinical data. TP, FB and AS performed evaluation regarding RECIST and PERCIST criteria.

Conflict of interest D. Kauffmann-Guerrero A. Schindler, A. Tufman, Z. Syunyaeva, T. Pfluger, R.M. Huber, F. Berger, and K. Kahnert declare that they have no competing interests.

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