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# Response to early treatment evaluated with $^{18}$F-18F-FDG PET and PERCIST 1.0 predicts survival in patients with Ewing sarcoma family of tumors treated with a monoclonal antibody to the insulin-like growth factor 1 receptor

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**Abstract**

To assess the prognostic and predictive value of early quantitative $^{18}$F-FDG PET to monitor therapy with an antibody to the insulin-like growth factor 1 receptor (IGF-1R antibody) in patients with Ewing sarcoma family of tumors (ESFT).

**Methods** $^{18}$F-FDG PET images at baseline and approximately 9 days after initiation of IGF-1R antibody therapy in 115 patients with refractory or relapsed ESFT were prospectively obtained as part of the Sarcoma Alliance for Research through Collaboration trial (SARC-11). Responses were centrally evaluated by PET response criteria in solid tumors (PERCIST) 1.0 in 93 patients. The 9 day PET responses were correlated to overall survival (OS), progression free survival (PFS), and clinical benefit after 6 weeks of therapy based on clinical observation and CT response by WHO anatomic criteria.

**Results** The median OS was 8.1 months (95% CI, 6.4 to 10.0 months). Using PERCIST, patients with progressive metabolic disease (PMD) showed shorter OS (median 4.7 months) compared to patients without progression (median 10.0 months, p=0.001). PMD on day 9 PET was associated with a significantly higher risk of death (hazard ratio=2.8; 95% CI, 1.5 to 5.5). Changes in $^{18}$F-FDG uptake after 9 days of therapy had an area under the curve (AUC) of receiver operating characteristic of 0.71 to predict 1 year OS. The AUC was 0.63 to predict progression at 3 months, and was 0.79 to predict clinical benefit after 6 weeks of therapy.

**Conclusion** Treatment response by quantitative $^{18}$F-FDG PET assessed by PERCIST 1.0 as early as 9 days into IGF-1R antibody therapy in patients with ESFT can predict the OS, PFS, and clinical response to therapy.

**Key words** sarcoma, insulin-like growth factor, $^{18}$F-FDG PET

## Introduction

R1507, a recombinant human monoclonal antibody to the insulin-like growth factor 1 receptor (IGF-1R antibody) showed a modest activity in unselected patients with relapsed or refractory Ewing sarcoma family of tumors (ESFT)(*1, 2*). The subgroup of patients with ESFT who will benefit the most from the IGF-1R antibody therapy has not been determined. A pre-treatment predictive assay, or an assay of treatment efficacy performed soon after treatment was initiated, would be valuable if it could predict the efficacy of anti-tumor treatment.

In previous studies, [$^{18}$F] fluorodeoxyglucose ($^{18}$F-FDG) uptake measured during induction chemotherapy in pediatric patients with ESFT was predictive of progression free survival (PFS)(*3*). In another group of patients with osteosarcoma, after only 1 cycle of chemotherapy $^{18}$F-FDG positron emission tomography (PET) could predict histological response(*4*). The association between early response to targeted therapy assessed by $^{18}$F-FDG PET and overall survival (OS) has not been reported in patients with ESFT to our knowledge.

Patients with recurrent or refractory ESFT treated with R1507 from the Sarcoma Alliance for Research through Collaboration (SARC) prospective phase II trial were studied. The goals of this imaging sub-study were to evaluate if early $^{18}$F-FDG PET response after 9 days of IGF-1R antibody therapy in patients with ESFT has (1) prognostic value for OS, and (2) predictive value for clinical benefit.

## Patients and Methods

The patients were 2 years or older, had no clinically significant unrelated systemic illness, no immunosuppressive agent within the last 6 months, no prior therapy with IGF inhibitor, and no other malignant disease diagnosed within the previous 5 years, except for treated non-melanoma skin cancer or intra-epithelial cervical neoplasia. The patients were enrolled from December 2007 through April 2010. There were 31 study locations from North America, Europe and Australia participating in the trial. 85 patients received 9 mg/kg of R1507 IV once a week. In 6 patients who were less than 21 years old, a dose of 27 mg/kg was given every 3 weeks for safety assessment. No difference in sarcoma response or patient outcomes was observed between the two patient cohorts receiving different drug schedules. Further details regarding the treatment data are available in a previous publication (1). The ClinicalTrials.gov identifier is NCT00642941. The institutional review board approved this study and all subjects signed a written informed consent.

Of 115 eligible patients enrolled in the SARC trial, 14 did not have baseline $^{18}$F-FDG PET ($PET_{baseline}$) and 1 patient did not have day 9 $^{18}$F-FDG PET ($PET_{day9}$) (figure 1). Image data for 7 patients had an error to preclude standardized uptake value (SUV) computation, as the data were in counts per second. Quantitative assessment of PET response was possible in 93 patients. Minor technical variations from the imaging protocols necessary to implement PERCIST were found in the images of 79 patients**.** The details of the technical variations are available in supplemental table (online only). They were included in the analysis with an exception of 2 patients with a liver average SUV greater than 10.0.

$^{18}$F-FDG PET was obtained at baseline within 4 weeks before IGF-1R antibody therapy began, and at a target date of 9 days after the start of therapy (acceptable window of 8 to 14 days after therapy began), per the SARC funded therapy protocol. The $^{18}$F-FDG PET data were obtained to perform an exploratory analysis of the correlation of $^{18}$F-FDG changes in sarcoma with outcomes. The PET data were not utilized for clinical decision making and did not alter the patient's therapeutic plans. The PET scanning was performed at the 31 participating institutions using their routine clinical PET scanning protocols. For this study, the digital PET images were collected, quantified and read at Johns Hopkins by the Image Response Assessment Team with 2 nuclear medicine physicians reaching a consensus. All images were loaded onto the same reading system and quantitative data were computed using Mirada XD3 software (Mirada Medical, Oxford, United Kingdom).

For our study, response by $^{18}$F-FDG PET was assessed quantitatively by PET response criteria in solid tumors 1.0 (PERCIST)(*5*). PERCIST response is based on the measurement of the SUV corrected for lean body mass in a 1 $cm^3$ sphere region of interest from the hottest tumor lesion (SULpeak). The percentage change in SULpeak (%$\Delta SUL_{peak}$) is defined as [($PET_{baseline}$ SULpeak - $PET_{day9}$ SULpeak) ÷ $PET_{baseline}$ SULpeak x 100]. The 4 response categories by PERCIST are: complete metabolic response (CMR); partial metabolic response (PMR) when %$\Delta SUL_{peak}$ decrease is at least 30% from the baseline and by 0.8 units of the absolute SULpeak value; stable metabolic disease (SMD); and progressive metabolic disease (PMD) when the increase is greater than 30% and 0.8 units, or a new lesion develops. The PET responses were dichotomized by metabolic response, and the CMR, PMR and SMD responses were collectively

considered as non-progressive metabolic disease (non-PMD).

Clinical response at 6 weeks was based on observation by the site investigator and the computed tomography (CT) findings. CT was obtained at baseline, and 6 weeks after IGF-1R antibody therapy was initiated. CT studies were performed at each of the participating institutions, and the response was also determined at the treating institution according to WHO criteria(*6*), which uses bi-dimensional measurements as a surrogate for tumor burden and four response groups: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The criteria for stopping treatment included unacceptable adverse events, patient decision to withdraw from the study, death, or disease progression as judged by the investigator. Patients having PD response on CT, OR clinical signs of progression that prevented further treatment were considered as the clinical non-benefit group; and the patients with CR, PR and SD responses on CT, AND no off-study criteria as seen by the investigator were collectively considered as the clinical benefit group.

*Statistical analysis*

We alternatively defined PET non-PMD at day 9 using a classification tree with one split to best separate the survival based on the $\%\Delta SUL_{peak}$. Associations of the clinical benefit at 6 weeks and the $^{18}$F-FDG PET measurements were summarized using boxplots and evaluated with Wilcoxon-Mann Whitney tests and kappa statistics.

Overall survival was calculated from the time of the first IGF-1R antibody treatment to the date of death or last clinical follow-up. PFS was calculated from the time of first IGF-1R

antibody treatment to the date of progression or death and censored at the last follow-up if no events occurred. Survival times were summarized using the Kaplan-Meier method and were compared using log-rank tests. Hazard ratios were estimated using univariate Cox proportional hazards models. Receiver operating characteristic (ROC) analysis was done to assess the predictive value of the $\%\Delta SUL_{peak}$ for clinical non-PD after 6 weeks of therapy. To evaluate the prognostic accuracy of the $\%\Delta SUL_{peak}$ at day 9 of treatment and of clinical benefit, time-dependent ROC analysis was performed to examine the sensitivity and specificity over time to predict OS and PFS outcomes(*7, 8*). Statistical analyses were performed using the R statistical package (version 2.15.1).

**Results**

Of the 115 patients, 101 patients died, and 14 were censored. The age of the patients ranged from 1 to 77 (median 21.9); 75 were male and 40 were female; the primary tumor location was in the bones in 65 patients and was extra-skeletal in 50 patients; and all patients had metastatic disease at the time of enrollment.

***Day 9 PET versus week 6 clinical response***

The $^{18}$F-FDG PET uptake changes from baseline to 9 days after IGF-1R therapy were measured quantitatively by $\%\Delta SUL_{peak}$ of the hottest tumor at each time point. The PET measurements according to dichotomized clinical responses at week 6 are shown in box plots in

figure 2. (A) The baseline SULpeak of lesions was not predictive of clinical benefit at 6 weeks. (B) The group with clinical non-benefit had a significantly higher SULpeak on $PET_{day9}$, and smaller declines in (C) absolute and (D) percent $\Delta SUL_{peak}$ compared to the clinical benefit group. The box plots including the outlier data points are in supplemental figure (online only). The area under the ROC curve (AUC) was obtained and the correlation of the $\%\Delta SUL_{peak}$ with the week 6 clinical-non-PD group was 0.79 (figure 3).

***Day 9 PET versus week 6 clinical response to predict overall survival (OS)***

The median OS was 8.1 months (95% CI, 6.4 to 10.0 months) for the 115 patients. The PET responses 9 days after therapy and the Kaplan Meier OS estimates are shown in table 1. Patients with PMD on $PET_{day9}$ had a significantly shorter survival time than the patients with CMR, PMR or SMD.

The Kaplan Meier estimation of OS using dichotomized $PET_{day9}$ and week 6 clinical response groups are shown in figure 4. Day 9 response by PERCIST showed shorter OS in patients with PMD (median 4.7 months, 95% CI 1.2 to 7.0 months) compared to non-PMD (median 10.0 months, 95% CI 6.9 to 12.9 months; log rank p value=0.001). When again dichotomized by best split cutoff for this study sample, the patients with a $\%\Delta SUL_{peak}$ decrease < 10.5% showed shorter OS (median 5.5 months, 95% CI 4.2 to 6.8 months) compared to patients with a decrease > 10.5% (median 11.7 months, 95% CI 8.9 to 18.1 months). The patients with clinical-non-benefit at week 6 also had shorter OS compared to patients with

clinical-benefit (median 5.6 months with 95% CI 4.2 to 7.7 months, versus median 13.9 months with 95% CI 10.3 to 18.6 months; log rank test p value<0.001).

The dichotomized clinical response, based on the week 6 CT plus clinical observation, and the dichotomized PERCIST response based on $PET_{day9}$ had a slight agreement with concordance in 44% of the cases (kappa 0.10). When dichotomized again by using the best split cutoff of 10.5% decline in $\%\Delta SUL_{peak}$, the concordance was 70% (kappa 0.41).

The different PET measurements, including the SULpeak changes from $PET_{baseline}$ to $PET_{day9}$, were associated with survival at different time points including 6, 12, 18 and 24 months after therapy by ROC analysis, as plotted in supplemental figure (online only). The $PET_{day9}$ SULpeak had an AUC of 0.75 for survival at 1 year, and the $\%\Delta SUL_{peak}$ had an AUC of 0.71 at 1 year. The $PET_{day9}$ response of PMD, higher SULpeak at $PET_{baseline}$ or $PET_{day9}$, and a rise in SULpeak from $PET_{baseline}$ to $PET_{day9}$ all showed increased hazard ratios for death at all the time points (table 2). The OS did not differ according to the site of the primary tumor, extra-skeletal versus bone, in this subset analysis of patients with PET images available for quantitative assessment (HR 1.04, 95% CI [0.7, 1.54]). The trade-offs of sensitivity and specificity of the day 9 PERCIST and week 6 clinical responses to predict survival at different time points can be seen in supplemental figure (online only).

***Day 9 PET vs. progression free survival (PFS)***

The predictive value of day 9 PET for PFS is discussed in the supplement section. The ROC curves of the PET measurements for PFS status at different time points are shown in supplemental figure (online only).

***Glucose level***

The fasting serum glucose level before and 2 weeks after IGF-1R therapy were compared in 100 of the 115 patients in this study. The glucose levels were not statistically different before or after therapy (99.5±27.0 mg/dl versus 100.8±33.6 mg/dl; p=0.68).

***Tumor site***

Though the SARC-11 study reported higher response rate in patients with bone primary compared to patients with extra-skeletal primary (1), in this study sub-population with PERCIST analysis the OS did not differ significantly according to the site of the primary tumor (HR 1.04, 95% CI [0.7, 1.54]). However, in an exploratory analysis, a statistically significant interaction was observed between the site and PET parameters of absolute SULpeak decrease > 0.8 units and $\%\Delta SUL_{peak}$ decrease > 30% (interaction term p-values 0.018 and 0.036, respectively), consistent with higher likelihood of response in patients with bone primary. This suggests that the prognostic effects of early PET response may depend on the site of the primary tumor in this sub-set of patients with quantitative PET analysis as well.

***SUVmax***

We also measured the SUVmax and analyzed the PET response according to the EORTC recommendations. For predicting survival at 1 year following therapy, the baseline SUVmax had ROC-AUC of 0.631 and the % change in SUVmax had ROC-AUC of 0.691. The OS of responder vs. non-responder based on EORTC recommendations were 305 days (95% CI 239, 371) vs. 151 days (95% CI 123, 179).

***Further PET follow-up***

Only 26 patients had PET assessment at week 12, and thus further evaluation of the later PET studies was not performed (supplemental table, online only). Understandably, the patients who had week 12 $^{18}$F-FDG PET were those with better response at day 9 as they survived longer. Only 2 patients showed greater improvement following further therapy. 13 patients showed worsened response (46%). 11 patients (42%) had the same response on early and late PET images.

**Discussion**

The signaling pathway for the insulin-like growth factor (IGF) is regulated by growth hormone and is involved in cell growth, human development, and metabolism(*9*). The hypothesis that the IGF signaling may also be a regulator of tumor growth led to several clinical trials testing anti-IGF-1R drugs for various types of cancer(*10*). It is highly likely that when the target of the targeted therapy is absent there would be no clinical benefit. IGF-1R expression in tumors is often not quantifiable. Even if IGF-1R gene expression was quantified, the composition of homodimers and hybrid IGF-1R and insulin receptors will vary(*9-11*). The IGF1R protein level was a weak predictor of the sensitivity to IGF-1R inhibition therapy in lung cancer(*12*). There is currently no routine clinical test available to check the receptor status. Early identification or separation of patients likely to have a good or bad outcome can spare patients from ineffective treatment and the healthcare system from unnecessary cost. $^{18}$F-FDG PET can be used as a biomarker for early patient selection of probable efficacy or non-efficacy - a hypothesis we explored in our study.

In this study, the prognostic and predictive value of early $^{18}$F-FDG PET response in patients with ESFT treated with IGF-1R antibody are reported for the first time. Response assessment at day 9 PET by PERCIST could distinguish patients with a favorable survival outcome. Previous publications that have shown the predictive or prognostic values of $^{18}$F-FDG PET in patients with ESFT were based on a relatively small number of patients with newly diagnosed disease, heterogeneous therapeutic approaches, or $^{18}$F-FDG PET performed at the end of induction chemotherapy(*3, 13, 14*). In contrast, our study is from a larger group of patients, who all had the same treatment with IGF-1R antibody as the single agent, and the

response to therapy was assessed early. Our study did not limit the assessment only to the primary tumor, but measured the metastatic lesions as well.

When assessing response to therapy by PERCIST, the change in $^{18}$F-FDG uptake is expressed as a continuous, quantitative variable - the %ΔSUL$_{peak}$ between the baseline and post-therapy PET studies. The dichotomization of PERCIST response according to PMD and non-PMD was an alternative categorization for the analysis of our current study. The cutoff of a 10.5% drop in %ΔSUL$_{peak}$ by 9 days after therapy showed two clearly distinct survival curves. However, the 10.5% decrease was computed retrospectively to obtain the statistically best split. Current clinical PET systems may not have the reproducibility to reliably detect a change of 10.5%(*15*). The 10.5% threshold will need to be prospectively confirmed as an appropriate cutoff for this form of therapy in this type of tumor. The %ΔSUL$_{peak}$ appears to have higher prognostic value than the absolute difference in SULpeaks as seen by the higher ROC-AUC. The findings on the PET$_{baseline}$ alone seemed to have only a weak independent prognostic value, and the post-therapy PET study provided additional prognostic value.

Of the 82 patients who did not have progression by PERCIST with PET$_{day9}$, 51 were considered to have progression using WHO criteria for the week 6 CT or clinical observation. The low sensitivity of PERCIST for future progressive disease could mean that the PERCIST criteria cutoff of 30% increase in SULpeak may be too high for response assessment very early into treatment such as in this study.

One concern with IGF-1R antibody therapy is the potential compensatory increase in growth hormone and IGF-1 production by the liver, leading to insulin resistance(*16*). If IGF-1R

disruption of the endocrine pathways leads to changes in the glucose level of the patients, the PET images could be affected by the competition between $^{18}$F-FDG, a glucose analogue, and serum glucose. The glucose levels were not statistically different before and after IGF-1R therapy in this study, and so the $^{18}$F-FDG uptake values were not affected by different serum glucose levels in the time period of this study.

The $^{18}$F-FDG PET images were collected from 31 different institutions, and often used earlier versions of PET systems, the institutions' clinical PET protocols and 2-dimensional reconstruction methods, instead of the currently available high definition PET systems. This study was one of the larger studies of PET done prospectively across many different centers in a large multi-institutional trial. The $^{18}$F-FDG PET images of 79(85%) of the patients in this "real-world" study done at multiple sites did not meet all the technical quality criteria defined by PERCIST for image acquisition and included variations in the injected $^{18}$F-FDG dose, variations in $^{18}$F-FDG uptake time and different scanners used for baseline and follow-up. There were 2 patients with the liver $^{18}$F-FDG uptake greater than 10, approximately 5 times greater than the reported normal range. They were excluded from the analyses of the absolute SULpeak values, but their $\%\Delta SUL_{peak}$ were included. These 2 patients did not have liver metastases. Despite the wide variations in imaging conditions and relatively inferior technical quality of the images included in this study, early $^{18}$F-FDG PET response using PERCIST had potential prognostic value, especially for selecting patients who will not go on to respond favorably to this novel treatment.

Early treatment response by $^{18}$F-FDG PET has been demonstrated to be a possible biomarker of clinical outcome for various types chemotherapies and for targeted cancer therapy, such as erlotonib for lung cancer therapy(*17*), and sunitinib or imatinib for gastrointestinal stromal tumors(*18, 19*).

Our current study includes a large number of patients with ESFT treated with IGF-1R antibody and indicates that $^{18}$F-FDG PET using PERCIST is a potential biomarker for early prediction of clinical response and survival. Such data with a novel biological treatment suggest the emerging role for $^{18}$F-FDG PET in early assessment of response to cancer treatment. From such early assessments, modifications of therapy may logically follow in "response adapted" paradigms.

**Conclusion**

$^{18}$F-FDG PET findings using PERCIST methods after only 9 days of therapy had a statistically significant association with subsequently determined clinical response, and more importantly with OS. Response assessment by $^{18}$F-FDG PET may be of use in early clinical decision making in patients with ESFT treated with IGF-1R antibody.

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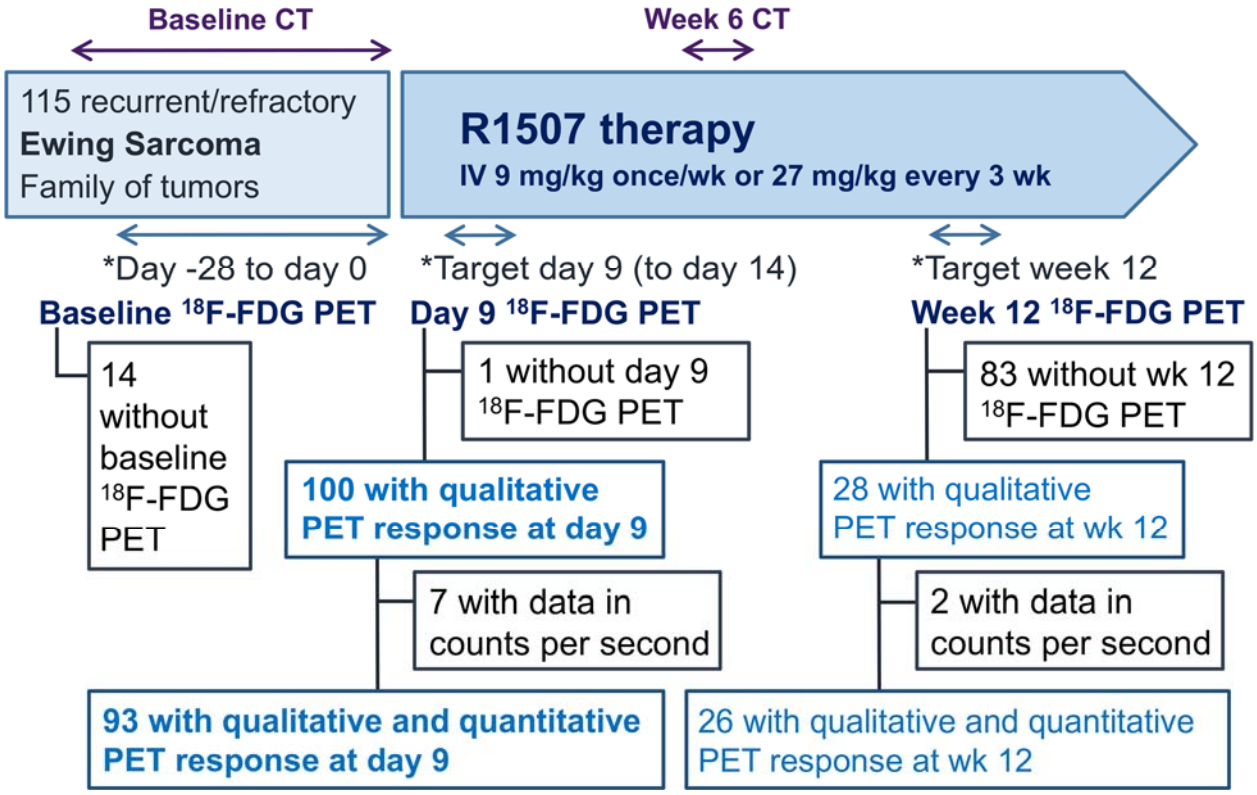


Figure 1. Schema of $^{18}$F-FDG PET images included in this study.

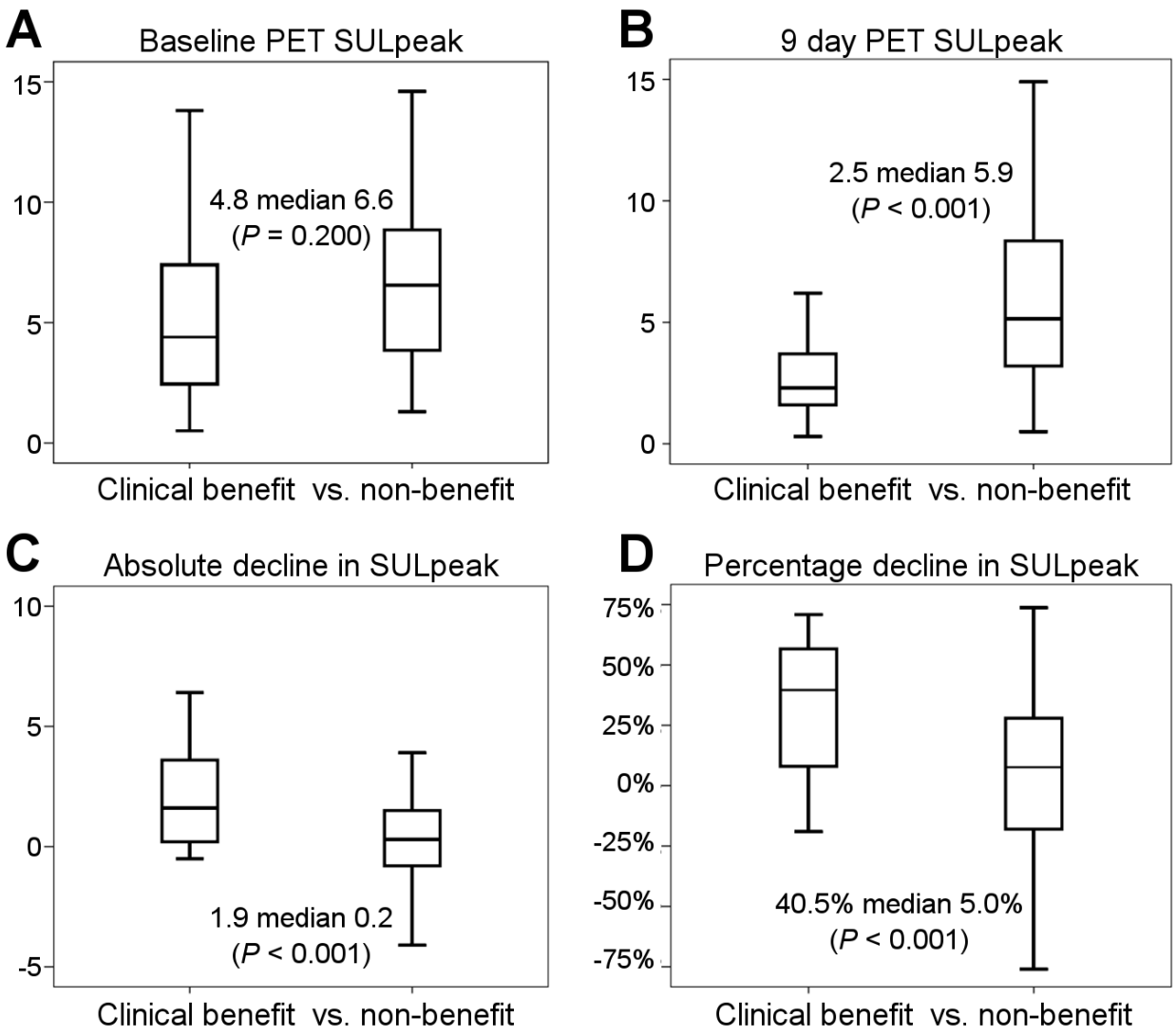


Figure 2. Box plots of SULpeak measurements at baseline and 9 days after therapy, and the status of the clinical response at 6 weeks after therapy. The median SULpeak from $PET_{day9}$ was significantly higher in the clinical non-benefit group. The absolute and percentage decline in SULpeak was significantly greater in the clinical benefit group.

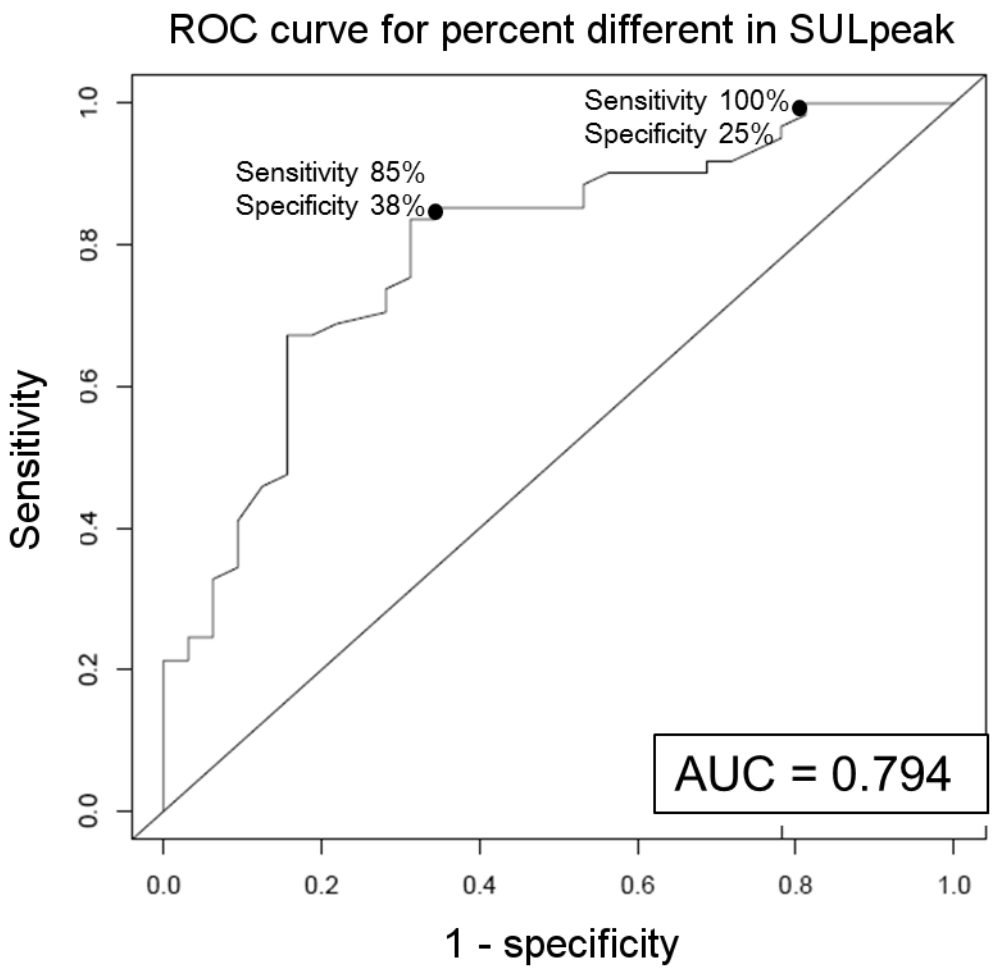


Figure 3. ROC curve of clinical-non-benefit at 6 weeks, using $\%\Delta SUL_{peak}$ from baseline to 9 days after therapy.

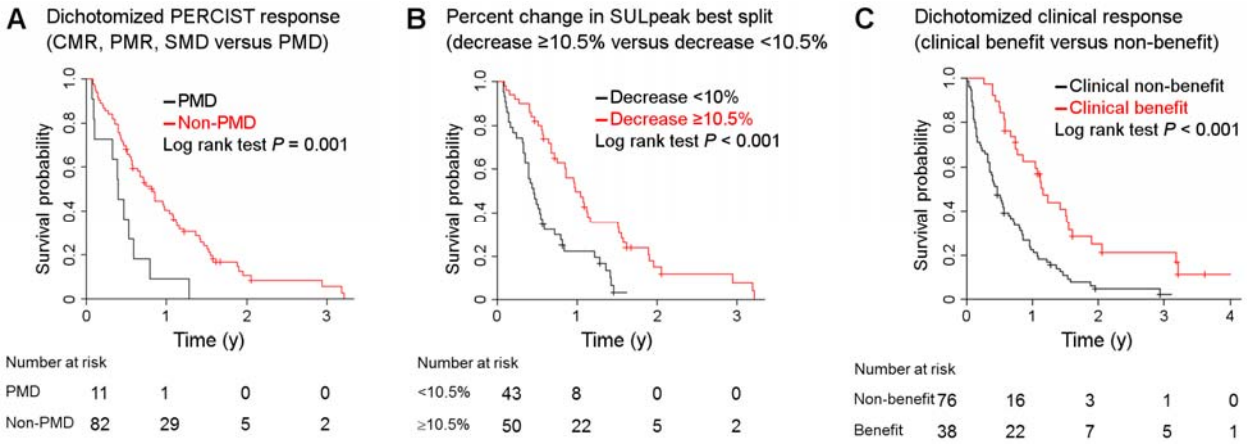


Figure 4. Kaplan Meier estimation of OS by dichotomized (A) day 9 PET response assessed by PERCIST, (B) $\%\Delta SUL_{peak}$ from $PET_{baseline}$ to $PET_{day9}$, and (C) week 6 clinical response based on WHO criteria assessment of week 6 CT and clinical observation.

Table 1. PET and CT responses and OS by each PET response category

| Modality and assessment time | Criteria | Response | Number of patients | OS (months) | |
|---|---|---|---|---|---|
| | | | | median | 95% CI |
| PET response after 9 days (n=93*) | PERCIST | CMR | 3 | 24.7 | (19.36, NA) |
| | | PMR | 29 | 12.9 | (10.2, 18.1) |
| | | SMD | 50 | 6.7 | (5.3, 10.0) |
| | | PMD | 11 | 4.7 | (1.2, 7.0) |
| Clinical response after 6 weeks (n=114*) | WHO and clinical observation | CR | 1 | - | - |
| | | PR | 17 | 17.0 | (9.2, 22.8) |
| | | SD | 20 | 12.5 | (6.1, 18.3) |
| | | PD | 76 | 5.6 | (4.2, 7.7) |

* 14 did not have baseline PET; 1 patient did not have day 9 PET; 7 patients had data in counts per second
*WHO criteria response data missing in 1 patient

Table 2. Proportional hazard models for mortality.

| | Hazard ratio | 95% CI | P value |
|---|---|---|---|
| Day 9 PERCIST response PMD vs. SMD, PMR or CMR | 2.86 | 1.46, 5.52 | 0.0017 |
| Week 6 WHO response PD vs. CR, PR or SD | 2.63 | 1.68, 4.12 | <0.0001 |
| | | | |
| Day 9 PERCIST response PMD or SMD vs. PMR or CMR | 1.95 | 1.21, 3.14 | 0.0058 |
| | | | |
| Baseline SULpeak > median of 5.9 vs. ≤ median | 2.06 | 1.32, 3.21 | 0.0015 |
| Day 9 SULpeak > median of 4.2 vs. ≤ median | 2.26 | 1.44, 3.56 | 0.0004 |
| | | | |
| Absolute SULpeak increase > 0.8 units vs. ≤ 0.8 units | 2.63 | 1.47, 4.71 | 0.0012 |
| Absolute SULpeak decrease > 0.8 units vs. ≤ 0.8 units | 0.70 | 0.45, 1.10 | 0.1200 |
| | | | |
| $\%\Delta SUL_{peak}$ increase > 30% vs. ≤ 30% | 2.15 | 1.09, 4.23 | 0.0267 |
| $\%\Delta SUL_{peak}$ decrease > 30% vs. ≤ 30% | 0.54 | 0.34, 0.87 | 0.0109 |