

Original Article

^{18}F -FDG-PET/CT and ^{18}F -NaF-PET/CT in men with castrate-resistant prostate cancer

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Abstract: To evaluate ^{18}F -labeled-fluorodeoxyglucose (^{18}F -FDG-) and ^{18}F -labeled-sodium fluoride (^{18}F -NaF-) positron emission tomography/computed tomography (PET/CT) as biomarkers in metastatic castrate-resistant prostate cancer (mCRPC). Nine men (53-75 years) in a phase 1 trial of abiraterone and cabozantinib had ^{18}F -FDG-PET/CT, ^{18}F -NaF-PET/CT and standard imaging ($^{99\text{m}}\text{Tc}$ -labeled-methylene-diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) bone scan and abdominal/pelvic CT) at baseline and after 8 weeks of therapy. Baseline disease was classified as widespread ^{18}F -FDG-avid, oligometastatic ^{18}F -FDG-avid (1 site), or non- ^{18}F -FDG-avid. Metabolic response was classified using European Organisation for Research and Treatment of Cancer (EORTC) criteria. Treatment response using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, Prostate Cancer Working Group 2 (PCWG2) guidelines and days on trial (DOT) were recorded. All men were followed for 1 year or until progression. Four men had ^{18}F -FDG-avid disease: two with widespread (DOT 53 and 76) and two with oligometastatic disease (DOT 231 and still on trial after 742+ days). Five men had non- ^{18}F -FDG-avid disease; three remained stable or improved (2 still on trial while one discontinued for non-oncologic reasons; DOT 225-563+), and 2 progressed (DOT 285 and 532). Despite the small sample size, Kaplan-Meier analysis showed a significant difference in progression free survival (PFS) between men with widespread ^{18}F -FDG-avid, oligometastatic ^{18}F -FDG-avid and non- ^{18}F -FDG-avid disease ($p < 0.01$). All men had ^{18}F -NaF-avid disease. Neither ^{18}F -NaF-avid disease extent nor intensity was predictive of treatment response. ^{18}F -FDG-PET/CT may be superior to ^{18}F -NaF-PET/CT and standard imaging in men with mCRPC on abiraterone and cabozantinib. ^{18}F -FDG-PET/CT may have potential to stratify men into 3 groups (widespread vs. oligometastatic ^{18}F -FDG-avid vs. non- ^{18}F -FDG-avid mCRPC) to tailor therapy. Further evaluation is warranted.

Keywords: PET/CT, FDG, NaF, prostate cancer, bone scan

Introduction

It is estimated that 233,000 new cases of prostate cancer will be diagnosed and 29,480 men will die of the disease in the United States in 2014 (<http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf>). Although most men initially respond to androgen deprivation therapy (ADT), progression to castration-resistant prostate cancer (CRPC) occurs in almost all cases and leads to death. Approximately 85% of men with metastatic CRPC (mCRPC) have bone metastases, and less than half have soft tissue disease [1].

Technetium- $^{99\text{m}}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) skeletal scintigraphy and diagnos-

tic abdominal/pelvic CT are the standard imaging modalities used to evaluate metastases and play an important role in patient management (<http://www.nccn.org/patients/guidelines/prostate/index.html#24>). Positron emission tomography/computed tomography with fluorine-18-sodium fluoride (^{18}F -NaF-PET/CT) has higher sensitivity and specificity for the detection of osseous metastases than standard imaging [2-5], however, it does not assess soft tissue disease and is not currently considered standard of care. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT can assess both soft tissue and osseous disease extent. Since mCRPC is often non- ^{18}F -FDG-avid, the utility of ^{18}F -FDG-PET/CT in this disease has been questioned [6-9]. Recently, a growing number of studies are

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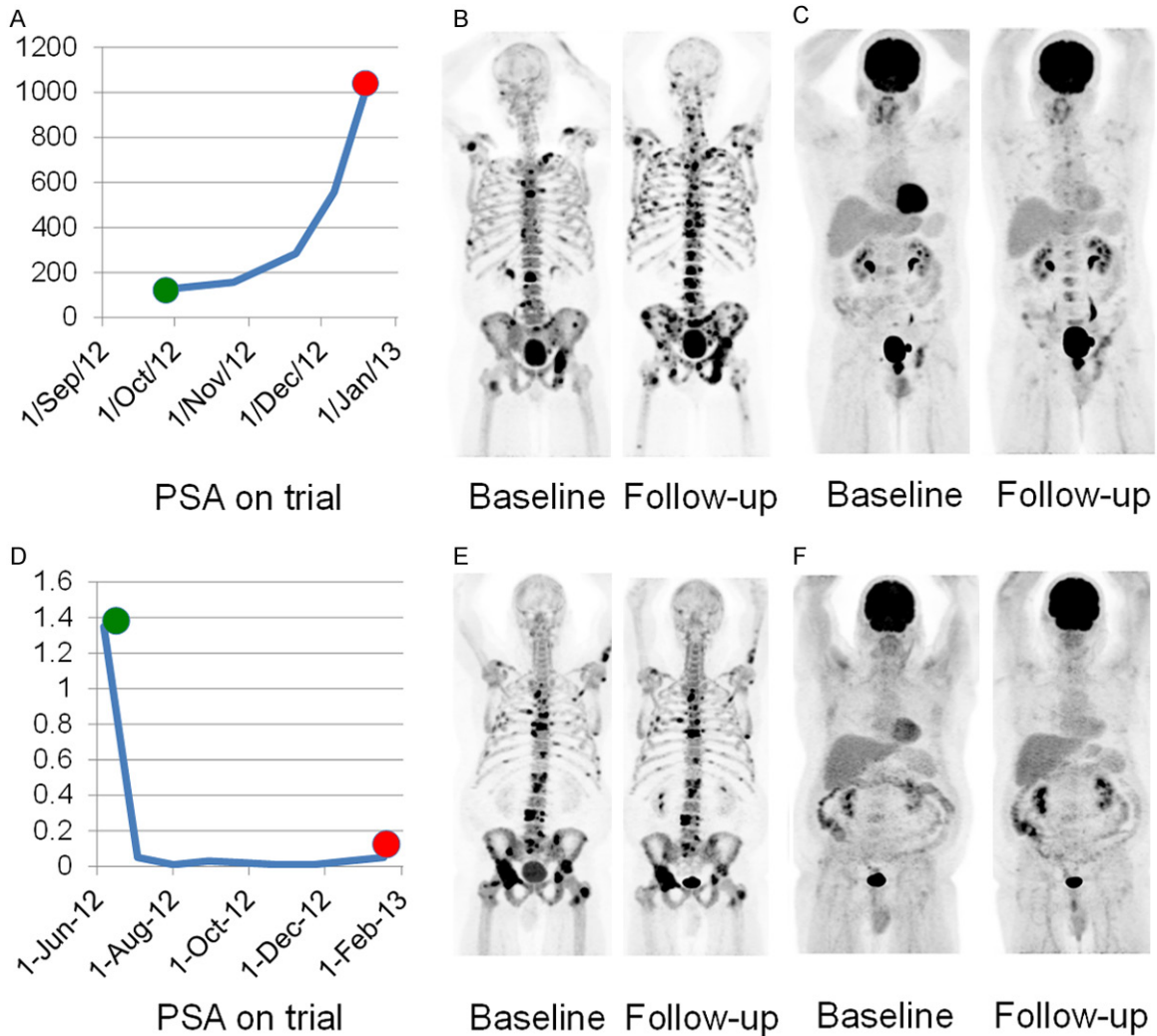


Figure 1. Change in PSA (A), ^{18}F -NaF-PET/CT (B) and ^{18}F -FDG-PET/CT (C) at baseline and 8 week follow-up in a man with mCRPC and widespread ^{18}F -NaF-avid and ^{18}F -FDG-avid disease who remained on trial for 53 days; Change in PSA (D), ^{18}F -NaF-PET/CT (E) and ^{18}F -FDG-PET/CT (F) at baseline and 8 week follow-up in a man with mCRPC, widespread ^{18}F -NaF-avid and non- ^{18}F -FDG-avid disease who remained on trial for 225 days.

showing that ^{18}F -FDG uptake is an independent prognostic factor in men with mCRPC and suggest ^{18}F -FDG-PET/CT may detect a subgroup of biologically more aggressive disease [10-14].

Over the last few years there has been a proliferation of therapies for men with mCRPC, although survival remains poor and determining the optimal approach to therapy is challenging [15-21]. Furthermore, certain medications such as cabozantinib, modulate osteoblastic turnover and can have a profound effect on $^{99\text{m}}\text{Tc}$ -MDP bone scans, limiting the ability of $^{99\text{m}}\text{Tc}$ -MDP bone scan to accurately reflect disease response to therapy [21-24]. ^{18}F -FDG- and ^{18}F -NaF-PET/CT have the potential to provide a quantitative evaluation of metastatic disease that may be complementary to standard imag-

ing. Our aim was to evaluate ^{18}F -FDG- and ^{18}F -NaF-PET/CT as biomarkers in men with metastatic castrate-resistant prostate cancer (mCRPC) enrolled in a phase 1 trial of abiraterone and cabozantinib. Namely we sought to evaluate the metabolic appearance and disease response of mCRPC in men on abiraterone and cabozantinib using ^{18}F -FDG- and ^{18}F -NaF-PET/CT and to compare this with standard imaging and progression-free survival (PFS).

Materials and methods

Experimental details & clinical trial conduct

The first nine men in a phase I multicenter trial of cabozantinib (Exelixis, San Francisco, CA) and abiraterone (Janssen Pharmaceuticals,

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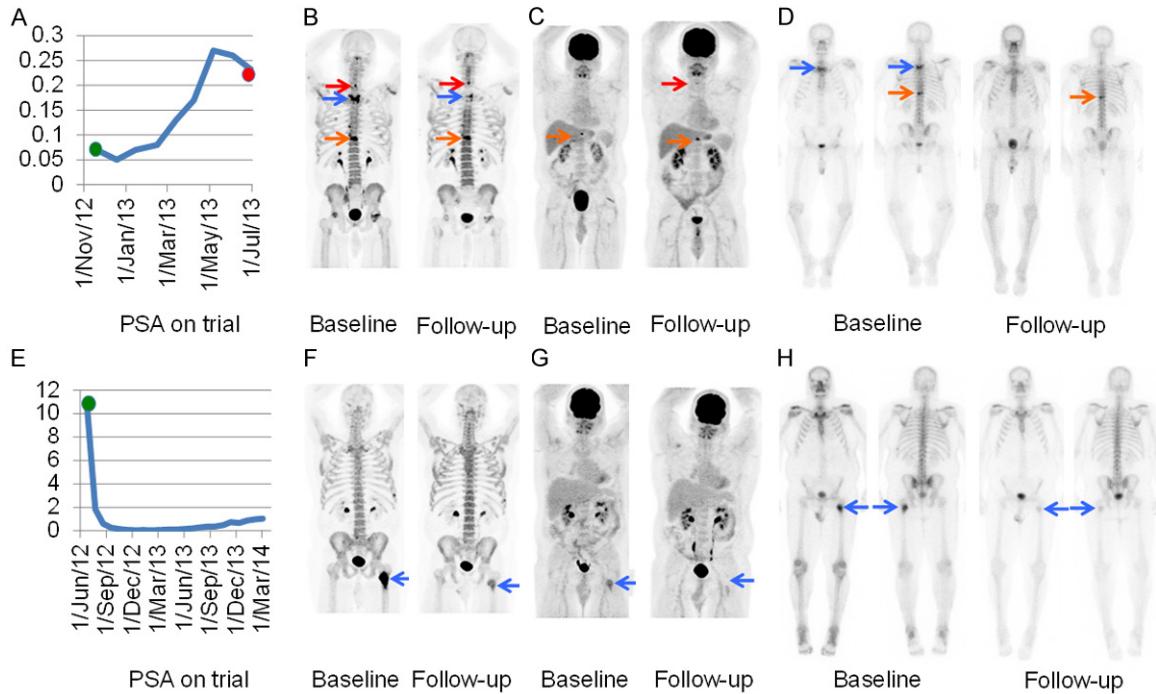


Figure 2. Change in PSA (A), ^{18}F -NaF-PET/CT (B), ^{18}F -FDG-PET/CT (C) and $^{99\text{m}}\text{Tc}$ -MDP bone scan (D) at baseline and 8 week follow-up in a man with baseline oligometastatic ^{18}F -FDG-avid disease, metabolic disease progression on ^{18}F -FDG-PET/CT, mixed change on ^{18}F -NaF-PET/CT and response on $^{99\text{m}}\text{Tc}$ -MDP bone scan following radiation from T1 to T4 prior to enrolling on the trial. Of note, the $^{99\text{m}}\text{Tc}$ -MDP bone scan performed after 6 months of therapy (not shown) suggested worsening disease similar to the ^{18}F -FDG-PET/CT performed at 8 weeks. The red, blue and orange arrows depict the C7, T2 and T10 lesions. Change in PSA (E), ^{18}F -NaF-PET/CT (F), ^{18}F -FDG-PET/CT (G) and $^{99\text{m}}\text{Tc}$ -MDP bone scan (H) at baseline and 8 week follow-up in a man with baseline oligometastatic ^{18}F -FDG-avid disease and metabolic disease response on ^{18}F -FDG-PET/CT, ^{18}F -NaF-PET/CT and $^{99\text{m}}\text{Tc}$ -MDP bone scan following radiation to the left femoral lesion (blue arrow) prior to enrolling on the trial.

Titusville, NJ) had whole-body ^{18}F -FDG- and ^{18}F -NaF-PET/CT at baseline and after 8 weeks of therapy as well as standard of care imaging ($^{99\text{m}}\text{Tc}$ -MDP bone scan and diagnostic abdominal/pelvic CT) at baseline and every 8 weeks on therapy. Institutional review board approval was obtained, each patient included in the study gave informed consent and the study was Health Insurance Portability and Accountability Act (HIPAA) compliant. All patients had progressive mCRPC and no prior treatment with cytochrome 17A1 (CYP17A1), mesenchymal-epithelial transition factor (MET) or vascular endothelial growth factor receptor (VEGFR) inhibitors. A history of radiation to a bone metastasis was allowed if this was more than 14 days prior to enrolling on the trial. Treatment cycles were 28 days with cycles repeated until disease progression or unacceptable toxicity. Efficacy of therapy was determined using standard criteria - a combination of symptomatic responses and PSA levels every 28 days as well as evaluation

of standard of care imaging. Treatment response using Prostate Cancer Working Group 2 (PWCG2) guidelines [25] and days on trial (DOT) were recorded. All men were followed prospectively until removed from the trial.

Image acquisition and analysis

Whole-body $^{99\text{m}}\text{Tc}$ -MDP bone scans were acquired in the anterior and posterior projections approximately 3 hours after IV administration of 20 mCi $^{99\text{m}}\text{Tc}$ -MDP. The diagnostic IV contrast-enhanced CT scans of the abdomen and pelvis were performed using collimation less than or equal to 3 mm and 5 mm reconstructed axial images. Each ^{18}F -FDG-PET/CT was acquired in three-dimensional mode, 60 ± 10 minutes after the intravenous administration of 10-15 mCi ^{18}F -FDG. Imaging was performed from the skull vertex through the mid thighs using a hybrid PET/CT scanner with images corrected for detector efficiency, attenuation,

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Table 1. Summary of response in 9 men with mCRPC

#	DOT	FDG category	Metabolic Response ¹⁸ F-NaF- PET/ CT SUV _{max}	Metabolic Response ¹⁸ F-NaF- PET/ CT SUV _{avg}	Metabolic Response ¹⁸ F-FDG- PET/ CT SUV _{max}	Metabolic Response ¹⁸ F-FDG- PET/ CT SUV _{avg}	Anatomic Response RECIST 1.1 after 8 weeks therapy	PCWG2 at time of last visit	TTP Based on clinical & radiologic findings
1	285	Non-avid	PR	SD	Non-avid	Non-avid	Non-measurable	SD	Clinical PD after 285 DOT
2	225	Non-avid	PR	PR	Non-avid	Non-avid	Non-measurable	SD	Suspected PD after 225 DOT determined to be non-oncologic on follow-up
3	742+	Oligometastatic disease	PR	PR	PR	N/A	Non-measurable	SD	Still on trial (DOT 742+)
4	53	Widespread disease	PD	PD	PD	PD	PD	SD	Clinical & imaging PD after 53 DOT
5	532	Non-avid	SD	SD	Non-avid	Non-avid	Non-measurable	SD	Clinical PD after 532 DOT
6	231	Oligometastatic disease	SD	SD	PD	N/A	Non-measurable	SD	Clinical PD after 231 DOT
7	563+	Non-avid	PR	PR	Non-avid	Non-avid	Non-measurable	SD	Still on trial (DOT 563+)
8	76	Widespread disease	PR	PR	PD	PD	SD	SD	Clinical PD after 76 DOT
9	516+	Non-avid	PR	PR	Non-avid	Non-avid	PR	PR	Still on trial (DOT 516+)

DOT = days on trial, TTP = time to progression, PR = partial response, SD = stable disease, PD = progressive disease.

Table 2. Semiquantitative PET/CT analysis in 9 men with mCRPC

Man #	SUV	¹⁸ F-NaF-PET/CT Baseline	¹⁸ F-NaF-PET/CT Follow-up	¹⁸ F-FDG-PET/CT Baseline	¹⁸ F-FDG-PET/CT Follow-up
1	SUV _{max}	33.1	23.5	Non-avid	Non-avid
	Average SUV _{max}	19.3	16.1		
2	SUV _{max}	68.8	47.1	Non-avid	Non-avid
	Average SUV _{max}	58.0	35.5		
3	SUV _{max}	51.2	14.3	4.9	2.9
	Average SUV _{max}	19.9	10.2	(1 lesion)	(1 lesion)
4	SUV _{max}	74.0	55.8	15.6	15.8
	Average SUV _{max}	45.7	38.7	7.0	5.7
5	SUV _{max}	33.7	32.1	Non-avid	Non-avid
	Average SUV _{max}	25.8	25.5		
6	SUV _{max}	61.8	59.8	7.0	9.1
	Average SUV _{max}	39.4	37.6	(1 lesion)	6.7 (2 lesions)
7	SUV _{max}	77.2	39.6	Non-avid	Non-avid
	Average SUV _{max}	40.2	16.7		
8	SUV _{max}	43.9	18.3	21.7	35.3
	Average SUV _{max}	37.4	14.5	15.1	13.8
9	SUV _{max}	19.1	11.6	Non-avid	Non-avid
	Average SUV _{max}	12.0	8.5		

scatter, decay and random coincidences. Patients fasted for 6 hours prior to the ¹⁸F-FDG-PET/CT. The ¹⁸F-NaF-PET/CT scan acquisition in three-dimensional mode from skull vertex to mid thighs was obtained 30-60 minutes after the IV injection of approximately 10 mCi ¹⁸F-NaF. There was no specific patient preparation required, however, patients were encouraged to drink 500-1000 ml of water shortly before and up to 500 ml water shortly after the radiopharmaceutical administration.

Consistency of image acquisition was maintained by adherence to a standard protocol and quality assurance program in accordance with National Cancer Institute (NCI) consensus guidelines [26]. Imaging was centrally reviewed for quality control and analysis without knowledge of patient status or outcome. Anatomic tumor response was classified where possible according to the best response achieved using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 applied to standard imaging obtained after 8 weeks of therapy and then at intervals of 2 months [27]. PET/CT studies were evaluated for disease extent and response. Baseline disease extent was classified as widespread ¹⁸F-FDG-avid disease, oligometastatic ¹⁸F-FDG-avid disease (1 site), and non-¹⁸F-FDG-

avid disease (**Figures 1 and 2**). For each PET/CT scan, the maximum standardized uptake value (SUV_{max}) of the most intense site of disease and the average SUV_{max} of up to the 5 most intense sites of disease (chosen to include as many involved organ systems as possible) were assessed at baseline and follow-up. Metabolic tumor response after 8 weeks of therapy was classified using European Organization for Research and Treatment of Cancer (EORTC) criteria based on thresholds in percentage change for SUV_{max} and average SUV_{max} of target lesions relative to baseline where: partial metabolic response (PR) ≤ -25% < stable metabolic disease (SD) < +25% ≤ progressive metabolic disease (PD) [28]. A new site of metabolically active met-

astatic disease was classified as PD regardless of percentage change.

Results

Nine men (age 53-75 years) with mCRPC had ¹⁸F-FDG- and ¹⁸F-NaF-PET/CT scans at baseline and after 8 weeks of therapy (**Table 1**). Four (44%) had ¹⁸F-FDG-avid disease and 5 (56%) had non-¹⁸F-FDG-avid baseline disease. All men with ¹⁸F-FDG-avid baseline disease had ¹⁸F-FDG-avid disease after 8 weeks of therapy while all men without ¹⁸F-FDG-avid baseline disease had non-¹⁸F-FDG-avid disease after 8 weeks of therapy. All 9 men had ¹⁸F-NaF-avid disease (widespread in 8 men) at baseline and follow-up.

Two of 4 men with ¹⁸F-FDG-avid baseline disease had widespread disease and the shortest time to progression (DOT 53 and 76); of the two patients with oligometastatic ¹⁸F-FDG-avid disease, one had progressive disease (DOT 231) and one is without progression (still on trial after 742+ days). Overall, the SUV_{max} and average SUV_{max} were higher in men with widespread versus oligometastatic ¹⁸F-FDG-avid disease (**Table 2**). Five men had non-¹⁸F-FDG-avid baseline disease and three had stable or

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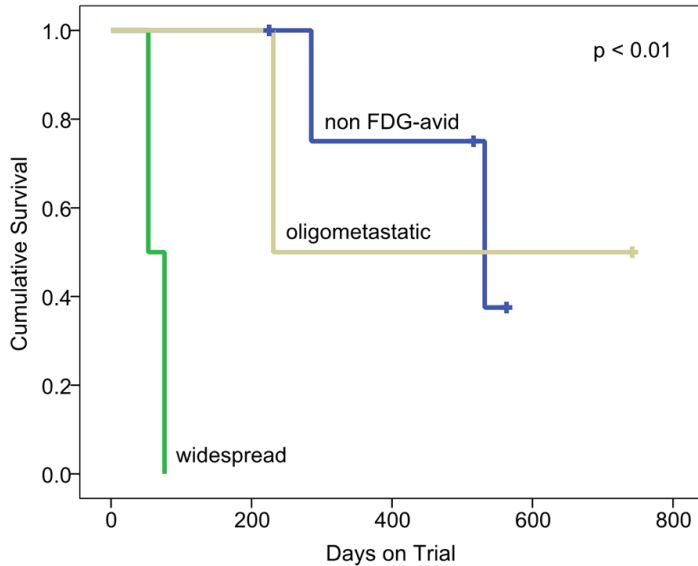


Figure 3. Progression-free survival of the 9 men with mCRPC included in the study according to baseline disease classification on ^{18}F -FDG-PET/CT.

improved disease. Of these three, two are still on trial (DOT 516+ and 563+, respectively) and one discontinued for non-oncologic reasons (DOT 225). The remaining 2 men with non- ^{18}F -FDG-avid baseline disease had progressive disease but with longer DOT (285 and 532) than the 3 men with ^{18}F -FDG-avid progressive disease. Despite our small sample size, univariate analysis (**Figure 3**) showed a statistically significant difference in response among the 3 groups of men ($p < 0.01$); those with widespread ^{18}F -FDG-avid disease progressed more rapidly than men with oligometastatic or non- ^{18}F -FDG-avid disease. Of the 2 men with oligometastatic disease, one had a single site of ^{18}F -FDG-avid disease at T10 and a history of radiation from T1 to T4 prior to enrolling on the trial. Follow-up ^{18}F -FDG-PET/CT showed a new site of ^{18}F -FDG-avid disease at C7 and progression of ^{18}F -FDG-avid disease at T10. This man was removed from the trial due to cord compression from mCRPC disease at T10, the only site of baseline ^{18}F -FDG-avid disease. The other patient had a single site of baseline ^{18}F -FDG-avid disease in the left femur, which was radiated prior to enrolling on the trial. Follow-up imaging showed disease improvement at this site (**Figure 2**).

All men had ^{18}F -NaF-avid disease, which was widespread in 8 men. Only one had relatively limited ^{18}F -NaF-avid disease (3 sites).

Subjectively ^{18}F -NaF-PET/CT detected more sites of skeletal metastatic disease than $^{99\text{m}}\text{Tc}$ -MDP bone scan regardless of whether the disease was sclerotic, lytic or ^{18}F -FDG-avid.

Subjectively ^{18}F -NaF-PET/CT and ^{18}F -FDG-PET/CT could identify therapy response at an earlier timepoint than standard imaging. Indeed, 6 of 9 men (67%) had metastatic disease only to bone and the disease response using RECIST 1.1 could not be measured. With PCWG2 criteria, 8 of 9 men (89%) had SD at the time of their last scheduled clinic trial visit and scanning; this included 2 men with rapid interval clinical progression on therapy (DOT 53 and 76) and 2 men who are still on trial (DOT 563+ and 742+) at the time of reporting. Further, we suggest that ^{18}F -FDG

appeared to be better than ^{18}F -NaF for the evaluation of therapeutic response (**Table 1**, **Figures 1-3**). Indeed, ^{18}F -NaF-avid baseline disease extent and intensity did not appear to be associated with clinical treatment response, while ^{18}F -FDG-avid baseline disease extent and intensity did appear to be associated with treatment response.

Discussion

Recent advances have led to the approval of several new therapies for men with mCRPC [15-19]. Another agent that is currently under investigation is cabozantinib. Results from a phase II randomized discontinuation trial have shown that cabozantinib is associated with pain response, decreased markers of bone turnover, improvement on bone scans, and longer PFS. In this trial, 171 men with mCRPC were given 100 mg cabozantinib daily, 149 men had evidence of bone metastases at baseline, and 116 men (78%) had at least one follow-up bone scan evaluable for response. Bone scans were improved in 79 men (68%). Baseline pain was reported by 92 men with bone metastases, with 71 men taking narcotics to control the pain. Among men with at least one available follow-up assessment of pain or narcotic use, 67% (56 of 83 men) reported an improvement in pain control and 56% (31 of 55 patients)

reported a decrease or discontinuation of narcotic use. Thirty-one men with stable disease after 12 weeks on trial were randomly assigned to receive cabozantinib or placebo and the median PFS was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) with cabozantinib versus 5.9 weeks (95% CI, 5.4 to 6.6 weeks) with placebo (hazard ratio, 0.12; $p < 0.001$) [21]. Preliminary results in the literature suggest there is an effect of cabozantinib at doses ranging from 20 mg to 100 mg on ^{99m}Tc -MDP bone scans [22]. However, this may be due to a combination of osteoblast modulation and anti-tumor effect [23-24]. Since ^{99m}Tc -MDP uptake is linked with osteoblastic activity and cabozantinib appears to block MET and VEGFR-2 phosphorylation in prostate cancer and osteoblast cells, bone scans may not be an accurate measure of anti-tumor therapy response. Therefore, in men on cabozantinib it is possible that standard imaging is limited and there is a need to pursue different imaging modalities such as PET/CT in this context.

^{18}F -NaF- and ^{18}F -FDG are the two most ubiquitous PET tracers available. Several studies have shown ^{18}F -NaF-PET/CT has superior sensitivity and specificity compared with ^{99m}Tc -MDP bone scans [2-5]. Single photon emission computed tomography (SPECT) alone or in combination with CT (SPECT/CT) can improve the sensitivity and specificity of ^{99m}Tc -MDP bone scans [3-4] but still remains inferior to ^{18}F -NaF-PET/CT. Tateishi et al. [5] published a meta-analysis on the topic in 2010 in which they concluded that the pooled sensitivity and specificity of ^{18}F -NaF PET/CT across 10 studies was 96% and 98% respectively compared with the pooled sensitivity and specificity of ^{99m}Tc -MDP bone scans (with and without SPECT) across 8 studies, which was 57% and 98% respectively. In an effort to assess ^{18}F -NaF-PET/CT for the detection of skeletal metastases, the National Oncologic PET Registry (NOPR), a collaboration of the American College of Radiology Imaging Network, the American College of Radiology, and the Academy of Molecular Imaging, enrolled 20,238 patients in a registry between February 2010 and April 2013 [29]. In total, 3,531 scans were performed in 3,396 men with prostate cancer. A preliminary data analysis published in 2014 showed ^{18}F -NaF-PET/CT significantly affected patient management in terms of initial staging, suspected first skeletal metastasis and progression of known skeletal disease.

Although ^{18}F -NaF-PET/CT likely provides a better estimate of disease burden than ^{99m}Tc -MDP bone scans, ^{18}F -NaF uptake is related to osteoblastic turnover and not to the presence of malignant cells themselves. Thus, ^{18}F -NaF-PET/CT provides an indirect measure of osseous metastases similar to ^{99m}Tc -MDP bone scans, and does not accurately measure the burden of malignant cells. ^{18}F -FDG-PET/CT has also been investigated in mCRPC. However, the benefit in men with prostate cancer is often questioned, largely because ^{18}F -FDG uptake by prostate cancer cells is variable and often low [30]. Minamimoto et al. and Watanabe et al. found that ^{18}F -FDG-PET/CT had a sensitivity $< 40\%$ for the detection of prostate cancer [6-7]. This may be due to a combination of factors including, low glucose metabolism related to decreased expression of glucose transporters (such as Glut-1), or to the use of fructose rather than glucose [31]. Jadvar et al. also found low sensitivity for ^{18}F -FDG-PET/CT in men with prostate cancer [8]. Indeed, the results of ^{18}F -NaF- and ^{18}F -FDG-PET/CT in 37 men with biochemical relapse after definitive therapy for localized prostate cancer suggested ^{18}F -NaF-PET/CT was useful to detect occult osseous metastases while ^{18}F -FDG-PET/CT was limited. However, these men were at an earlier stage in the continuum of prostate cancer disease than men in our study (biochemical recurrence versus mCRPC, respectively) and had limited long-term follow-up (median 24 weeks, range 1-49 weeks). Thus, it might be expected that the burden of aggressive disease would be lower in the cohort of men studied by Jadvar et al. Further, based on the reported results, it is difficult to determine if sites of ^{18}F -FDG-avid disease was more aggressive in the long-term. Recently, several studies have shown ^{18}F -FDG uptake reflects prognosis. When Jadvar and colleagues evaluated ^{18}F -FDG-PET/CT in 87 men with mCRPC they found the sum of lesions' SUVmax contributed independent prognostic information on overall survival (OS) [12]. Vargas et al. studied ^{18}F -FDG-PET/CT in 38 men with mCRPC and suggested that the number of lesions was associated with OS [32].

In our study, we assessed 9 men with mCRPC treated with abiraterone and cabozantinib. The majority of men (89%) had extensive baseline osseous metastatic disease, which is consistent with the skeleton being the most common site of prostate cancer metastases [1] and the

men in our study had advanced disease. ^{18}F -NaF-PET/CT showed more skeletal lesions than conventional imaging. Results in the literature suggest the number of osseous lesions is an independent prognostic factor in prostate cancer [32-34], however the large number of men with mCRPC and extensive ^{18}F -NaF-avid disease makes it difficult to adopt a practical approach using ^{18}F -NaF-PET/CT to stratify patients in a way that provides *a priori* insight into prognosis. Also, the intensity of baseline ^{18}F -NaF-avid disease did not provide information on therapy response and changes on ^{18}F -NaF-PET/CT following therapy did not consistently reflect DOT. Since cabozantinib may impact both osteoblastic and cancer cells, ^{18}F -NaF-PET/CT may be limited in its ability to measure anti-cancer therapy response in this population.

^{18}F -FDG-PET/CT provided complementary information to ^{18}F -NaF-PET/CT and conventional imaging. Five of nine men (56%) had non- ^{18}F -FDG-avid disease at baseline. We found that ^{18}F -FDG-PET/CT identified patients likely to respond to abiraterone and cabozantinib therapy *a priori*. Of the 4 men with ^{18}F -FDG-avid disease at baseline, DOT was significantly shorter than for the 5 men with non- ^{18}F -FDG-avid disease. Our results suggest ^{18}F -FDG-PET/CT may be a practical tool for classifying baseline disease into one of 3 categories: widespread ^{18}F -FDG-avid disease, oligometastatic ^{18}F -FDG-avid disease (1 lesion) and non- ^{18}F -FDG-avid disease. The main limitation of this study was the small sample size as this was conducted to generate pilot data in this patient population. However, despite our small sample size, univariate analysis revealed a statistically significant difference ($p < 0.01$) among these 3 groups. The two men with widespread disease did worse than the two men with oligometastatic disease, while the five men with non- ^{18}F -FDG-avid disease did better.

The concept of an oligometastatic disease state has previously been defined as a state where the number of metastatic deposits is limited [35]. The literature suggests that eradication of oligometastatic tumors either with surgery or radiation may increase survival [36-39]. Although not standard of care, it has been suggested that it may be worth considering aggressive local treatment to all sites of metastases in men with prostate cancer and ≤ 5 metastatic

lesions [40]. There were two men with a single site of ^{18}F -FDG-avid oligometastatic disease included in our preliminary data. One man, with a solitary site of baseline ^{18}F -FDG-avid disease and no history of radiation prior to enrolling on the trial, developed cord compression from progression at this site of baseline ^{18}F -FDG-avid disease while on the trial and was radiated to this site of disease following removal from the trial (DOT 231). The other man, with a solitary site of baseline ^{18}F -FDG-avid disease, had a history of radiation to the only site of ^{18}F -FDG-avid prior to enrolling on the trial. Although this site of disease demonstrated baseline ^{18}F -FDG avidity, it improved on follow-up imaging and this man had significantly longer PFS (DOT 742+). Our preliminary data suggest that a lower burden of ^{18}F -FDG-avid disease is associated with longer PFS. Also, radiation targeted to the site of ^{18}F -FDG-avid oligometastatic disease may provide benefit despite the presence of more extensive ^{18}F -NaF-avid disease elsewhere (**Figure 2**).

Finally, we found that, overall, the SUV_{max} and average SUV_{max} was higher in men with widespread versus oligometastatic ^{18}F -FDG-avid disease. Although both men with widespread intensely ^{18}F -FDG-avid osseous disease had ^{18}F -FDG-avid soft tissue disease as well, and did poorly (DOT 53 and 76), there was one man who had non- ^{18}F -FDG-avid soft tissue and skeletal disease, who remained on the trial for a considerably longer period of time (DOT 516+). This suggests that ^{18}F -FDG-avid bone disease rather than the presence of soft tissue disease may be a more important factor in terms of survival.

Conclusion

Our data suggest that baseline ^{18}F -FDG-PET/CT may identify men with mCRPC who are likely to benefit from cabozantinib and abiraterone therapy more reliably than standard imaging. Further, ^{18}F -FDG may be superior to ^{18}F -NaF in this patient population. Finally, ^{18}F -FDG-PET/CT has the potential to stratify men with mCRPC into 3 groups (widespread ^{18}F -FDG-avid disease, oligometastatic ^{18}F -FDG-avid disease and non- ^{18}F -FDG-avid disease) to tailor therapy. A major unmet clinical need in men with mCRPC is the development of biomarkers to identify those who will benefit from therapy while avoiding futile expensive and toxic treatment. Ideally,

a non-invasive biomarker could be used to personalize therapy. Given the relatively easy access to ^{18}F -FDG compared with novel PET tracers, ^{18}F -FDG-PET/CT may prove to be an attractive, practical tool to triage men with mCRPC to receive appropriate therapy that could easily be adopted into clinical practice. Further evaluation is warranted.

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Disclosure of conflict of interest

Dr. Sweeney and Dr. Kantoff served as a consultant for from Exelixis and Janssen during the conduct of the study; the remaining co-authors have nothing to disclose.

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