Interlesional Response Assessment With ^{18}F-Sodium Fluoride (^{18}F-NaF) PET/CT in Men With Chemotherapy-Naive Bone Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated With Enzalutamide

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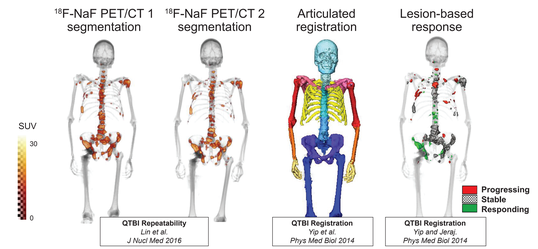
BACKGROUND

- ^{18}F-NaF positron emission tomography/computed tomography (PET/CT) scan is an approved tool to detect and evaluate osteoblastic metastases that is more sensitive and specific than conventional bone scintigraphy.[1,2]
- Quantitative total bone imaging (QTBI) is an advanced image quantification method that can identify, quantitate, and determine treatment response at the lesion level between ^{18}F-NaF PET/CT scans (**Figure 1**).[3-5]
- Although biologic heterogeneity is reported in solid tumors,[6] interlesional response to heterogeneity is under-recognized and is a critical clinical issue.
- Here we assess the proportion of men treated with enzalutamide with responding lesions by ^{18}F-NaF PET/CT scan at the time of prostate-specific antigen (PSA), standard radiographic, or clinical progression.

Figure 1. Examples of QTBI

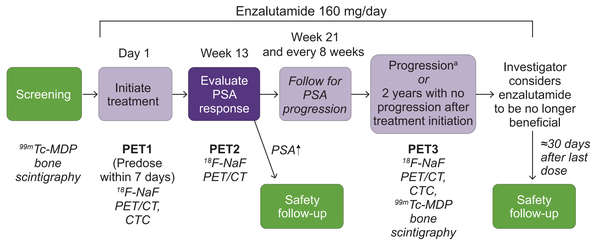


Abbreviations: NaF, sodium fluoride; QTBI, quantitative total bone imaging; SUV, standardized uptake value.

METHODS

- The study schema is presented in **Figure 2**.

Figure 2. Study Schema



Abbreviations: ^{18}F-NaF, ^{18}F-sodium fluoride; ^{99m}Tc-MDP, technetium-99m-methylene diphosphonate; CTC, circulating tumor cells; PET1, baseline; PET2, week 13; PET3, time of PSA progression, standard radiographic or clinical progression, or 2 years without progression; PET/CT, positron emission tomography/computed tomography; PSA, prostate-specific antigen.
[a]PSA, radiographic (bone or soft tissue), or clinically relevant (eg, significant bone pain or skeletal-related event). Patients who did not progress on enzalutamide and were considered to benefit from treatment by the investigator had the option to continue enzalutamide.

Objectives and Endpoints

- The primary objective was to evaluate ^{18}F-NaF PET/CT imaging as a method to determine treatment response in metastatic bone lesions at the time of disease progression (PSA, bone or soft tissue, or other clinically relevant progression) or at 2 years without progression after treatment in patients with chemotherapy-naive mCRPC treated with enzalutamide.
- ^{18}F-NaF PET/CT scans were obtained at baseline (PET1), week 13 (PET2), and at the time of PSA progression (defined per Prostate Cancer Working Group 2 guidelines as an increase of ≥ 25% and ≥ 2.0 ng/mL above nadir[7]), standard radiographic or clinical progression, or at 2 years without progression (PET3) based on QTBI.
  - Circulating tumor cells for genomic analysis were obtained; results will be presented at a later date.
- The primary endpoint was the proportion of men with ≥ 1 responding bone lesion on PET3 (defined as a lesion with a total ^{18}F-NaF standardized uptake value [SUV] less than baseline).
  - Evaluable men had scans at PET1 and PET3.

Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or signet-cell or small-cell features.
- Presence of bone metastatic disease, as assessed by ≥ 2 lesions on whole-body radionuclide ^{99m}Tc-MDP bone scintigraphy.
- Progressive disease on androgen deprivation therapy at screening, defined as a minimum of 2 sequentially rising PSA values, with the last PSA value at ≥ 2 ng/mL.
- No prior enzalutamide, abiraterone acetate, aminoglutethimide, ketoconazole, radium-223 dichloride (or other bone-targeting radionuclides), cytotoxic chemotherapy, or investigational agents that inhibit the androgen receptor or androgen synthesis for CRPC.
- No visceral metastasis.
- No radiation therapy within 4 weeks.

RESULTS

Demographics and Baseline Characteristics

- A total of 23 men with a median age of 72 years (range, 51-93) and a median PSA of 20.5 ng/mL (range, 3.9-133.6) were enrolled (**Table 1**).

Table 1. Demographic and Baseline Patient Characteristics

Characteristic	Enzalutamide (N = 23)
Median age (range), y	72 (51-93)
Race, white, no. (%)	21 (91.3)
ECOG PS, no. (%)	
0	16 (69.6)
1	7 (30.4)
Median serum PSA (range), ng/mL	20.5 (3.9-133.6)
Median Gleason score, range	7.0 (5.0-9.0)
Prior radiotherapy, no. (%)	
Yes	14 (60.9)
No	9 (39.1)
Prior surgery, no. (%)	
Yes	15 (65.2)
No	8 (34.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

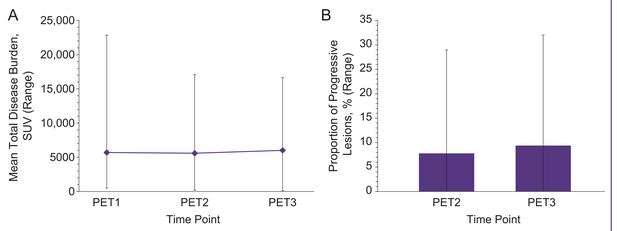
Primary Endpoint

- The study met its primary endpoint, with 22 out of 22 (100%) evaluable men having ≥ 1 responding bone lesion on QTBI at PET3.

Disease Burden

- The mean disease burden, as measured by total SUV, did not change significantly over time (**Figure 3A**).
- The proportion of progressive lesions increased from a mean 7.8% (range, 0-29) at PET2 to a mean 9.4% (range, 0-32) at PET3 (**Figure 3B**).

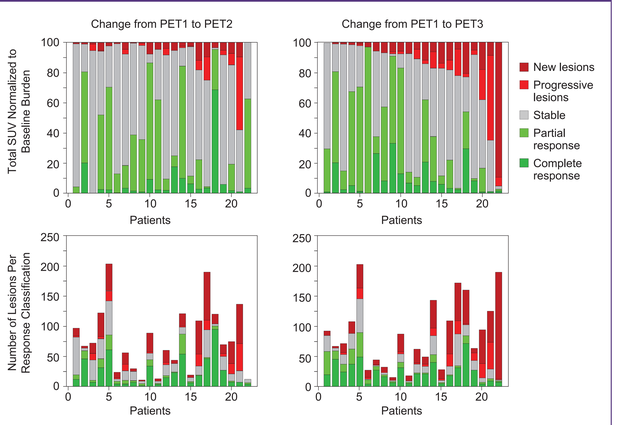
Figure 3. Disease Burden (A) and Number of Progressing Lesions (B) Over Time



Abbreviations: PET1, baseline; PET2, week 13; PET3, time of PSA progression, standard radiographic or clinical progression, or 2 years without progression; SUV, standardized uptake value.

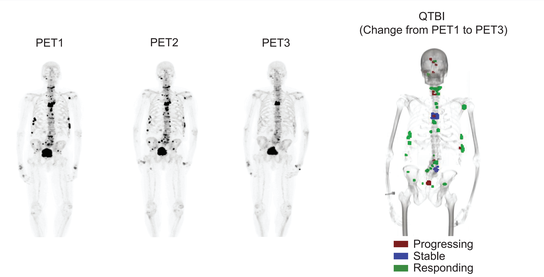
- All patients had a mixture of progressive, stable, and responding lesions at PET3 (**Figures 4 and 5**).

Figure 4. Change in Disease Burden and Number of Lesions Per Response Classification



Abbreviations: PET1, baseline; PET2, week 13; PET3, time of PSA progression, standard radiographic or clinical progression, or 2 years without progression; SUV, standardized uptake value.

Figure 5. Example of QTBI in a Patient



Abbreviations: PET1, baseline; PET2, week 13; PET3, time of PSA progression, standard radiographic or clinical progression, or at 2 years without progression; QTBI, quantitative total bone imaging.

Safety

- Enzalutamide was generally well tolerated.

CONCLUSIONS

- All patients had responding disease at the time of progression or at 2 years.
  - This supports the hypothesis that a substantial number of lesions continue to benefit from enzalutamide treatment beyond progression.
- While overall functional disease burden improved during treatment, an eventual increase in global burden was seen at the time of progression as measured by ^{18}F- NaF PET/CT.
- At the time of primary endpoint analysis, the proportion of progressing lesions is low.
  - This supports the concept of treating beyond progression and selectively targeting nonresponding lesions while keeping patients on enzalutamide.
- QTBI allows identification of men with suboptimal response to treatment that may benefit from more aggressive approaches, including the following:
  - Addition of, or change to, more intensive systemic therapies.
  - In men with oligoresistant disease, early ablation of nonresponding lesions to maximize treatment response and delay progression.
  - In men with oligoprogressive disease at the time of PSA progression, identification and ablation of progressive lesions to extend clinical benefit with enzalutamide.

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