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Assessment of the bone scan index in a randomized placebo-controlled trial of tasquinimod in men with metastatic castration-resistant prostate cancer (mCRPC)

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Abstract

Introduction: Drug development and clinical decision making for patients with metastatic prostate cancer (PC) have been hindered by a lack of quantitative methods of assessing changes in bony disease burden that are associated with overall survival (OS). Bone scan index (BSI), a quantitative imaging biomarker of bone tumor burden, is prognostic in men with metastatic PC. We evaluated an automated method for BSI calculation for the association between BSI over time

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6. Conflicts of interest

Armstrong, Pili, Stadler, Carducci, and Damber received research support from Active Biotech. Nordle, Forsberg, and Hansen are employees of Active Biotech. Edenbrandt is an employee of EXINI. Morris receives research support from Exini.

Appendix A. Supplemental materials

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with clinical outcomes in a randomized double-blind trial of tasquinimod (TASQ) in men with metastatic castration-resistant PC (mCRPC).

Methods: Bone scans collected during central review from the TASQ trial were analyzed retrospectively using EXINIbone^{BSI}, an automated software package for BSI calculation. Associations between BSI and other prognostic biomarkers, progression-free survival, OS, and treatment were evaluated over time.

Results: Of 201 men (57 TASQ and 28 placebo), 85 contributed scans at baseline and week 12 of sufficient quality. Baseline BSI correlated with prostate-specific antigen and alkaline phosphatase levels and was associated with OS in univariate (hazard ratio [HR] = 1.42, $P = 0.013$) and multivariate (HR = 1.64, $P < 0.001$) analyses. BSI worsening at 12 weeks was prognostic for progression-free survival (HR = 2.14 per BSI doubling, $P < 0.001$) and OS (HR = 1.58, $P = 0.033$) in multivariate analyses including baseline BSI and TASQ treatment. TASQ delayed BSI progression.

Conclusions: BSI and BSI changes over time were independently associated with OS in men with mCRPC. A delay in objective radiographic bone scan progression with TASQ is suggested; prospective evaluation of BSI progression and response criteria in phase 3 trials of men with mCRPC is warranted.

Keywords

Tasquinimod; Image analysis; Radionuclide imaging; Bone metastases; Prostate cancer; Automated detection; Computer-assisted diagnosis; Progression-free survival

1. Introduction

Bone scan interpretation regarding the presence or absence of bone metastases and for the progression of bone metastases over time has been subjective and without uniform or quantitative measures that permit standardization. This interpretation may lead to misclassification of disease burden and changes over time. Only moderate interobserver agreement was found in a study of 37 observers from different hospitals when observers were compared pairwise [1]. Determination of progression in men with metastatic castration-resistant prostate cancer (mCRPC) is confounded by the occurrence of flare or healing reactions in response to active systemic agents, and can lead to misclassification of radiographic progression in clinically responding patients [2,3]. This misclassification problem led to the Prostate Cancer Working Group 2 (PCWG2) guidelines, which instituted criteria of 2 new lesions and confirmatory scans requiring ongoing additional new bone scan lesions before determining bone scan progression [2]. Bone scan progression using older guidelines that do not account for this treatment effect on bone is often misclassified, leading to spurious and weak associations between progression-free survival (PFS) and overall survival (OS) and increases the potential for premature cessation of active therapeutic agents in the clinic. Objective, quantifiable, and reproducible measures of bone scan burden and changes over time that are associated with improvements in OS are thus needed, which may facilitate the earlier identification and optimal utilization of active systemic agents in the clinic.

The imaging biomarker bone scan index (BSI) is a quantitative measure of tumor burden in bone as a percentage of the total skeletal mass [4,5]. Dennis et al. [6] recently showed that BSI progression during treatment was strongly associated with worse OS in a small study of men with mCRPC receiving chemotherapy. Mitsui et al. [7] and Kaboteh et al. [8] also found that a reduction in BSI was associated with OS improvements in men with mCRPC receiving chemotherapy. However, BSI has never been studied in the context of a randomized or controlled clinical trial.

Prognostic information can also be obtained through the assessment of tumor burden with bone scan analysis. For example, in the ALSYMPCA trial of the radiopharmaceutical agent radium-223, an improved OS was observed in patients receiving radium-223, with a subgroup analysis demonstrating a greater improvement in survival particularly in men with a high degree of bone metastases or elevations in alkaline phosphatase (ALP) level (6) [9], suggesting that quantifying bone burden may be predictive of the benefits of bone-targeting systemic agents. In other studies, a BSI value more than 1.0 was associated with a poor prognosis at the time of diagnosis, whereas men with bone metastases and a BSI less than 1.0 showed a 5-year survival rate close to that of patients without bone metastases (BSI = 0) [5,10]. Meirelles et al. [11] studied patients who underwent bone scan before therapy initiation and demonstrated a median survival of 27.0 months for patients with BSI under the median value of 1.27 in comparison with that of 14.4 months for those with a BSI greater than 1.27. These findings indicate the ability for BSI to risk-stratify men with mCRPC and to provide potentially independent prognostic and predictive information in the clinic.

The BSI studies mentioned previously demonstrate the prognostic utility of BSI; however, these studies relied on manual BSI calculation [6,11] and studies of men with prostate cancer (PC) in which the indication for bone scan examination was not controlled [5,8,10]. We therefore sought to evaluate the BSI using a prospective randomized placebo-controlled trial and an automated method for BSI calculation. This study could be a part of an evidentiary process qualifying BSI as an imaging biomarker for mCRPC in the context of clinical trials [12].

The advantages of the automated BSI method are its high reproducibility and rapid processing time. An automated method has been shown to reduce variability in bone scan interpretation between a large group of bone scan readers [13]. Automatic BSI shows 100% reproducibility on repeat testing of the same scan, which is not the case if the same scan is presented to the same reader at different occasions. Ulmert et al. [5] studied the intraobserver agreement for 2 manual BSI ratings of 133 bone scans and found a correlation coefficient of 0.95, although this correlation was lower at BSI scores higher than 9%.

Tasquinimod (TASQ) is an oral quinoline-3-carboxamide derivative that is currently in phase III clinical development for the treatment of mCRPC. It binds to S100A9 [14,15] and targets the tumor microenvironment displaying immunomodulatory, antiangiogenic, and antimetastatic properties [15–17]. In a randomized double-blinded phase II study, 201 men with mCRPC received TASQ/placebo once daily. The primary end point to demonstrate an improvement in progression at 6 months was met [18], with a more pronounced effect seen in men with bone metastases. A recent update of this trial suggested that TASQ led to an

improvement in OS, particularly among men with CRPC and bone metastases [19]. Thus, this trial represents an ideal setting to evaluate the association of an objective measure of bone burden with the outcome and longitudinal changes in objective bone burden across treatment arms.

Given the body of work showing the usefulness of BSI and the activity of TASQ in delaying progression in men with bone metastases, we sought to evaluate the relation of the BSI with other prognostic biomarkers, PFS, OS, and the effect of TASQ on BSI.

2. Methods

2.1. Patients

This retrospective analysis was based on a prospective randomized double-blinded placebo-controlled phase II clinical trial in which 201 men with mCRPC received TASQ/placebo once daily; it has been described elsewhere [19]. Briefly, men with asymptomatic or minimally symptomatic mCRPC were randomized (2:1) and treated with either TASQ once daily escalating to 1.0 mg/d or placebo with an option to cross over after disease progression or after 6 months. The eligibility criteria included patients with histologically confirmed PC with castrate levels of testosterone not more than 50 ng/dL, Karnofsky performance score of 70 to 100, pain score of at least 3 on a visual analog scale (VAS) from 0 to 10, and radiologically confirmed metastatic disease with progression defined by rising prostate-specific antigen (PSA) levels, progression of soft tissue metastasis, or new bone lesions detected by bone scan. The exclusion criteria included regular intake of opiates or previous anticancer chemotherapy within 6 months before treatment with TASQ. A stable dose of concomitant antiandrogen use was permitted. Symptomatic disease progression was defined as at least 1 of the following: (1) pain criteria, including regular consumption of narcotic analgesics (single intravenous narcotic medication administration or more than 10 of 14 d of oral narcotic use) or radiation therapy for control of tumor-related pain, a VAS pain rating >4 due to cancer pain on 2 consecutive ratings and (2) need for radiotherapy or surgery for pathological fracture or spinal cord compression. PFS was defined as the earliest of a composite of symptomatic progression, radiographic progression (using RECIST or PCWG2 bone scan progression guidelines), or death. Increased PSA level was not a criteria for progression. Survival data were collected through a separate long-term follow-up protocol. Latest collection was on May 9, 2012. This study was approved by related institutional review boards, and all patients provided written informed consent.

2.2. Bone scan analysis

BSI, the measure of the tumor burden in bone as a percentage of the total skeletal mass, was calculated retrospectively using the software package EXINIbone^{BSI} (EXINI Diagnostics AB, Lund, Sweden). BSI progression was not prospectively defined but rather changes over time were described in a retrospective analysis. Fig. 1 shows the principle of BSI measurement and 3 patients from the study group: 1 without bone metastases (BSI = 0), 1 with limited metastatic spread (BSI = 0.7), and 1 with a high burden of bone metastatic disease (BSI = 6.3).

The automated method has been described in detail elsewhere [5]. In summary, the skeleton is segmented and the image area of different anatomical regions such as the skull, ribs, lumbar vertebra, and pelvis is calculated. Hotspots are detected and classified as a metastatic lesion or not. The area of metastatic hotspots is calculated and thereafter divided by the area of the corresponding anatomical region and multiplied by a constant representing the weight fraction of the present skeletal region with respect to the weight of the total skeleton. This product gives an estimate of the volumetric fraction of the skeleton occupied by the metastatic hotspot. The BSI is the sum of all such fractions. Hotspots in a bone scan are nonspecific, and they may be due to metastatic lesions, healing of metastatic lesions (flare), degenerative disease, fractures, etc. Therefore, a hotspot classification method is used based on a statistical learning method and examples with a known classification. The automated software has proved to be as capable of interpreting bone scans and differentiating metastatic lesions from degenerative abnormalities as an experienced physician [13]. However, the automatic method is capable of assessing flare over time but still requires a manual assessment of new lesions and clinical correlation with other outcome measures (pain and PSA responses) to account for this flare phenomenon, and definitions of flare using the BSI method are not yet established. Thus, posttreatment BSI changes by the automatic method do not currently distinguish progression from healing/flare. The quality of the image data and the automated analysis were checked by 2 operators who were blinded to the treatment arm, survival data, and other biomarkers. Images not stored with sufficient quality as determined by 2 experienced bone scan readers for the automated analysis were excluded. Manual corrections for obvious misclassifications (3 cases due to bladder interference and 9 cases due to low-quality images) of bone lesions by the automated software were performed. We did not further assess BSI changes beyond 12 weeks due to the limited availability of high-quality scans at 24 weeks and due to censoring due to crossover or dropout on the study.

2.3. Statistical analysis

The association between BSI and other prognostic biomarkers at baseline was assessed using Spearman rank correlation. Cox proportional hazards regression models were used to investigate the association between BSI, prognostic factors, PFS and OS, both in univariate and multivariable modeling. Prognostic baseline markers included tumor pain by VAS, Karnofsky score, Gleason score, lactate dehydrogenase (LDH) level, hemoglobin (Hb) level, ALP level, and PSA level, and historic PSA doubling time (PSA DT). PSA DT was calculated using all available PSA values in the 52 weeks preceding trial registration, typically with 5 to 7 time points. Hazard ratios (HRs) were estimated from the Cox models. Model selection through backward selection of variables was conducted, where factors with $P > 0.05$ were removed. Patients were stratified based on baseline BSI using the cut level of 1.0 that has been used in previous BSI studies [5,10]. All statistical analyses were conducted using SAS version 9.3.

3. Results

Bone scans from 170 of 201 patients obtained for central review were collected, with 31 unavailable for this central analysis. Of these 170 patients, 85 provided paired digitally

stored scans both at baseline and at week 12 of sufficient quality, as determined by the 2 operators blinded to treatment arm, survival data, and other biomarkers (Fig. 2). These 85 patients (57 TASQ vs. 28 placebo) comprised the study population. Patient characteristics in the total population ($n = 201$) and the study group ($n = 85$) are presented in Supplementary Table S1. The study group was well balanced and had baseline characteristics similar to those of the total study population [18]. In this trial, 61% of the placebo patients crossed over to TASQ after disease progression or 6 months of placebo.

Baseline BSI ranged between 0.0 (11 patients) and 10.0 (median = 0.9, SD = 1.6) in the study group ($n = 85$). In the TASQ group, baseline median BSI was 0.9 (SD = 1.2, range: 0.0–5.9), and in the placebo group, baseline median BSI was 0.7 (SD = 2.2, range: 0.0–10.0). The median number of bone metastases at baseline in this trial was low (3.0 bone metastases in the TASQ arm and 2.5 bone metastases in the placebo arm), with 1 patient in each treatment group having a BSI greater than 9%.

BSI at baseline moderately correlated with PSA, ALP and bone ALP (BAP) levels, with Spearman correlation coefficients of 0.29 to 0.44. Baseline PSA DT and LDH and Hb levels were not associated with BSI (Table 1). Of note, BSI correlated well with number of bone lesions determined locally on site (Spearman rank correlation = 0.70, $P < 0.0001$). The number of lesions was not available for this central analysis because of image quality issues, and thus, this correlation could not be performed using the current automated software platform.

In the univariate analysis, TASQ treatment (HR = 0.53; 95% CI: 0.29–0.99; $P = 0.045$), BSI at baseline (HR = 1.42 per doubling in BSI; 95% CI: 1.08–1.87; $P = 0.013$), ALP and PSA levels, and PSA DT were all statistically significantly associated with OS (Table 2). BSI remained associated with OS (HR = 1.64 per doubling in BSI; 95% CI: 1.22–2.21; $P < 0.001$) in a multivariate analysis including TASQ treatment (HR 0.32; 95% CI: 0.16–0.62; $P < 0.001$), Hb level, VAS pain, and PSA DT. BSI at baseline was not significantly associated with PFS. Of note, the HR for improved PFS or OS with TASQ over placebo did not statistically differ according to baseline BSI quartiles (Supplementary Fig. S1).

Men with mCRPC and a baseline BSI greater than a threshold of 1.0 had reduced survival in comparison with men who had a BSI less than 1.0, a value chosen given the close approximation to the median baseline BSI value. TASQ improved OS numerically in each of these subgroups (Fig. 3A). A Kaplan-Meier plot for OS by BSI quartiles is shown in Fig. 3B, demonstrating the relationship of baseline BSI with survival.

BSI at baseline and week 12 by treatment arm is presented in Fig. 4, and the relationship of BSI change with OS improvement by treatment arm is presented in Supplementary Fig. S2. The median increase in BSI at week 12 vs. baseline was modestly slower with TASQ vs. placebo (0.16 ± 0.41 increase vs. 0.26 ± 0.49 BSI increase, respectively). TASQ led to a decrease in the BSI in 11/57 evaluable men (19%), as compared with 3/28 placebo-treated men (11%). A doubling or more in BSI occurred in 7/57 men (12%) treated with TASQ, as compared with 5/28 (18%) of placebo-treated men. The relative benefits of TASQ in improving survival were observed regardless of the change in BSI at 12 weeks

(Supplementary Fig. S2). The relative change in BSI from baseline to 12 weeks on treatment was prognostic for PFS (HR = 2.14 per doubling in BSI, $P < 0.001$) and OS (HR = 1.58 per doubling in BSI, $P = 0.033$) in multivariate analyses including baseline BSI and TASQ treatment (Table 3).

4. Discussion

BSI is an objective method to quantitatively describe bone metastatic tumor burden in men with mCRPC. The application of BSI includes assessment of bone burden at the time of inclusion in a clinical trial or initiation of a new therapy and during treatment response assessment. Several studies have indicated the potential of BSI as an important prognostic imaging biomarker for OS [5–8,10,11], and this study contributes to the process of a rigorous validation of BSI [12]. We calculated and evaluated BSI using an automated method to reduce interobserver variability and studied a defined cohort of minimally symptomatic men with mCRPC from a prospective randomized clinical phase II study who had assessments on treatment at a fixed time interval. These men had a low burden of disease in the bone, which permits a reliable assessment of the association of BSI with outcomes. In this report, we have demonstrated and confirmed the independent prognostic association of baseline BSI for survival for the first time in a cohort of men with mCRPC treated in the context of a clinical trial using automated image interpretation. We have also shown the independent association of BSI changes over time with survival. Although an exact threshold for determining BSI progression, including a BSI definition for flare, cannot be determined from this study, these present results should provide information on the development of BSI as a biomarker of bone progression in this setting.

We demonstrated that BSI at baseline correlated with PSA levels and the known bone formation biomarkers ALP and BAP, but not with PSA kinetics or LDH levels. These results are in agreement with those in the study by Wakabayashi et al. [20], who also showed that BSI correlated significantly with BAP and PSA in a group of 52 patients with PC. These data suggest that the objective measurement of bone burden with an automatic BSI provides independent clinical utility beyond many traditionally used biomarkers of disease burden, and inclusion of BSI in future prospective multivariate models and nomograms of mCRPC is warranted.

Baseline BSI was significantly associated with OS in the univariate analysis. Kaboteh et al. [10] also found a significant association between BSI and OS at the time of diagnosis in a group of 130 consecutive patients with PC who are at high risk, based on clinical stage (T2c/T3/T4), Gleason score (8–10), and PSA level (>20 ng/ml), who received primary hormonal therapy. They also showed that the 5-year survival probabilities for patients without bone metastases (M0); with metastases and BSI < 1 ; BSI = 1 to 5; and BSI > 5 were 55%, 42%, 31%, and 0%, respectively. The 2-year survival probabilities in this and Kaboteh's studies are in the same order for patients with BSI below or above 1. Meirelles et al. [11] studied a group of 43 patients with PC before treatment and found a significant difference in OS between patients with BSI above and below the median value of 1.27 (median survival = 14.7 vs. 28.2 mo). The results from these studies show that prognosis can be ascertained at diagnosis using the BSI method.

BSI also remained associated with OS in the multivariate analysis including TASQ treatment, Hb level, VAS pain and PSA DT. These results are in agreement with the studies by Ulmert et al. [5] and Kaboteh et al. [10] in which multivariate analyses showed significant association between BSI obtained at the time of diagnosis and OS, independent of baseline clinical T stage, Gleason score, and PSA.

BSI may therefore become a valuable biomarker during considerations of eligibility for clinical trial participation, either for risk stratification or to select patients who are more likely to benefit from bone-targeting therapy. For example, a more homogenous patient group in terms of survival prognosis can be selected by the use of BSI. It might also be the case that one treatment is more efficient for patients with minimal metastatic disease and another is more efficient in patients with extensive metastatic disease (predictive value). BSI might prove to be valuable to explore such differences in treatment effect. However, a limitation of the current analysis, was the lack of ability to quantify the number of bone lesions over time, which would have permitted a quantitative analysis of bone scan flare if present. The BSI itself may reflect on the intensity of lesions and the absolute number of lesions, and future studies will be needed to evaluate the associations between various automated BSI definitions of progression that include or omit number of bone lesions, and how these compare with standard radiology interpretations. In addition, future studies of randomized trials of men with bone metastatic CRPC will be required to develop an optimal BSI progression criteria.

A modest delay in objective radiographic bone scan progression over time with TASQ is suggested, and this delay may be associated with improvements in OS, as recently suggested in the long-term follow-up of this phase 2 trial [19]. Although the magnitude of changes in BSI between the 2 groups are small, the current data set is limited to 12 weeks and does not reflect the overall treatment course or changes beyond 12 weeks. In addition, we observed a benefit of TASQ treatment with respect to improved OS independent of the posttreatment BSI change. Relative change in BSI was associated with OS in a multivariate analysis in this study, and these results are in agreement with those by Dennis et al. [6] who found that change in BSI from baseline to 3 and 6 months on treatment was prognostic for OS. Mitsui et al. [7] studied patients who underwent docetaxel-based combination chemotherapy and found that OS was significantly longer in patients with on-treatment decrease of BSI from baseline to week 16 as compared with those who showed an increase of BSI. Kaboteh et al. [8] also studied patients who underwent docetaxel chemotherapy, and they found change in BSI to be significantly associated with OS. They showed that the 2-year survival for patients with increasing and decreasing BSI from baseline to follow-up scans were 18% and 57%, respectively. The results from these studies suggest that further evaluation of BSI as an end point in larger prospective controlled trials of men with mCRPC is warranted.

Several new drugs for patients with mCRPC have recently become available because of positive results from clinical trials, including bone-targeting agents such as radium-223 and the novel hormonal agents abiraterone acetate and enzalutamide. Studies assessing optimal sequencing and possible combinations of these drugs are badly needed, and in this type of studies alternative end points to OS are of utmost importance. Patients most likely receive different combinations of treatment during the progress of their disease, and this makes an

analysis of OS more difficult. Surrogate end points based on 1 or a combination of biomarkers will be most useful. Imaging biomarkers may play an important role, and at present, bone scanning is the most common method for monitoring progress of bone metastases in patients with PC. BSI may become an imaging biomarker, providing a quantitative measure of tumor burden development.

An alternative method of quantifying bone lesions is lesion counting by a trained radiologist or investigator. The PCWG2 defined progression in bone as the presence of 2 or more new lesions on a bone scan compared with a prior scan [2], attempting to account for the presence of a flare reaction in bone at the initial posttreatment assessment. In the case of new lesions, a confirmatory scan should be performed 6 or more weeks later. This method was established in an effort to make bone scan interpretation more standardized and quantitative and to avoid misclassification of progression. The method offers a process to detect progression, which in clinical trials is commonly important for the decision to continue or withdraw treatment. BSI offers a quantitative and automated approach that could add further objective validity to this PCWG2 guideline if prospectively validated and associated with survival in larger controlled studies. The use of an automated BSI could reduce the variability in bone scan interpretation. Reduced variability does not necessarily result in better association with survival, but Ulmert et al. [5] showed that automated BSI performed slightly better in concordance index than manual BSI in a cohort of 384 patients with PC using PC death as end point. Thus, automated BSI could provide objective end points based on BSI changes over time in clinical trials in PC. Although we did not assess lesion number in this study, future studies of BSI should incorporate BSI inclusive of lesion number to ascertain the optimal association of these measures with survival.

This study was limited by a relatively small number of patients included in the analysis. It was a retrospective analysis of the bone scans from the TASQ phase II study in which the primary end point was progression defined as 1 or more of 4 criteria, 1 being bone scan progression according to the PCWG2 criteria. Not all sites contributed scans explaining why 31 patients were not available for central review. Several postbaseline scans were missing owing to early withdrawals and some scans could not be retrieved, explaining why 78 did not have both baseline and 12 week bone scans. Of the remaining 92 cases, 7 (8%) had image quality problems mainly because of screen capture images instead of raw data being stored. However, in future prospective studies, these image quality problems can easily be solved by defining the routines for image storing. An advantage with BSI as an imaging biomarker is that it is based on bone scans that are acquired in the same way in almost all imaging departments worldwide using cameras that produce images of similar quality. The variation in image quality of modern, 3-dimensional imaging modalities is a much bigger problem. The use of an automated BSI could reduce the variability in bone scan interpretation and provide objective end points based on BSI changes over time in clinical trials in PC. Although we did not assess lesion number in this study, future studies of BSI should incorporate BSI inclusive of lesion number to ascertain the optimal association of these measures with survival.

Both BSI measurements and the PCWG2 criteria suffer from the limitations of the imaging modality bone scanning itself. The lesions that appear in a bone scan are nonspecific and are

not a direct measure of disease. They can be caused by metastatic disease but also by degenerative disease or fractures or healing osteoblastic reactions. Flare response early during treatment may also result in misjudgments, both in BSI measurements and lesion counting. These shortcomings of the bone scan method have for a long time inspired researchers to develop an alternative more accurate and less variable method for clinical use, and bone scans and standard radiology interpretations remained highly enmeshed in clinical trials and in clinical practice of men with PC. However, the experience from using an imaging biomarker reflecting the tumor burden will most likely be of value when an alternative, less variable, and more accurate method of disease burden ascertainment replaces the bone scan method.

This study was limited by a relatively small number of patients included in the analysis. Bone scans were not available from all patients of the phase II clinical trial and some of them were not digitally stored in a way that they could be analyzed retrospectively. Future trials of men with mCRPC may be designed to include BSI and bone lesion enumeration as an end point so that bone scans from all patients can be available for analysis and such that optimal thresholds for BSI changes can be ascertained.

5. Conclusion

BSI and BSI changes on treatment were associated with OS in men with mCRPC. BSI correlates with known biomarkers of OS, but adds independent prognostic information. Although modest, a short-term delay in objective radiographic bone scan progression with TASQ is suggested, and the evaluation of BSI and BSI changes in the context of controlled phase III trials of men with mCRPC is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- [1]. Sadik M, Suurkula M, Hoglund P, Jarund A, Edenbrandt L. Quality of planar whole-body bone scan interpretations—a nationwide survey. *Eur J Nucl Med Mol Imaging* 2008;35:1464–72, 10.1007/s00259-008-0721-5. [PubMed: 18373092]
- [2]. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;26:1148–59. [PubMed: 18309951]
- [3]. Ryan CJ, Shah S, Efsthathiou E, Smith MR, Taplin M-E, Bubley GJ, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res* 2011;17:4854–61. [PubMed: 21632851]
- [4]. Erdi YE, Humm JL, Imbriaco M, Yeung H, Larson SM. Quantitative bone metastases analysis based on image segmentation. *J Nucl Med* 1997;38:1401–6. [PubMed: 9293797]

- [5]. Ulmert D, Kaboteh R, Fox JJ, Savage C, Evans MJ, Lilja H, et al. A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the bone scan index. *Eur Urol* 2012;62:78–84, 10.1016/j.eururo.2012.01.037. [PubMed: 22306323]
- [6]. Dennis ER, Jia X, Mezheritskiy IS, Stephenson RD, Schoder H, Fox JJ, et al. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. *J Clin Oncol* 2012; 30:519–24. [PubMed: 22231045]
- [7]. Mitsui Y, Shiina H, Yamamoto Y, Haramoto M, Arichi N, Yasumoto H, et al. Prediction of survival benefit using an automated bone scan index in patients with castration-resistant prostate cancer. *BJU Int* 2012;110:E628–34. [PubMed: 22788759]
- [8]. Kaboteh R, Gjerdtsson P, Leek H, Lomsky M, Ohlsson M, Sjöstrand K, et al. Progression of bone metastases in patients with prostate cancer-automated detection of new lesions and calculation of bone scan index. *EJNMMI Res* 2013;3:1–6. [PubMed: 23281702]
- [9]. Parker C, Nilsson S, Heinrich D, Helle S, O'Sullivan J, Fosså S, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013;369:213–23. [PubMed: 23863050]
- [10]. Kaboteh R, Damber J-E, Gjerdtsson P, Höglund P, Lomsky M, Ohlsson M, et al. Bone scan index: a prognostic imaging biomarker for high-risk prostate cancer patients receiving primary hormonal therapy. *EJNMMI Res* 2013;3:1–6. [PubMed: 23281702]
- [11]. Meirelles GS, Schöder H, Ravizzini GC, Gönen M, Fox JJ, Humm J, et al. Prognostic value of baseline [^{18}F] fluorodeoxyglucose positron emission tomography and $^{99\text{m}}\text{Tc}$ -MDP bone scan in progressing metastatic prostate cancer. *Clin Cancer Res* 2010;16: 6093–6099. [PubMed: 20975102]
- [12]. Fox JJ, Morris MJ, Larson SM, Schöder H, Scher HI. Developing imaging strategies for castration resistant prostate cancer. *Acta Oncol* 2011;50:39–48. [PubMed: 21604939]
- [13]. Sadik M, Suurkula M, Höglund P, Järund A, Edenbrandt L. Improved classifications of planar whole-body bone scans using a computer-assisted diagnosis system: a multicenter, multiple-reader, multiple-case study. *J Nucl Med* 2009;50:368–75. [PubMed: 19223423]
- [14]. Björk P, Björk A, Vogl T, Stenström M, Liberg D, Olsson A, et al. Identification of human S100A9 as a novel target for treatment of autoimmune disease via binding to quinoline-3-carboxamides. *PLoS Biol* 2009;7:e1000097.
- [15]. Källberg E, Vogl T, Liberg D, Olsson A, Björk P, Wikström P, et al. S100A9 interaction with TLR4 promotes tumor growth. *PLoS One* 2012;7:e34207. [PubMed: 22470535]
- [16]. Isaacs JT, Pili R, Qian DZ, Dalrymple SL, Garrison JB, Kyprianou N, et al. Identification of ABR-215050 as lead second generation quinoline-3-carboxamide anti-angiogenic agent for the treatment of prostate cancer. *Prostate* 2006;66:1768–78. [PubMed: 16955399]
- [17]. Jennbacken K, Welen K, Olsson A, Axelsson B, Törngren M, Damber JE, et al. Inhibition of metastasis in a castration resistant prostate cancer model by the quinoline-3-carboxamide tasquinimod (ABR-215050). *Prostate* 2012;72:913–24. [PubMed: 22287276]
- [18]. Pili R, Häggman M, Stadler WM, Gingrich JR, Assikis VJ, Björk A, et al. Phase II randomized, double-blind, placebo-controlled study of tasquinimod in men with minimally symptomatic metastatic castrate-resistant prostate cancer. *J Clin Oncol* 2011;29:4022–8. [PubMed: 21931019]
- [19]. Armstrong A, Häggman M, Stadler W, Gingrich J, Assikis V, Polikoff J, et al. Long-term survival and biomarker correlates of tasquinimod efficacy in a multicenter randomized study of men with minimally symptomatic metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2013;19:6891–901. [PubMed: 24255071]
- [20]. Wakabayashi H, Nakajima K, Mizokami A, Namiki M, Inaki A, Taki J, et al. Bone scintigraphy as a new imaging biomarker: the relationship between bone scan index and bone metabolic markers in prostate cancer patients with bone metastases. *Ann Nucl Med* 2013; 27:802–7. [PubMed: 23828554]

Fig. 1. Principle of BSI measurement and examples of skeletal tumor burden expressed as BSI measures. The product “metastasis area/anatomical region area $\times$ region-specific constant” is calculated for each hotspot classified as a metastasis and BSI is calculated as the sum of the products of all metastases.

Fig. 2. Flowchart detailing the patients studied. BS = bone scan; P = placebo.

Fig. 3.

Overall survival (A) by treatment arm for patients with baseline BSI below, or greater than or equal to, a threshold of 1.0 and (B) by baseline BSI quartiles, regardless of treatment group. P = placebo.

Fig. 4. BSI at baseline and week 12 by treatment arm. Quartiles indicated by the boxes, median indicated by the line in the boxes and mean by the + symbol ($n = 85$).

Table 1

Spearman correlation coefficients and *P* values of baseline BSI with baseline markers in the study group (*n* = 85)

Baseline marker	Spearman correlation	<i>P</i> value
PSA	0.29	0.007
PSA DT	−0.1	0.38
LDH	0.15	0.17
ALP	0.38	0.0003
BAP	0.44	<0.0001
Hb	−0.13	0.25

Univariate and multivariate survival analysis demonstrating association between TASQ treatment, baseline markers, and overall survival in the study group ($n = 85$). Population median PSA DT = 3.6 months. Karnofsky score low = 70% to 80%. Model selection in the multivariate analysis was conducted through backward selection of variables, where factors with $P > 0.05$ were removed

Table 2

Baseline factor	BSI study population ($n = 85$)			
	Univariate		Multivariate	
	P value	HR (95% CI)	P value	HR (95% CI)
Tumor pain (VAS)	0.317	1.28 (0.79–2.08)	0.019	1.78 (1.10–2.88)
Karnofsky score low	0.378	0.59 (0.18–1.91)		
Gleason score	0.130	1.21 (0.94–1.55)		
LDH ^a	0.097	1.87 (0.89–3.91)		
Hemoglobin ^a	0.064	0.18 (0.03–1.10)	0.005	0.053 (0.007–0.42)
Tasquinimod arm	0.045	0.53 (0.29–0.99)	<0.001	0.32 (0.16–0.62)
BSI ^a	0.013	1.42 (1.08–1.87)	0.001	1.64 (1.22–2.21)
Alkaline phosphatases ^a	0.003	2.42 (1.34–4.37)		
PSA ^a	0.003	1.24 (1.08–1.43)		
PSA DT <median	<0.001	3.27 (1.67–6.42)	<0.001	3.15 (1.60–6.23)

VAS linear pain rating = 0 to 10.

^aLog₂ transformed value, baseline values of 0 are replaced by 0.5 to allow log₂ transformation.

Table 3

Multivariate analysis demonstrate TASQ treatment, baseline BSI, and relative change in BSI from baseline to week 12 association with OS ($n = 85$)

Factor	BSI study population ($n = 85$) multivariate analysis	
	<i>P</i> value	HR (95% CI)
Tasquinimod arm	0.038	0.51 (0.27–0.96)
BSI ^a	0.002	1.60 (1.18–2.15)
BSI (12 wk/baseline) ^a	0.033	1.58 (1.04–2.39)

^aLog₂ transformed value, baseline values of 0 are replaced by 0.5 to allow log₂ transformation