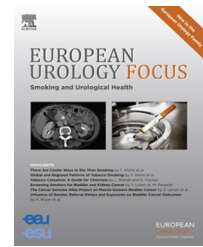


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Prostate Cancer

Bone Scan Index and Progression-free Survival Data for Progressive Metastatic Castration-resistant Prostate Cancer Patients Who Received ODM-201 in the ARADES Multicentre Study

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Abstract

Background: ODM-201, a new-generation androgen receptor inhibitor, has shown clinical efficacy in prostate cancer (PCa). Quantitative methods are needed to accurately assess changes in bone as a measurement of treatment response. The Bone Scan Index (BSI) reflects the percentage of skeletal mass a given tumour affects.

Objective: To evaluate the predictive value of the BSI in metastatic castration-resistant PCa (mCRPC) patients undergoing treatment with ODM-201.

Design, setting, and participants: From a total of 134 mCRPC patients who participated in the Activity and Safety of ODM-201 in Patients with Progressive Metastatic Castration-resistant Prostate Cancer clinical trial and received ODM-201, we retrospectively selected all those patients who had bone scan image data of sufficient quality to allow for both baseline and 12-wk follow-up BSI-assessments ($n = 47$). We used the automated EXINI bone BSI software (EXINI Diagnostics AB, Lund, Sweden) to obtain BSI data.

Outcome measurements and statistical analysis: We used the Cox proportional hazards model and Kaplan-Meier estimates to investigate the association among BSI, traditional clinical parameters, disease progression, and radiographic progression-free survival (rPFS).

Results and limitations: In the BSI assessments, at follow-up, patients who had a decrease or at most a 20% increase from BSI baseline had a significantly longer time to progression in bone (median not reached vs 23 wk, hazard ratio [HR]: 0.20; 95% confidence interval [CI], 0.07–0.58; $p = 0.003$) and rPFS (median: 50 wk vs 14 wk; HR: 0.35; 95% CI, 0.17–0.74; $p = 0.006$) than those who had a BSI increase >20% during treatment.

Conclusions: The on-treatment change in BSI was significantly associated with rPFS in mCRPC patients, and an increase >20% in BSI predicted reduced rPFS. BSI for quantification of bone metastases may be a valuable complementary method for evaluation of treatment response in mCRPC patients.

Patient summary: An increase in Bone Scan Index (BSI) was associated with shorter time to disease progression in patients treated with ODM-201. BSI may be a valuable method of complementing treatment response evaluation in patients with advanced prostate cancer.

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1. Introduction

Prostate cancer (PCa) is the most common primary cancer in men in Europe and the second-most common cause of cancer death in the European male population [1]. Despite initial treatment in the early stages of the disease, many patients still progress to metastatic castration-resistant PCa (mCRPC) [2]. This phase is characterised by a persistent, high-level androgen receptor (AR) function and has been related to lower survival rates [3]. AR signalling can be targeted at different levels, and its inhibition is the aim of the development of new drugs [4]. ODM-201, a potent oral, new-generation androgen inhibitor, binds to the AR with high affinity and inhibits the receptor function by blocking its nuclear translocation. ODM-201 recently showed encouraging results in a phase 1 and 2 clinical trial (Activity and Safety of ODM-201 in Patients with Progressive Metastatic Castration-resistant Prostate Cancer, or ARADES) in patients with progressive mCRPC. The drug is well tolerated and exhibits high antitumour activity in both chemotherapy-naïve patients (prechemotherapy) and chemotherapy-treated patients (postchemotherapy) [5].

Biomarkers are measurable parameters with an important role in the prognostic evaluation of PCa patients when predicting the response to treatments and monitoring the disease. The Bone Scan Index (BSI) is a recently validated imaging biomarker and the most objective quantification method currently available for measuring tumour burden in bone [6]. It represents the percentage of the total skeletal mass affected by metastasis, and it can be calculated automatically from images acquired in bone scintigraphy, the most widely used imaging modality in this group of patients [7]. The value of the BSI has been studied in mCRPC patients treated with docetaxel [8] and more recently in the context of a randomised, phase 2, placebo-controlled trial of mCRPC patients treated with tasquinimod [9], showing that the BSI strongly correlates with overall survival (OS). The definition of end points is of the utmost importance in clinical trials, and in daily clinical practice, end points earlier than OS could have added value, for example, in decisions about whether to continue or change treatment at earlier stages [10].

In mCRPC, bone is the most commonly affected tissue, and clinical or biologic parameters related to bone metastases have a major prognostic value [11]. Therefore, the study of an objective biomarker such as the BSI was of interest for the evaluation of patients with bone metastasis undergoing ODM-201 treatment. Thus, in this group of patients, we decided to study the prognostic value of tumour status in bone pre- and posttreatment. As far as we know, this is the first report of the BSI used for patients undergoing AR inhibitor treatment as part of a clinical trial. The aim of this study was to evaluate the prognostic value of the BSI at baseline and the value of on-treatment change in the BSI from baseline as a biomarker of response to treatment with ODM-201 in mCRPC patients. We also studied possible associations between the BSI and other prognostic biomarkers, such as prostate-specific antigen (PSA), circulating tumour cells (CTC) count, and CTC

conversion, as well as the value of the BSI in predicting time to radiologic progression in soft and bone tissue and radiographic progression-free survival (rPFS).

2. Materials and methods

2.1. Patient cohort

This study was carried out based on the ARADES clinical trial, which was an open-label phase 1 and 2 multicentre trial with long-term follow-up [5]. Patients were enrolled at 23 hospitals in Europe and the United States. All 134 patients presented with histologically confirmed adenocarcinoma of the prostate and progressive metastatic disease despite ongoing androgen-deprivation therapy, serum testosterone concentrations < 1.7 nmol/l, and an Eastern Cooperative Oncology Group performance status of 0 or 1. None of the patients had received previous therapy with enzalutamide or any other investigational AR inhibitor. During the ARADES trial, patients received ODM-201 and were stratified into three groups based on previous treatment received: prechemotherapy/cytochrome P17 inhibitor (CYP17i) naïve ($n = 42$), postchemotherapy/CYP17i naïve ($n = 35$), and post-CYP17i ($n = 57$).

From a total of 134 mCRPC patients who participated in the ARADES clinical trial, 51 had bone scans obtained for central review. Of these 51 patients, 47 had bone scan image data of sufficient quality to allow for retrospective baseline and 12 wk of follow-up BSI assessments. This last group represents the BSI study group. Among these 47 patients, 36 had bone metastases verified at inclusion in the ARADES trial (Fig. 1). We conducted this study in accordance with the Declaration of Helsinki, and it was approved by the investigational review board of each centre participating in the ARADES trial.

2.2. Data management

Bone scan data obtained for central review were transferred to Skåne University Hospital, Malmö, Sweden, for BSI analysis. The BSI value was

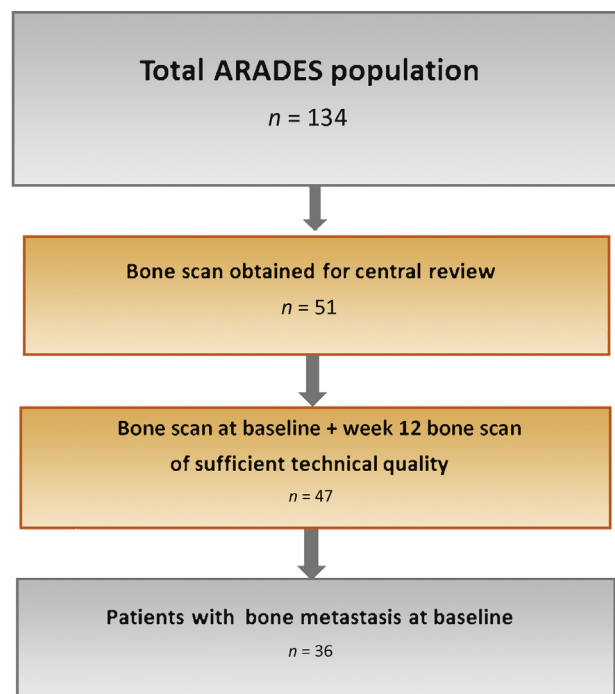


Fig. 1 – Flowchart showing the distribution of patients participating in the study. ARADES = Activity and Safety of ODM-201 in Patients with Progressive Metastatic Castration-resistant Prostate Cancer.

Table 1 – Patient characteristics

| Progressive mCRPC patients | BSI data (n = 47), n (%) | Total (n = 134), n (%) |
|---|--------------------------|------------------------|
| Age, yr, median (range) | 68.0 (55–82) | 69.0 (53–89) |
| ECOG | | |
| 0 (Fully active) | 29 (62) | 72 (54) |
| 1 (Restricted) | 18 (38) | 62 (46) |
| Baseline PSA, ng/ml, median (range) | 83.1 (4–1294) | 98.9 (3–5000) |
| CTC count, no. (%): | | |
| <5 cells per 7.5 ml blood | 25 (57) | 65 (53) |
| ≥5 cells per 7.5 ml blood | 19 (43) | 57 (47) |
| NA | 3 | 12 |
| Haemoglobin, g/l, median (range) | 126 (72–152) | 127 (72–152) |
| Albumin, g/l, median (range) | 38 (28–51) | 39 (23–51) |
| Serum alkaline phosphatase, U/l, median (range) | 81.0 (40–568) | 105.5 (39–1867) |
| Lactate dehydrogenase, U/l, median (range) | 232.6 (147–491) | 226.5 (145–598) |

BSI = Bone Scan Index; CTC = circulating tumour cells; ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; PSA = prostate-specific antigen.

calculated using the automated quantification software EXINI bone BSI (EXINI Diagnostics AB, Lund, Sweden). The image data analysis was performed independently by two experienced bone scan reviewers in a blinded fashion, without any knowledge of clinical data. Each reviewer could, if necessary, manually correct misclassifications of hotspots. A consensus was used in cases of inconsistent BSI results among reviewers, and the final BSI data were used in the statistical analysis.

At baseline, we used a threshold of BSI = 1.0, which has been used in previous studies [9,12,13], to stratify patients. At follow-up, we used a BSI value increase from baseline to follow-up of at least 0.01 to stratify the patients according to the presence or absence of any BSI value change. When evaluating BSI percentage change, we used the threshold of a 20% BSI increase to stratify patients. We chose this last value based on close approximation to the median BSI percentage change value. Clinical data (age, PSA, and CTC count) were derived from the ARADES database at Orion Pharma (Espoo, Finland).

2.3. Outcome measures

We used the following five outcome measures in the statistical analysis [5]: (1) PSA progression was defined as a PSA increase >25% and >2 ng/ml above the documented nadir in two consecutive visits at least 3 wk apart; (2) disease progression in soft tissue was defined by modified Response Evaluation Criteria in Solid Tumors (version 1.1) [14]; (3) disease progression in bone was defined by two or more new lesions identified on 12-wk bone scans; (4) time to progression in bone was defined by time in months to disease progression in bone; and (5) radiographic progression-free survival was defined by time in months to progression in bone and/or soft tissue or death.

2.4. Statistical analysis

We assessed the association between BSI value and the other prognostic biomarkers by using Cox proportional hazards regression models and Kaplan-Meier estimates of the progression curves. We used two methods, Pearson and Spearman, to evaluate the correlations between baseline BSI value and the change in BSI value from baseline (expressed as BSI unit difference or percentage change) with the other prognostic biomarkers: PSA percentage change, soft tissue response, CTC change from baseline, CTC percentage change, and CTC conversion rate. The statistical calculations were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

3. Results

The patient characteristics of the total ARADES population (n = 134) and of the BSI study group (n = 47) are summarised in Table 1. The BSI study group was well balanced and showed baseline characteristics similar to those of the total study population [5]. These 47 patients had received previous treatment as follows: prechemotherapy/CYP17i naive (n = 20), postchemotherapy/CYP17i naive (n = 16), and post-CYP17i (n = 11). BSI analysis by the blinded bone scan reviewers produced a high level of agreement, showing an identical outcome in all but a few (<5%) cases for which consensus among readers was reached.

Baseline BSI values ranged between 0 and 9.6 (median: 0.5 [standard deviation (SD): 2.5]). When analysing the BSI study group (n = 47), patients with a baseline BSI value <1 (n = 28) had a significantly longer median time to progression in bone than patients with a baseline BSI value >1 (n = 19; median not reached [NR] vs 35 wk; hazard ratio [HR]: 0.25; 95% confidence interval [CI], 0.09–0.66; p = 0.006) (Fig. 2). PSA percentage change from baseline, soft tissue response, bone response, and CTC conversion did not correlate with BSI values at baseline, but CTC change

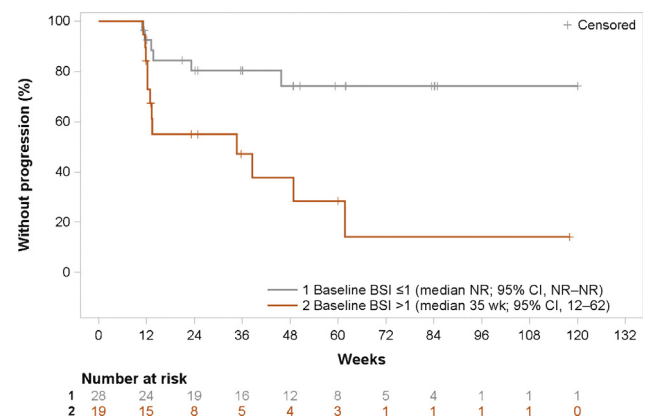


Fig. 2 – Kaplan-Meier curves showing patient time to progression in bone stratified by Bone Scan Index values at baseline, before treatment. BSI = Bone Scan Index; CI = confidence interval; NR = not reached.

Table 2 – Pearson and Spearman correlations (*p* value) of Bone Scan Index and other prognostic biomarkers in the follow-up group

| Pearson and Spearman correlations among variables | Baseline BSI, <i>r</i> value (<i>p</i> value) | BSI change from baseline, <i>r</i> value (<i>p</i> value) | BSI percentage change from baseline, <i>r</i> value (<i>p</i> value) |
|--|--|--|---|
| Soft tissue response (<i>n</i> = 17) | 0.21 (0.422) | 0.50 (0.042) | 0.51 (0.038) |
| | 0.13 (0.631) | 0.61 (0.010) | 0.70 (0.002) |
| Bone response (<i>n</i> = 36) | 0.22 (0.201) | 0.37 (0.024) | 0.14 (0.387) |
| | 0.23 (0.178) | 0.23 (0.178) | 0.16 (0.345) |
| CTC change from baseline (<i>n</i> = 29) | 0.10 (0.619) | 0.66 (<0.001) | 0.14 (0.477) |
| | -0.40 (0.031) | 0.16 (0.407) | 0.47 (0.011) |
| PSA percentage change from baseline (<i>n</i> = 36) | -0.07 (0.691) | 0.14 (0.404) | 0.76 (<0.001) |
| | -0.14 (0.428) | 0.12 (0.483) | 0.42 (0.010) |
| CTC percentage change from baseline (<i>n</i> = 24) | 0.15 (0.480) | 0.37 (0.071) | 0.62 (0.001) |
| | 0.21 (0.315) | 0.32 (0.131) | 0.28 (0.190) |
| CTC conversion (<i>n</i> = 29) | 0.01(0.971) | 0.32 (0.094) | 0.67 (<0.001) |
| | -0.06 (0.759) | 0.34 (0.070) | 0.50 (0.005) |

BSI = Bone Scan Index; CTC = circulating tumour cells; PSA = prostate-specific antigen.

from baseline showed a negative correlation with BSI values at baseline when using Spearman’s correlation coefficient measure ($r = -0.40$; $p = 0.03$) (Table 2).

BSI value change from baseline also correlated with time to progression in bone when analysing the BSI study group ($n = 47$); patients who had a decrease or no increase in BSI value during the study ($n = 17$) had a significantly longer time to progression in bone than those showing an increase in BSI value of at least 0.01 from baseline to follow-up ($n = 30$) (median NR vs 39 wk; HR: 0.24; 95% CI, 0.07–0.84; $p = 0.025$) (Fig. 3). PSA progression did not show a significant statistical correlation with BSI value change, but using the Pearson correlation, soft tissue response and CTC change from baseline were correlated with BSI value change from baseline ($r = 0.50$, $p = 0.042$, and $r = 0.66$, $p < 0.001$, respectively) (Table 2).

When analysing the BSI study group ($n = 47$), a decrease in BSI percentage change or an increase in BSI percentage change from baseline to follow-up of up to 20% ($n = 27$) was associated with a significantly longer median time to progression in bone (Fig. 4) and rPFS (Fig. 5) than an increase >20% ($n = 20$; median NR vs 23 wk; HR: 0.2; 95% CI, 0.07–0.58; $p = 0.003$ and median 50 wk vs 14 wk; HR: 0.35; 95% CI, 0.17–0.74; $p = 0.006$, respectively). PSA progression

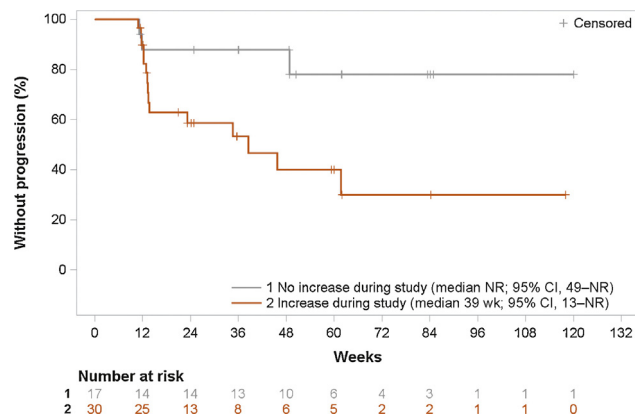


Fig. 3 – Kaplan-Meier curves showing patient time to progression in bone stratified by Bone Scan Index change from baseline after 12 wk of treatment. CI = confidence interval; NR = not reached.

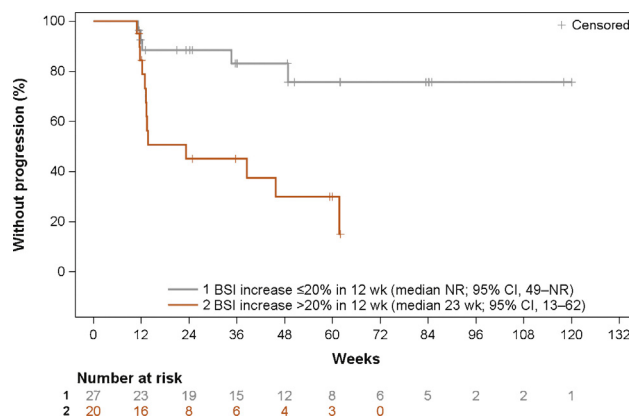


Fig. 4 – Kaplan-Meier curves showing patient time to progression in bone stratified by Bone Scan Index percentage change from baseline after 12 wk of treatment. BSI = Bone Scan Index; CI = confidence interval; NR = not reached.

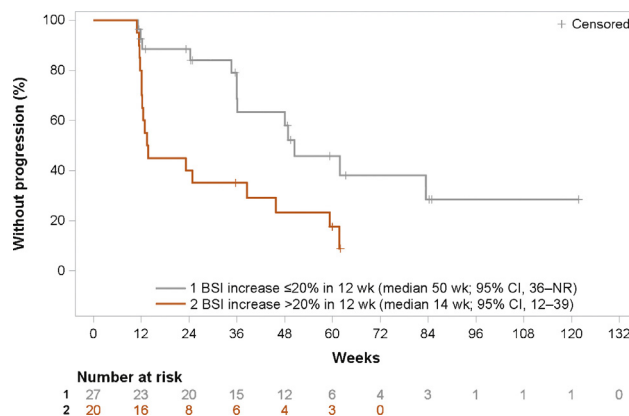


Fig. 5 – Kaplan-Meier curves showing patient radiographic progression-free survival stratified by Bone Scan Index percentage change from baseline after 12 wk of treatment. BSI = Bone Scan Index; CI = confidence interval; NR = not reached.

did not show a significant statistical correlation with BSI percentage change ($p = 0.133$).

Patients who presented with a BSI value >0 before ODM-201 treatment initiation ($n = 36$) showed baseline BSI values

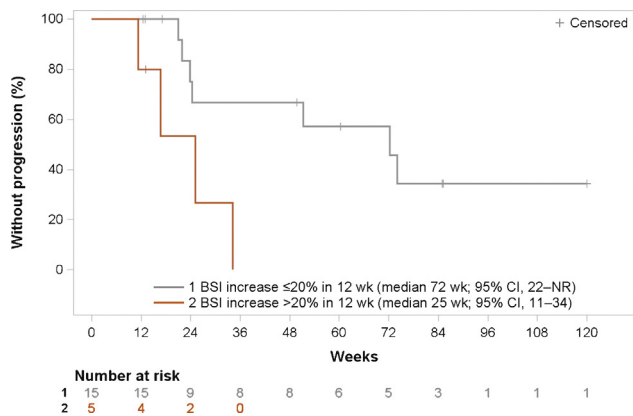


Fig. 6 – Kaplan-Meier curves showing patient time to prostate-specific antigen progression stratified by Bone Scan Index changes at follow-up after 12 wk of treatment initiation in the chemotherapy/CYP17i-naïve patient subgroup.
BSI = Bone Scan Index; CI = confidence interval; NR = not reached.

ranging between 0.03 and 9.6 (median: 2.39 [SD: 2.6], and BSI percentage change from baseline in this group ranged between -21% and 473% (median: 30% [SD: 93]). Using the Pearson correlation, BSI percentage change significantly correlated with PSA percentage change ($r = 0.76$; $p < 0.001$), disease progression in soft tissue ($r = 0.51$; $p = 0.038$), CTC percentage change ($r = 0.62$; $p = 0.001$), and CTC conversion rate ($r = 0.67$; $p < 0.001$) (Table 2).

When analysing all subgroups with different pretreatments, among the prechemotherapy/CYP17i-naïve patients ($n = 20$), 15 patients showed a decrease or only a small increase in BSI percentage change from baseline to follow-up, at most 20%. These patients had a significantly longer time to PSA progression (median: 72 wk vs 25 wk; HR: 0.2; 95% CI, 0.05–0.83; $p = 0.027$) (Fig. 6) than those with an increase $>20\%$ ($n = 5$). Patients from the other two pretreatment subgroups—postchemotherapy/CYP17i naïve ($n = 16$) and post-CYP17i ($n = 11$)—did not show significant differences in time to PSA progression related to BSI percentage change ($p = 0.34$ and $p = 0.99$, respectively).

4. Discussion

The present study shows that mCRPC patients with a baseline BSI value >1 had a significantly shorter median time to progression in bone involvement than mCRPC patients with a baseline BSI value ≤ 1 . We was also observed that patients with a decrease or at most a 20% increase from baseline BSI value had a significantly longer time to progression in bone and rPFS than those with an on-treatment BSI increase $>20\%$ during treatment. In the subpopulation of prechemotherapy/CYP17i-naïve patients, those who had only small on-treatment increases ($<20\%$) in BSI value had a significantly longer time to PSA progression than when analysing all the subgroups together.

Results from the present study are in accordance with previous studies showing that baseline BSI values could be used as a prognostic biomarker in PCa [6,12,13].

Furthermore, this study supports the use of the BSI for treatment monitoring as indicated by previously observed strong correlations between BSI value changes from baseline and survival in PCa at different disease stages [8,9,12,15]. The present study adds to previous results suggestive of the clinical utility of the BSI in advanced PCa as an adjunct to established biomarkers. It could be of value for patient stratification and for quantitative assessment of treatment effects on bone metastases in clinical trials on top of known clinical and biologic parameters with prognostic value [11,16].

As the number of emerging candidate drugs for the treatment of mCRPC rapidly increases, new tools are needed to identify target patient populations more objectively and reproducibly and to individualise treatment. The use of the BSI at baseline as a prognostic tool for better risk stratification before treatment decisions has now been demonstrated in different studies [6,12,13]. There is also a need for tools that assist in the objective follow-up of bone status after treatment initiation. Use of the BSI during treatment could guide clinicians in identifying which patients would benefit from a certain therapy and should remain on treatment and which patients would no longer benefit from treatment and therefore should be offered other types of therapy. In clinical trials, parameters with demonstrated surrogacy to OS are desperately needed in CRPC, and change in BSI values during treatment is a potential candidate.

The limitations of the bone scintigraphic technique itself include the risk of false-positive signals caused by a flare reaction induced by the initiation of a new treatment. Flare phenomena occur most commonly during the first 3 mo of treatment, but the duration of this local reaction in bone tissue after induced cell death may vary. Therefore, we decided to include only patients who had a follow-up bone scan at 12 wk or more from the start of treatment with ODM-201 in accordance with the Prostate Cancer Working Group 2 guidelines [17]. Despite precautions taken to avoid false positive-signals because of flare and despite the absence of any such signs upon visual inspection of the bone scans, the influence of flare phenomena cannot completely be ruled out in this investigation. In future studies, it may be advisable to include a further follow-up bone scan examination at 6 or 9 mo after treatment initiation.

Patients were enrolled at 23 different hospitals in Europe and the United States, and this could partially explain the heterogeneity of the image data in both bone scans and computed tomography scans. The low number of evaluable images of sufficient quality resulted in a reduced number of observations, which could in some cases have limited the power to detect statistically significant differences. In future studies, it may be advisable to include specific resolution requirements in the image protocol for further imaging analysis.

Because the BSI enables us to quantify the tumour burden in bone and its changes after therapy, it is a useful imaging biomarker that could be used to enhance the prognostic evaluation of patients undergoing clinical trials. Despite the increasing number of available biomarkers in the field of PCa research, there is still a need for more

quantifiable prognostic biomarkers that can be used not only for research purposes but also for routine clinical situations when stratifying the patient population and monitoring the response to treatment given. Therefore, further investigation is warranted of the BSI in the context of prospective clinical studies.

5. Conclusions

The BSI measured at baseline is related to median time to progression in bone in mCRPC patients treated with ODM-201, and on-treatment increases in BSI values is associated with a shorter time to PSA progression, a shorter time to progression of the disease in bone, and a shorter rPFS. The BSI as an imaging biomarker for quantification of bone metastases could be a valuable complement to traditional methods for evaluation of treatment response in mCRPC patients undergoing clinical trials.

Author contributions: Mariana Reza had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Reza, Jones, Massard, Edenbrandt, Wollmer, Trägårdh, Bondesson, Fizazi, Bjartell, Mattila, Mustonen.

Acquisition of data: Reza, Edenbrandt, Jones, Massard, Mattila, Mustonen.

Analysis and interpretation of data: Reza, Jones, Edenbrandt, Trägårdh, Bondesson, Fizazi, Bjartell.

Drafting of the manuscript: Reza, Jones, Edenbrandt, Trägårdh, Bondesson, Fizazi, Bjartell.

Critical revision of the manuscript for important intellectual content: Reza, Jones, Aspegren, Massard, Edenbrandt, Wollmer, Trägårdh, Bondesson, Fizazi, Bjartell, Mattila, Mustonen.

Statistical analysis: Aspegren.

Obtaining funding: Mattila, Mustonen, Edenbrandt, Bjartell.

Administrative, technical, or material support: Aspegren.

Supervision: Edenbrandt, Trägårdh, Bjartell.

Other (specify): None.

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