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## Research Letter

# Whole-body Diffusion-weighted Magnetic Resonance Imaging for Assessment of the Bone Response Rate in Patients with Metastatic Hormone-sensitive Prostate Cancer Receiving Enzalutamide

Alberto Dalla Volta<sup>a,\*</sup>, Francesca Valcamonico<sup>a</sup>, Andrea Zivi<sup>b,c</sup>, Giuseppe Procopio<sup>d</sup>, Pierangela Sepe<sup>d</sup>, Gianluca Del Conte<sup>e</sup>, Nunzia Di Meo<sup>f</sup>, Silvia Foti<sup>e</sup>, Stefania Zamboni<sup>g</sup>, Caterina Messina<sup>h</sup>, Eleonora Lucchini<sup>i</sup>, Anna Rizzi<sup>j</sup>, Marco Ravanelli<sup>f</sup>, Stefano Calza<sup>k</sup>, Francesca Zacchi<sup>b,c</sup>, Giovannino Ciccone<sup>l</sup>, Nazareno Suardi<sup>g</sup>, Roberto Maroldi<sup>f</sup>, Davide Farina<sup>f</sup>, Alfredo Berruti<sup>a</sup>

Bone is often the dominant metastatic site in patients with prostate cancer. However, conventional imaging techniques (computed tomography [CT] and bone scans) are not suitable for evaluating bone tumor responses to systemic anti-neoplastic treatments because of their inability to measure metastatic extent in bone and detect bone repair within osteoblastic lesions [1]. Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) offers significant advantages over conventional imaging, as it can identify bone marrow infiltration, tumor necrosis induced by treatment, and bone marrow restoration [2,3].

BONENZA is a phase 2 randomized clinical trial in which the primary endpoint was the bone response rate measured via WB-DW-MRI in patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated with enzalutamide and androgen deprivation therapy, with or without zoledronic acid. Of the 126 patients who were randomized, 109 were fully evaluated via WB-DW-MRI after at least 6 mo of treatment. The reasons for exclusion from response evaluation were the absence of bone target lesions at baseline ( $n = 9$ ), withdrawal of consent ( $n = 4$ ), absolute contraindications to MRI ( $n = 3$ ), and death from other causes ( $n = 1$ ). The scheme for evaluation of treatment response was adapted from the standardized method proposed by Padhani et al [4]. In brief, the response assessment criteria were as follows:

- Complete response (CR): disappearance of all lesions on DWI.
- Partial response (PR): reduction in lesion size of  $\geq 30\%$ ;  $\geq 15\%$  reduction in b800 signal intensity normalized by muscle sig-

nal; increase in of apparent diffusion coefficient (ADC) of  $>1500 \mu\text{m}^2/\text{s}$ ; increase in fat fraction within the lesions of at least 10%.

- Progressive disease (PD): appearance of new lesions; increase in lesion size; increase in b800 signal intensity without a significant increase in ADC; decrease in fat fraction.
- Stable disease (SD): lesions with stable size, b800 signal intensity, and fat fraction.

Representative cases of CR, PR, and PD on WB-DW-MRI are shown in Figure 1.

In the intention-to-treat population, 20/126 patients (15.9%) achieved CR, 68/126 (53.9%) achieved PR, and 9/126 (7.1%) achieved SD, while 12/126 (9.5%) experienced PD. The overall response rate was 69.8% (95% confidence interval [CI] 57.5–79.9%). In the per-protocol population of 109 evaluable patients, the corresponding response rates were 18.3%, 62.4%, 8.3%, and 11%, and the overall response rate was 81% (95% CI 73.6–88.4%). Bone and soft-tissue responses on WB-DW-MRI were highly consistent (Cohen's  $\kappa = 0.477$ ).

In comparison to WB-DW-MRI, CT and bone scans showed poor agreement for the bone metastatic response rate (32.3% and 45.8% respectively; Cohen's  $\kappa < 0.1$ ), while PSA responses were more consistent (78.5%, Cohen's  $\kappa = 0.3$ ).

The clinical relevance of bone responses on WB-DW-MRI was reinforced by a significant association with overall survival in the per-protocol population. CR on WB-DW-MRI was correlated with a lower risk of death (hazard ratio

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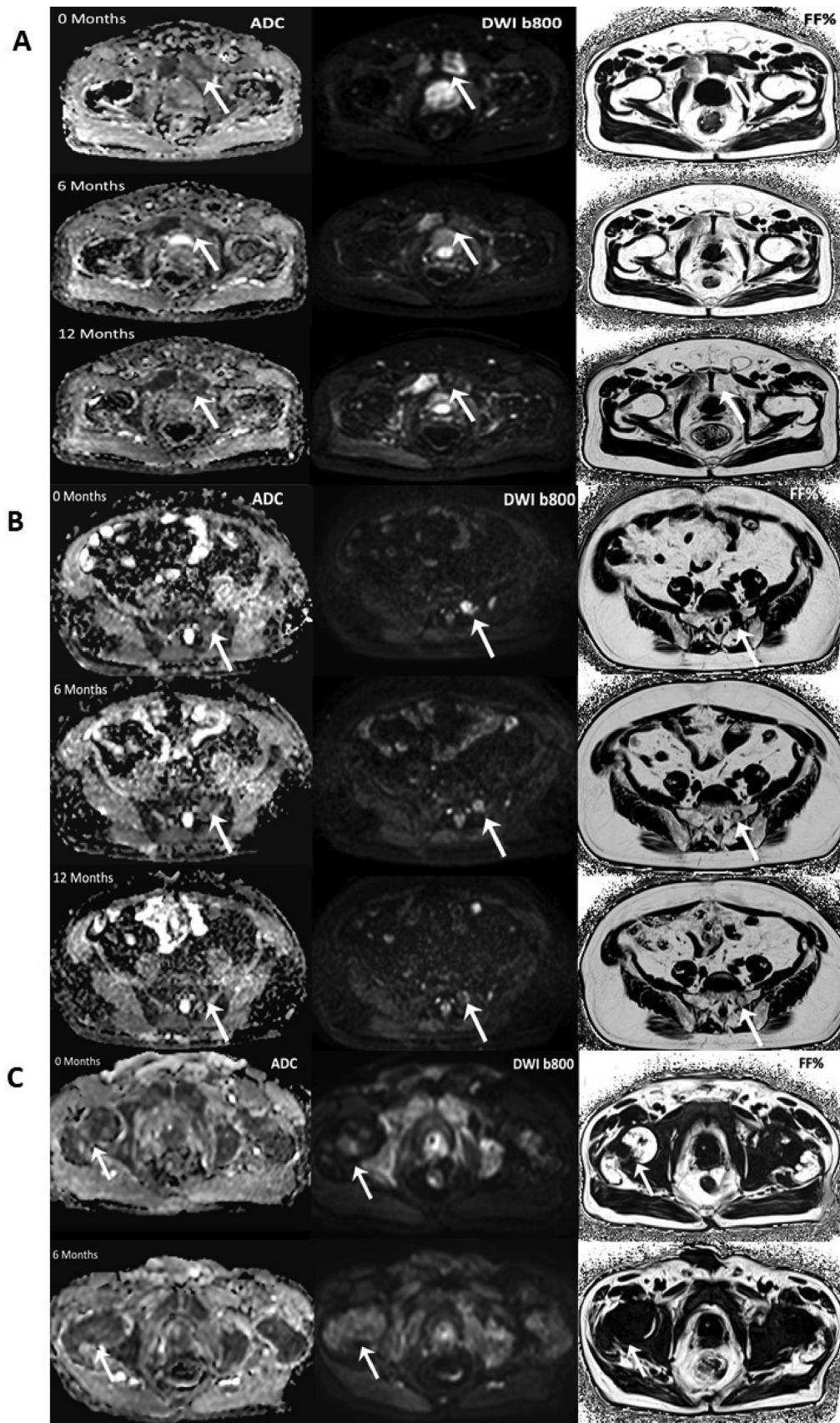


Fig. 1 – (A) Complete response of a metastatic lesion on the left pubic bone. The image shows a left pubic bone lesion before and 6 and 12 mo after treatment. There is complete response of the metastatic lesion, with normalization of the signal intensity on the high b-value sequence at 6- and 12-mo follow-up, fat repopulation of the bone marrow (fat fraction [FF%] sequence), high apparent diffusion coefficient (ADC) values (>1400) at 6-mo follow-up, and a reduction to normal bone ADC values at 12-mo follow-up and complete disappearance on the T1-weighted sequence. (B) Partial response of a metastatic lesion on the left sacral ala. This patient had a left sacral ala lesion (white arrow) before treatment, with a slight reduction in signal on the high b-value sequence at 6- and 12-mo follow-up without changes in ADC values and the appearance of intratumoral fat within the lesion. (C) Progression of a metastatic lesion on the right femur. This patient had a small lesion at the neck of the right femur (white arrow) that had increased in size at 6-mo follow-up, with ADC and FF% values indicating an active lesion. DWI = diffusion-weighted imaging.

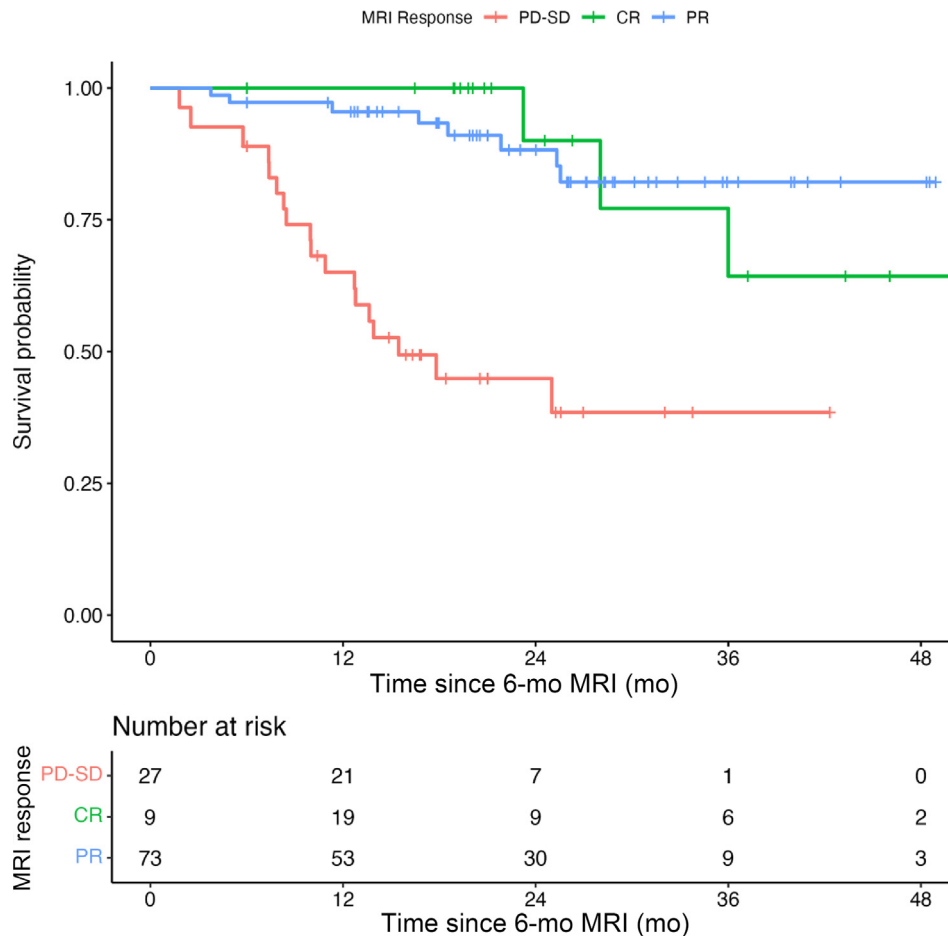


Fig. 2 – Prognostic role of bone response at the 6-mo MRI assessment. MRI = magnetic resonance imaging; PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response.

[HR] 0.16, 95% CI 0.06–0.48;  $p < 0.001$ ), as was PR (HR 0.14, 95% CI 0.06–0.32;  $p < 0.001$ ) and CR/PR versus SD/PD (HR 0.15, 95% CI 0.07–0.30;  $p < 0.001$ ; Fig. 2). To the best of our knowledge, this is the first prospective randomized study in which the primary aim was evaluation of objective responses in bone metastases from prostate cancer via WB-DW-MRI.

The high bone response rate observed is comparable to the disease response in soft tissues in the same study and in the pivotal phase 3 study of enzalutamide in mHSPC [5].

Despite being highly concordant with other parameters (PSA and soft-tissue imaging), WB-DW-MRI data could add some unique information, such as more precise spatial resolution of disease progression in bone, which could facilitate metastasis-directed treatments in oligoprogressive disease.

The ineligibility rate of 13.5% for WB-DW-MRI evaluation is a potential limitation for application of this procedure to a broader population. On the basis of results from the current study and those reported by Garcia-Ruiz et al in *European Urology* [6], WB-DW-MRI may become the reference imaging technique in future prospective studies enrolling patients with metastatic prostate cancer.

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- <sup>a</sup> *Unit of Medical Oncology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy*
- <sup>b</sup> *Division of Oncology, Verona University and Hospital Trust, Verona, Italy*
- <sup>c</sup> *Oncology Area, Section of Innovation Biomedicine, Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy*
- <sup>d</sup> *Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*
- <sup>e</sup> *Department of Oncology, Fondazione IRCCS San Raffaele Hospital, Milan, Italy*
- <sup>f</sup> *Unit of Radiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy*
- <sup>g</sup> *Unit of Urology, Department of Medical and Surgical Specialties, Radiological Science and Public Health, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy*
- <sup>h</sup> *Unit of Medical Oncology, ASST Papa Giovanni XXIII, Bergamo, Italy*
- <sup>i</sup> *Unit of Medical Oncology, ASST Garda, Desenzano, Italy*
- <sup>j</sup> *Unit of Medical Oncology, ASST Garda, Manerbio, Italy*
- <sup>k</sup> *Unit of Biostatistics and Bioinformatics, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy*
- <sup>l</sup> *Unit of Clinical Epidemiology, AOU Città della Salute e della Scienza di Torino and CPO Piemonte, Turin, Italy*
- \*Corresponding author. Oncologia Medica, ASST Spedali Civili di Brescia, Piazzale Spedali Civili 1, Brescia 25123, Italy.  
E-mail address: [alberto.dallavolta@gmail.com](mailto:alberto.dallavolta@gmail.com) (A. Dalla Volta).

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