UNIVERSITÀ DEGLI STUDI DI BRESCIA

Dott. Marco Bergamini

Università degli Studi di Brescia

Oncologia Medica ASST Spedali Civili di Brescia

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Metastasi ossee e tumore della prostata: ruolo degli ARSI e dei PARP-inhibitors - loro impatto sull'osso e sul dolore

INTRODUCTION

Bone is the most common site of spread of metastatic prostate cancer [1].

The volume of bone metastases correlates with **survival** [2].

Bone metastases are an important cause of morbidity.

Skeletal related events (**SREs**): pathologic fractures, spinal cord compression, need for surgery or radiation therapy to bone, hypercalcemia [3].

Time to SREs is an important prognostic marker in metastatic prostate cancer [4].

1. Gralow JR, J Natl Compr Canc Netw 2009
2. Sweeney CJ, NWJM 2015
3. Saylor PJ, JCO 2011
4. Sathiakumar N, Prostate Cancer Prostatic Dis 2011

INTRODUCTION

In 2008, the Prostate Cancer Clinical Trials Working Group 2 (**PCWG2**) identified the following key unmet needs: delaying time to SREs and delaying time to onset of significant pain [1].

In 2015, the PCWG3 identified the reduction in the frequency of SREs as an approvable end point of prostate cancer clinical trials [2].

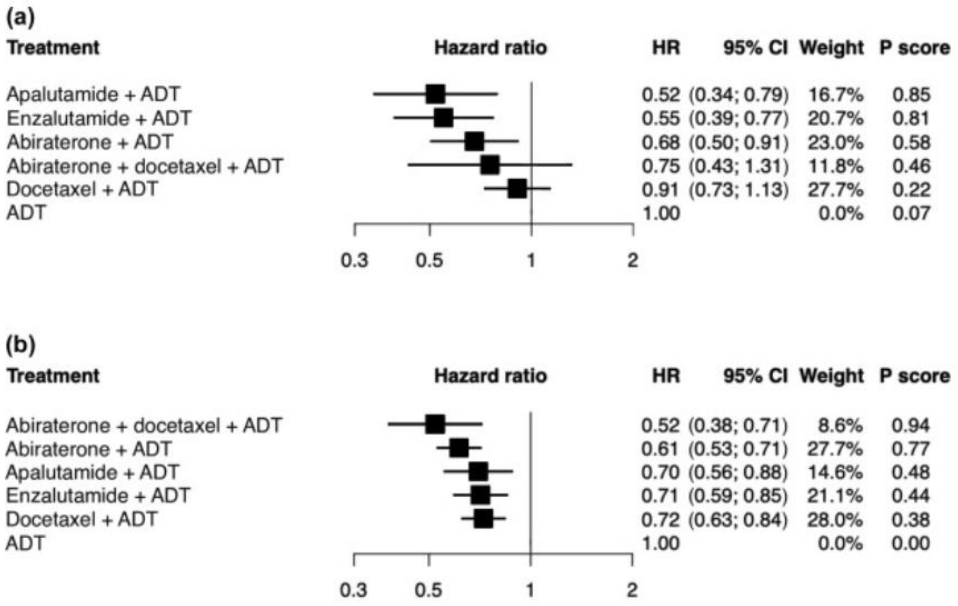
The use of bone scintigraphy as the standard for **bone imaging** is retained in PCWG3 [2].

It is difficult to interpret the clinical significance of changes in size or intensity of bone metastases on bone scan.

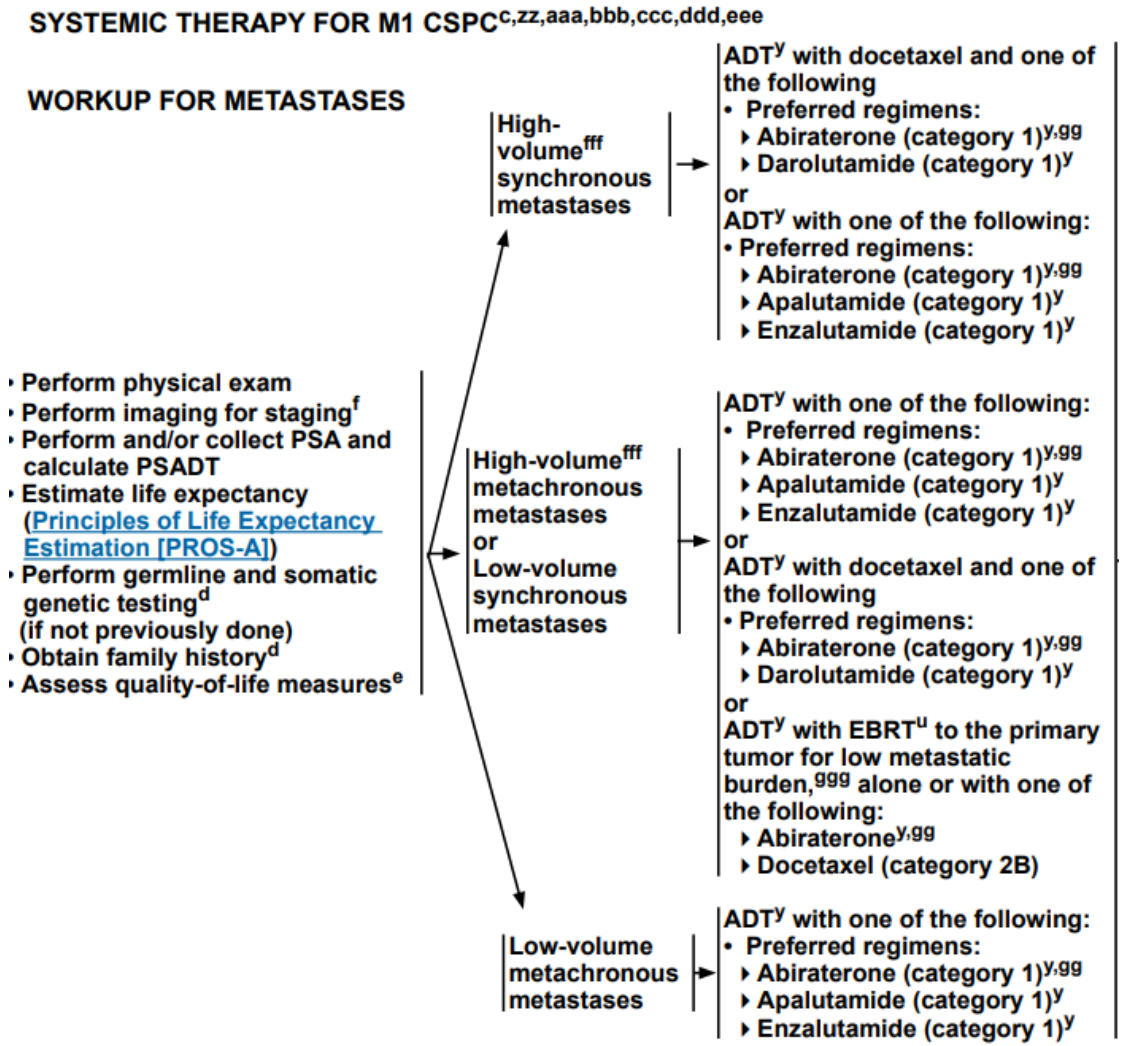
Positron emission tomography (PET) imaging, whole-body magnetic resonance imaging (WB-MRI) and other modalities that are in use to image bone should be approached as new biomarkers subject to independent validation [2].

1. Scher H., JCO 2008
2. Scher H., JCO 2016

ARSI



Mandel P. Eur Urol Focus 2023



NCCN guidelines 2024

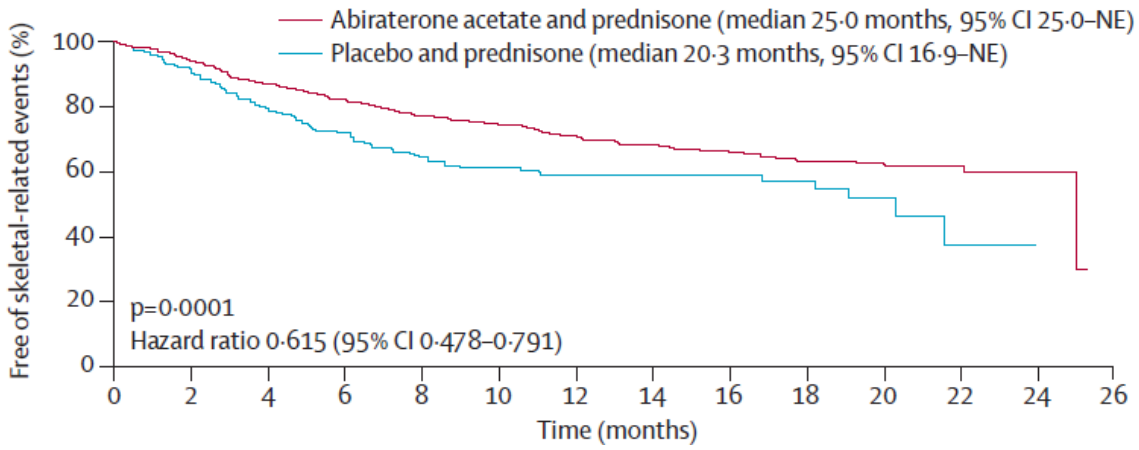
ABIRATERONE - mCRPC

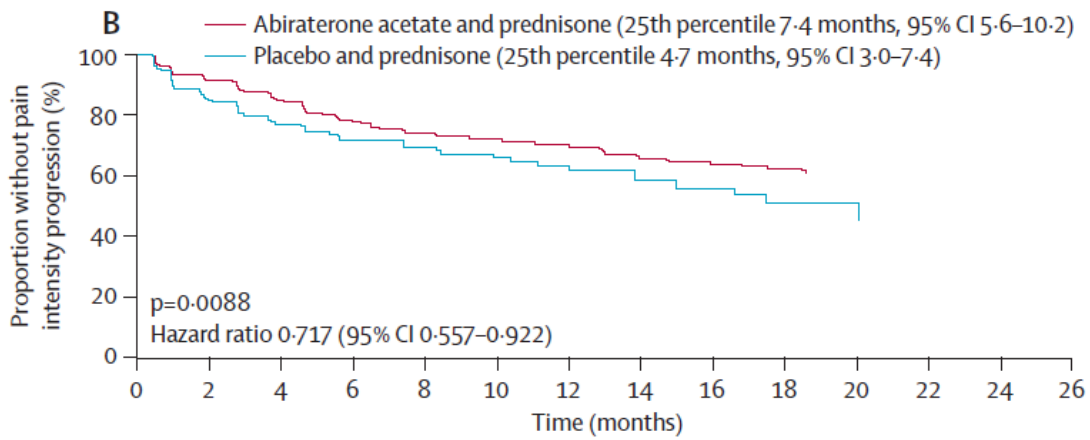
Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial

Christopher J Logothetis, Ethan Basch, Arturo Molina, Karim Fizazi, Scott A North, Kim N Chi, Robert J Jones, Oscar B Goodman, Paul N Mainwaring, Cora N Sternberg, Eleni Efstathiou, Dennis D Gagnon, Margaret Rothman, Yanni Hao, Cameron S Liu, Thian S Kheoh, Christopher M Haqq, Howard I Scher, Johann S de Bono**

Disease location		
Bone	710/797 (89·1%)	358/398 (89·9%)
Node	361/797 (45·3%)	164/398 (41·2%)
Liver	89/797 (11·2%)	29/398 (7·3%)

SRE rate per 100 patients-years of exposure (%)*	38·9%	65·1%
Radiation to bone (%)	24·0%	46·1%
Pathological fracture (%)	6·0%	4·0%
Surgery to bone (%)	1·7%	1·0%
Spinal cord compression (%)	7·3%	14·0%





Lancet Oncology 2012

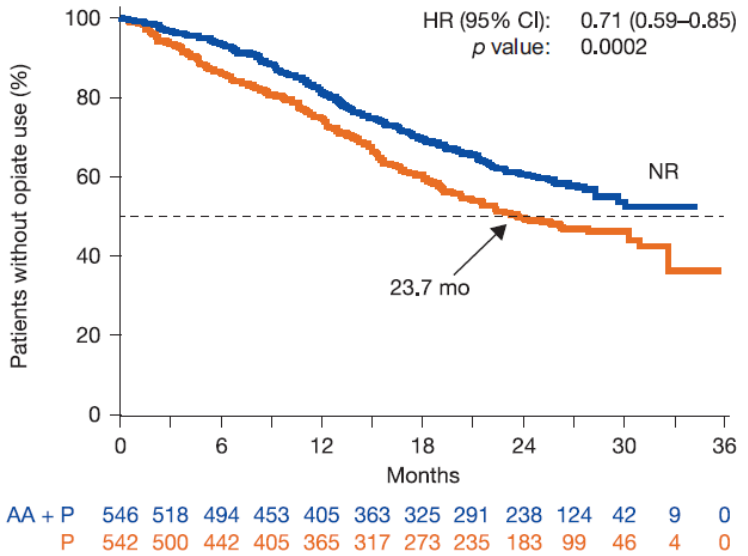
ABIRATERONE - mCRPC

Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302)

Dana E. Rathkopf[a,], Matthew R. Smith[b], Johann S. de Bono[c], Christopher J. Logothetis[d], Neal D. Shore[e], Paul de Souza[f], Karim Fizazi[g], Peter F.A. Mulders[h], Paul Mainwaring[i], John D. Hainsworth[j], Tomasz M. Beer[k], Scott North[l], Yves Fradet[m], Hendrik Van Poppel[n], Joan Carles[o], Thomas W. Flaig[p], Eleni Efstathiou[d], Evan Y. Yu[q], Celestia S. Higano[q], Mary-Ellen Taplin[r], Thomas W. Griffin[s], Mary B. Todd[t], Margaret K. Yu[s], Youn C. Park[t], Thian Kheoh[s], Eric J. Small[u], Howard I. Scher[a], Arturo Molina[v], Charles J. Ryan[u], Fred Saad[w]*

Bone metastases	452 (83)	432 (80)
>10	264 (49)	253 (47)

PRO end points	Abiraterone plus prednisone, $n = 546$	Prednisone alone, $n = 542$	Hazard ratio* (95% CI)	p value†
Median time to pain progression, mo				
Mean pain intensity‡	26.7	18.4	0.83 (0.68–1.01)	0.06
Pain interference###	10.3	7.4	0.80 (0.68–0.93)	0.005
Worst pain intensity‡ (prespecified analysis)	25.8	20.3	0.85 (0.69–1.04)	0.1



Eur Urol 2014

ABIRATERONE - mHSPC

ORIGINAL ARTICLE

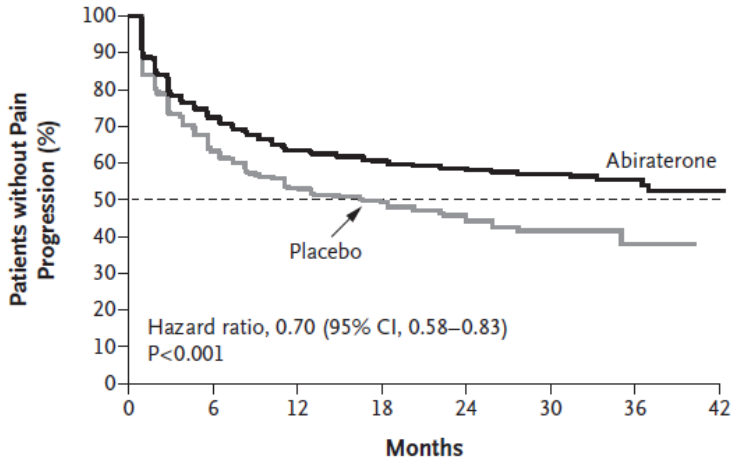
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüroğlu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

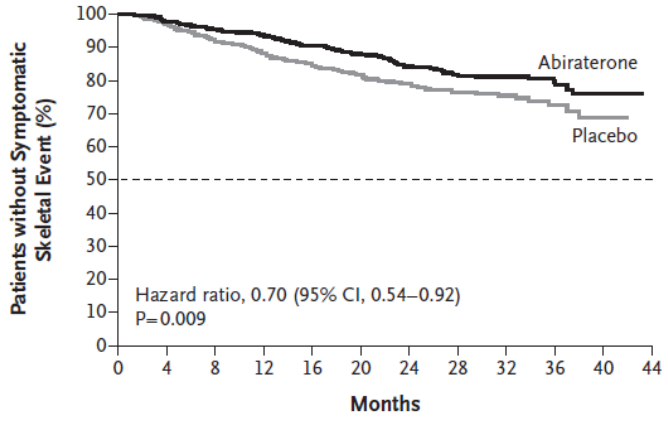
Extent of disease, n (%)		
n	596	600
Bone	580 (97)	585 (98)
Liver	32 (5)	30 (5)
Lungs	73 (12)	72 (12)
Node	283 (47)	287 (48)
Prostate mass	151 (25)	154 (26)
Viscera	18 (3)	13 (2)
Soft tissue	9 (2)	15 (3)
Other	2 (0.3)	0

End Point	Abiraterone Group (N=597)	Placebo Group (N=602)	Hazard Ratio (95% CI)	P Value†
Secondary end points				
Median time to pain progression (mo)	NR	16.6	0.70 (0.58–0.83)	<0.001
Median time to PSA progression (mo)	33.2	7.4	0.30 (0.26–0.35)	<0.001
Median time to next symptomatic skeletal event (mo)	NR	NR	0.70 (0.54–0.92)	0.009

A Pain Progression



C Symptomatic Skeletal Event



NEJM 2017

ABIRATERONE - mHSPC

Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer

Alex P. Hoyle[a,b], Adnan Ali[a], Nicholas D. James[c], Adrian Cook[d], Christopher C. Parker[e], Johann S. de Bono[e], Gerhardt Attard[f], Simon Chowdhury[g], William R. Cross[h], David P. Dearnaley[i], Christopher D. Brawley[d], Clare Gilson[d], Fiona Ingleby[e], Silke Gillessen[j,k,l,m], Daniel M. Aebersold[n], Rob J. Jones[o,p], David Matheson[q,1], Robin Millman[r,1], Malcolm D. Mason[s], Alastair W.S. Ritchie[e], Martin Russell[o,p], Hassan Douis[c], Mahesh K.B. Parmar[d], Matthew R. Sydes[d], Noel W. Clarke[a,b,] on behalf of the STAMPEDE Investigators[2]*

STAMPEDE abiraterone LATITUDE criteria (All M1 patients)	ADT Alone	ADT + AAP		
	No. of events/ No. of patients		Adjusted HR (95% CI)	Interaction between metastatic subgroups *p* value
Skeletal-related events				
Overall	164/452	93/449	0.47 (0.36–0.60)	
Low	49/220	17/208	0.31 (0.18–0.54)	
High	115/232	76/241	0.48 (0.36–0.64)	0.21

STAMPEDE abiraterone CHAARTED criteria (All M1 patients)	ADT Alone	ADT + AAP		
	No. of events/ No. of patients		Adjusted HR (95% CI)	Interaction between metastatic subgroups *p* value
Skeletal-related events				
Overall	164/452	93/449	0.47 (0.36—0.60)	
Low	46/196	25/206	0.46 (0.28—0.75)	
High	118/256	68/243	0.47 (0.35—0.63)	0.98

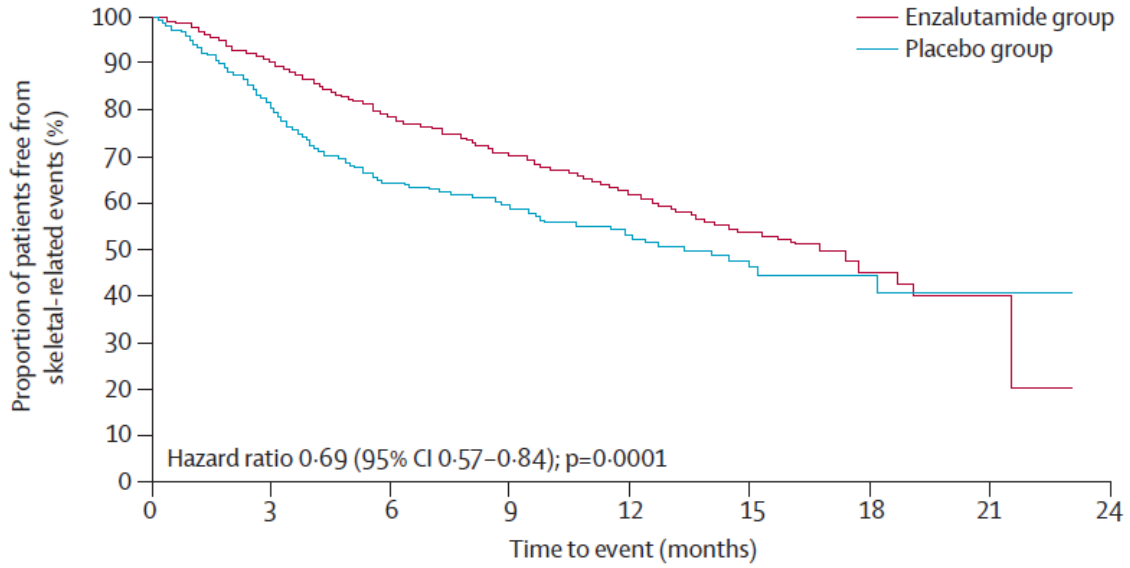
Eur Urol 2019

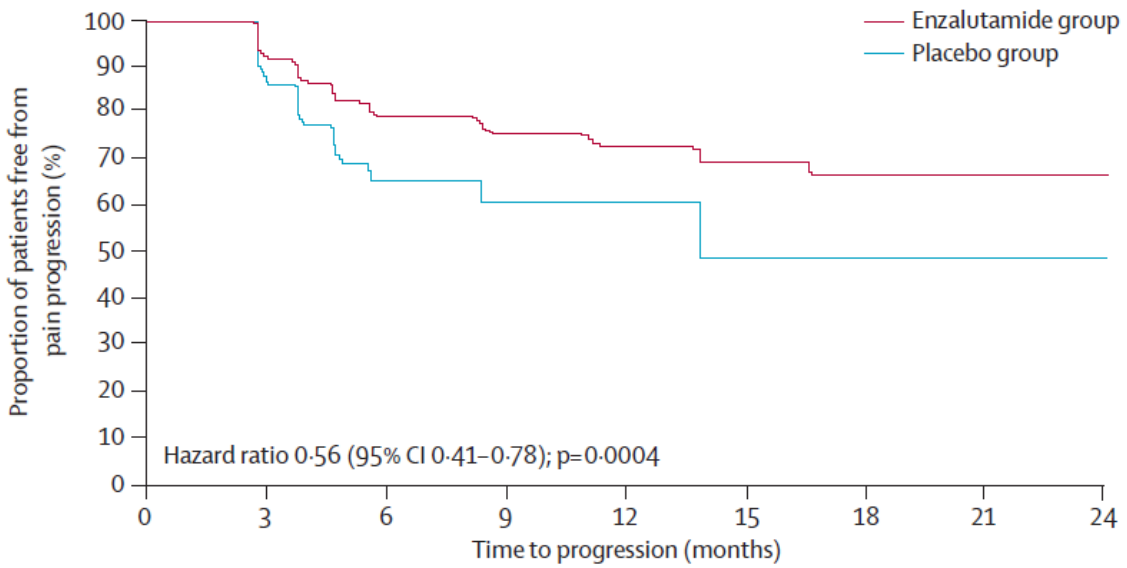
ENZALUTAMIDE - mCRPC

Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial

Karim Fizazi, Howard I Scher, Kurt Miller, Ethan Basch, Cora N Sternberg, David Cella, David Forer, Mohammad Hirmand, Johann S de Bono

Bone metastases at screening		
0	70 (9%)	35 (9%)
1	28 (4%)	21 (5%)
2–4	112 (14%)	45 (11%)
5–9	121 (15%)	68 (17%)
10–20	167 (21%)	79 (20%)
>20	302 (38%)	151 (38%)





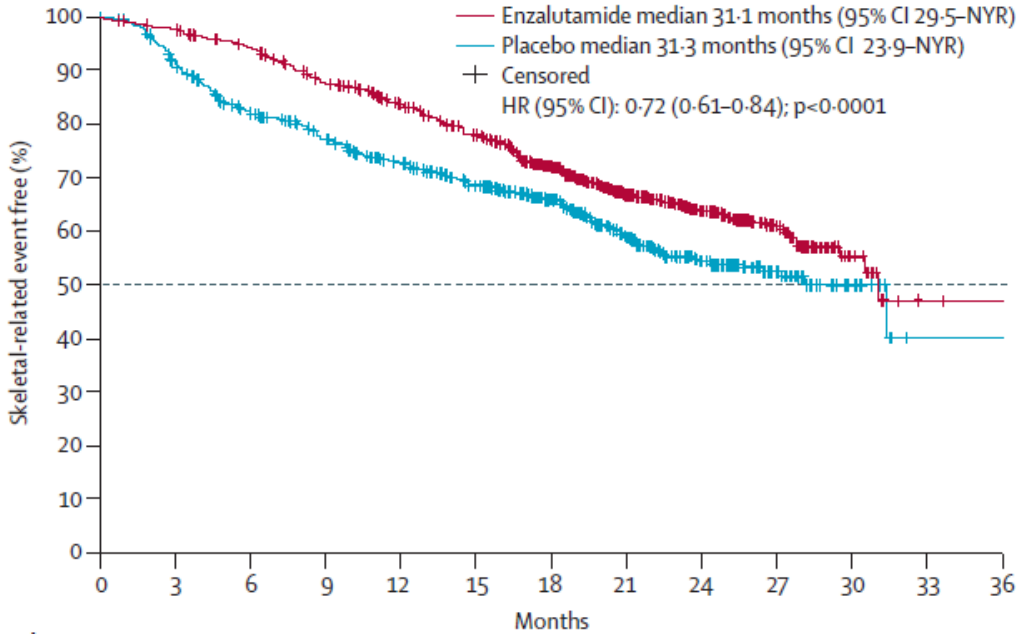
Lancet Oncol. 2014

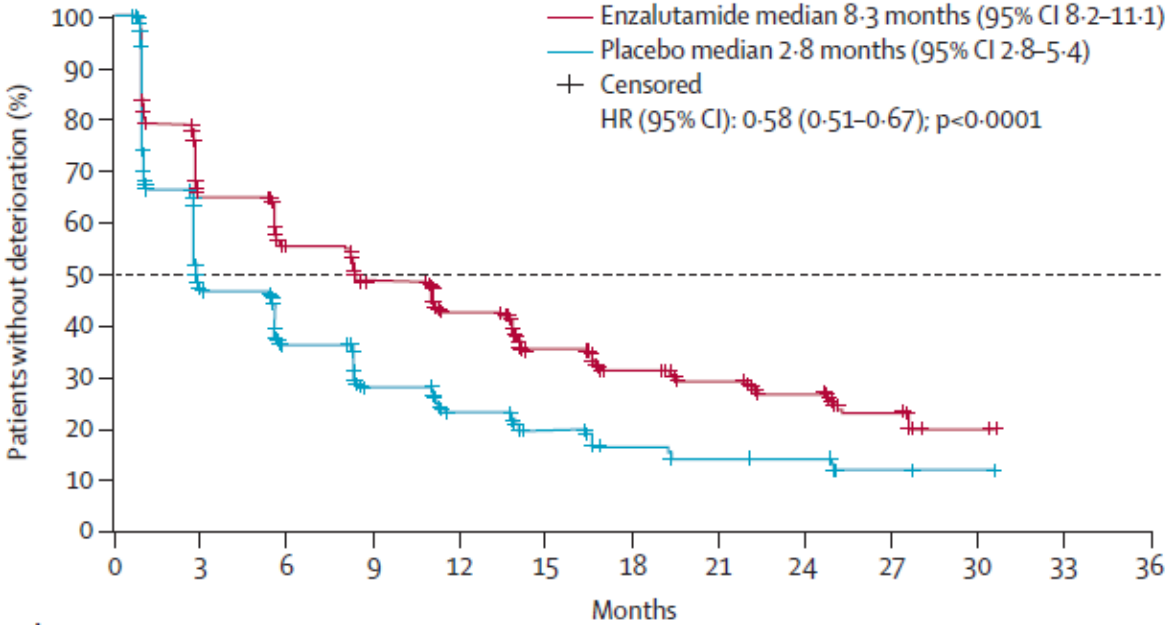
ENZALUTAMIDE - mCRPC

Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial

Yohann Loriot, Kurt Miller, Cora N Sternberg, Karim Fizazi, Johann S De Bono, Simon Chowdhury, Celestia S Higano, Sarah Noonberg, Stefan Holmstrom, Harry Mansbach, Frank G Perabo, De Phung, Cristina Ivanescu, Konstantina Skaltsa, Tomasz M Beer, Bertrand Tombal

Distribution of disease at screening – no. (%)		
Bone	741 (85.0)	690 (81.7)
Lymph node	437 (50.1)	434 (51.4)
Visceral disease (lung or liver)	98 (11.2)	106 (12.5)
Visceral liver	40 (4.6)	34 (4.0)
Visceral lung	64 (7.3)	75 (8.9)
Visceral lung and liver	6 (0.7)	3 (0.4)
Other soft tissue†	113 (13.0)	105 (12.4)





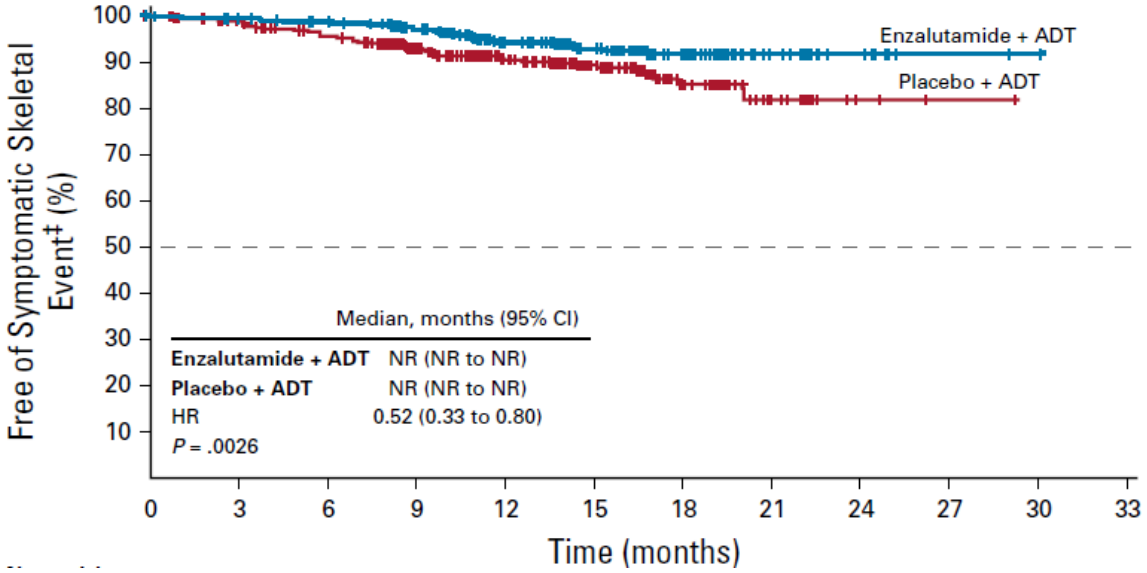
Lancet Oncol. 2015

ENZALUTAMIDE - mHSPC

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

Andrew J. Armstrong, MD, ScM[1]; Russell Z. Szmulewitz, MD[2]; Daniel P. Petrylak, MD[3]; Jeffrey Holzbeierlein, MD[4]; Arnauld Villers, MD[5]; Arun Azad, MBBS, PhD[6]; Antonio Alcaraz, MD, PhD[7]; Boris Alekseev, MD[8]; Taro Iguchi, MD, PhD[9]; Neal D. Shore, MD[10]; Brad Rosbrook, MS[11]; Jennifer Sugg, MS[12]; Benoit Baron, MS[13]; Lucy Chen, MD[12]; and Arnulf Stenzl, MD[14]

Localization of confirmed metastases at screening[b]		
Bone only	268 (46.7)	245 (42.5)
Soft tissue only	51 (8.9)	45 (7.8)
Bone and soft tissue	217 (37.8)	241 (41.8)



Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)

JCO 2019

ENZALUTAMIDE vs ABIRATERONE - mCRPC

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

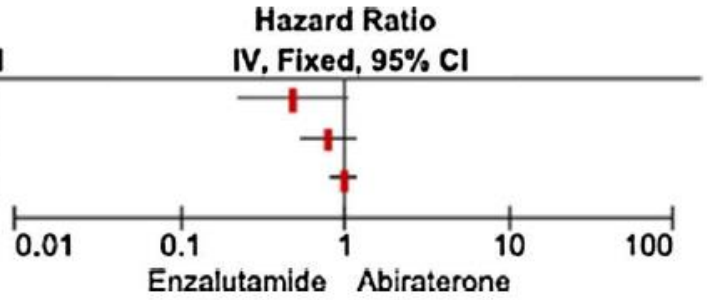
Review

The effects of enzalutamide and abiraterone on skeletal related events and bone radiological progression free survival in castration resistant prostate cancer patients: An indirect comparison of randomized controlled trials

Sergio Rizzo[a,1], Antonio Galvano[a,1], Francesco Pantano[b], Michele Iuliani[b], Bruno Vincenzi[b], Francesco Passiglia[a], Silvia Spoto[c], Giuseppe Tonini[b], Viviana Bazan[a], Antonio Russo[a,2,*], Daniele Santini[b,2]

Two new drugs, the CYP17 inhibitor abiraterone acetate and the androgen receptor (AR) antagonist enzalutamide, have recently shown to prolong OS prior chemotherapy or in docetaxel treated mCRPC patients, using steroidal therapy or placebo as control group. Updated analyses underlined the role of these new agents on two prostate-specific endpoints as radiographic progression-free survival (rPFS) and time to first skeletal-related event (tSRE). On the basis of these reports, we made an indirect comparison between abiraterone and enzalutamide. We obtained a clinically but not significant difference favouring enzalutamide over abiraterone in terms of rPFS (HR 0.48, 95% CI 0.22–1.02). No significant difference was shown in term of tSRE (HR 0.99, 95% CI 0.83–1.17). In conclusion, abiraterone and enzalutamide have both demonstrated to significantly delay the bone progression resulting in similar improvements in bone-related endpoints in patients with mCRPC.

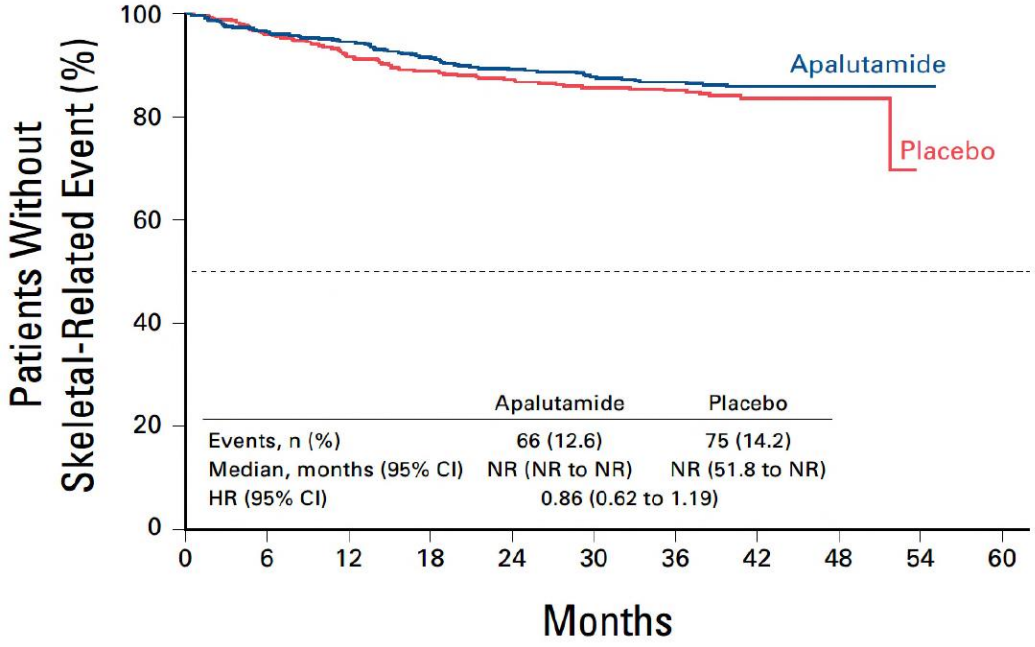
Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
rPFS	-0.74	0.39	0.48 [0.22, 1.02]
Time to pain deterioration	-0.238	0.188	0.79 [0.55, 1.14]
ISRE	-0.013	0.0873	0.99 [0.83, 1.17]



APALUTAMIDE - mHSPC

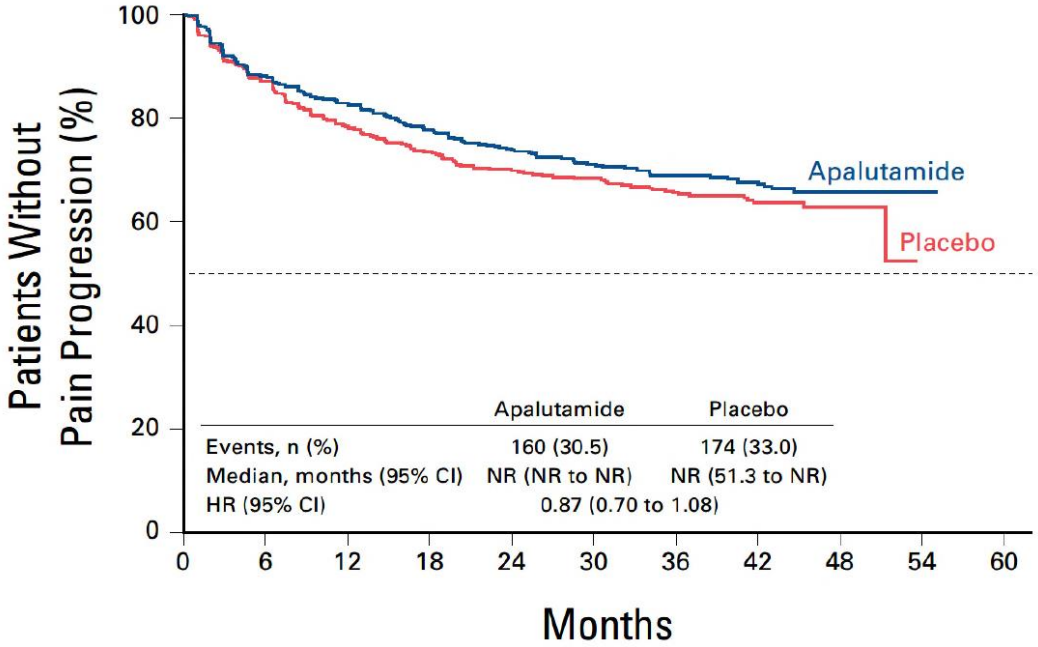
Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study

Kim N. Chi, MD[1]; Simon Chowdhury, MD, PhD[2]; Anders Bjartell, MD, PhD[3]; Byung Ha Chung, MD, PhD[4]; Andrea J. Pereira de Santana Gomes, MD[5]; Robert Given, MD[6]; Alvaro Juárez Soto, MD[7]; Axel S. Merseburger, MD, PhD[8]; Mustafa Özgüroğlu, MD[9]; Hirotsugu Uemura, MD, PhD[10]; Dingwei Ye, MD, PhD[11]; Sabine Brookman-May, MD[12,13]; Suneel D. Mundle, PhD[13]; Sharon A. McCarthy, BPharm[13]; Julie S. Larsen, PharmD[14]; Weili Sun, MD, PhD[14]; Katherine B. Bevans, PhD[15]; Ke Zhang, PhD[16]; Nibedita Bandyopadhyay, PhD[13]; and Neeraj Agarwal, MD[17]



PATIENTS AND INTERVENTIONS

Eligible patients were required to have documented adenocarcinoma of the prostate and distant metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement. All the



JCO 2021 NEJM 2019

DAROLUTAMIDE - mHSPC

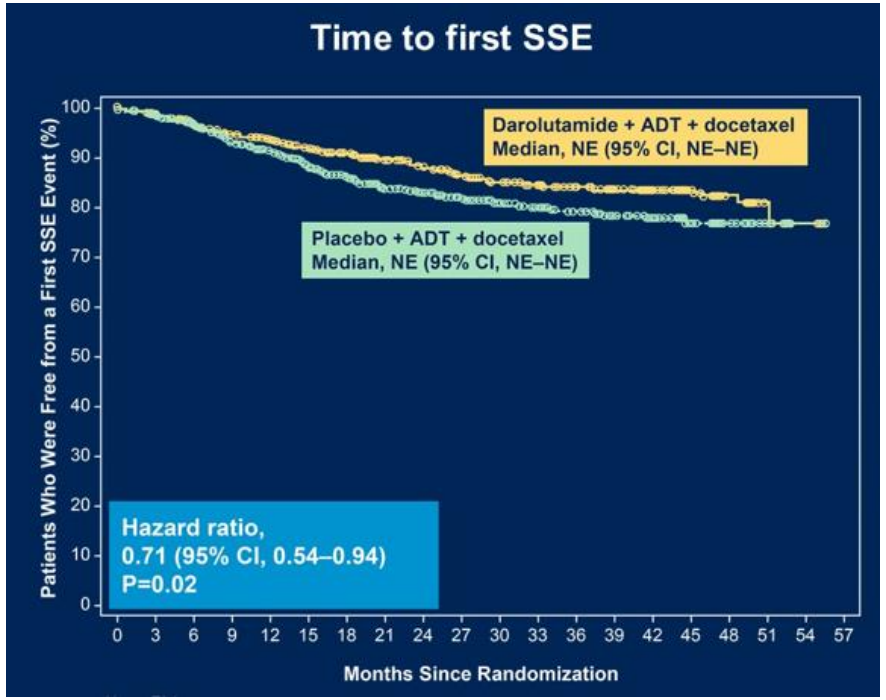
ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

Metastasis stage at screening — no. (%)		
M1a, nonregional lymph-node metastases only	23 (3.5)	16 (2.4)
M1b, bone metastases with or without lymph-node metastases	517 (79.4)	520 (79.5)
M1c, visceral metastases with or without lymph-node or bone metastases	111 (17.1)	118 (18.0)

End Point	Darolutamide–ADT–Docetaxel (N=651)†		Placebo–ADT–Docetaxel (N=654)†		Hazard Ratio (95% CI)	P Value
	Median	Patients with Event	Median	Patients with Event		
	mo	*no. (%)*	*mo*	*no. (%)*		
Time to castration-resistant prostate cancer	NR	225 (35)	19.1	391 (60)	0.36 (0.30–0.42)	<0.001
Time to pain progression	NR	222 (34)	27.5	248 (38)	0.79 (0.66–0.95)	0.01
Symptomatic skeletal event–free survival	51.2	257 (40)	39.7	329 (50)	0.61 (0.52–0.72)	<0.001
Time to first symptomatic skeletal event	NR	95 (15)	NR	108 (17)	0.71 (0.54–0.94)	0.02



Smith M., ASCO GU 2022

NEJM 2022

BONE RESPONSE ASSESSMENT

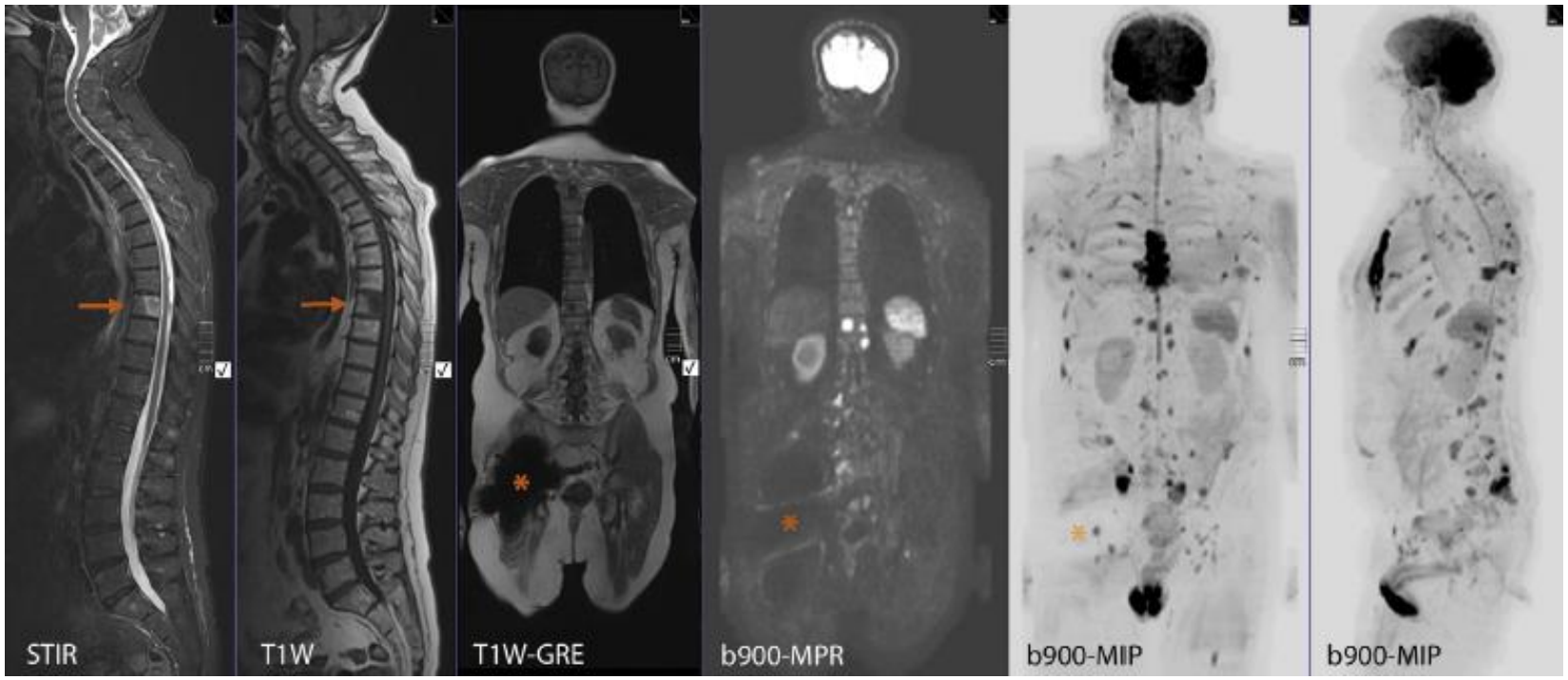
Evaluation of bone metastasis in metastatic prostate cancer remains a clinical challenge.

CT scan and **bone scan** are not suitable for the evaluation of bone tumor response to systemic antineoplastic treatments because of their inability to measure metastatic extent in bone and detect bone repair inside osteoblastic lesions [1].

Whole-body diffusion-weighted magnetic resonance imaging (**WB-DW-MRI**) offers significant advantages with respect to conventional imaging, as it does identify bone marrow infiltration, tumor necrosis induced by treatment and bone marrow restoration [2,3].

1. Berruti A., Br J Cancer 1996
2. Mosavi F., AJR Am J Roentgenol. 2012
3. Padhani AR., J Magn Reson Imaging 2014

BONE RESPONSE ASSESSMENT

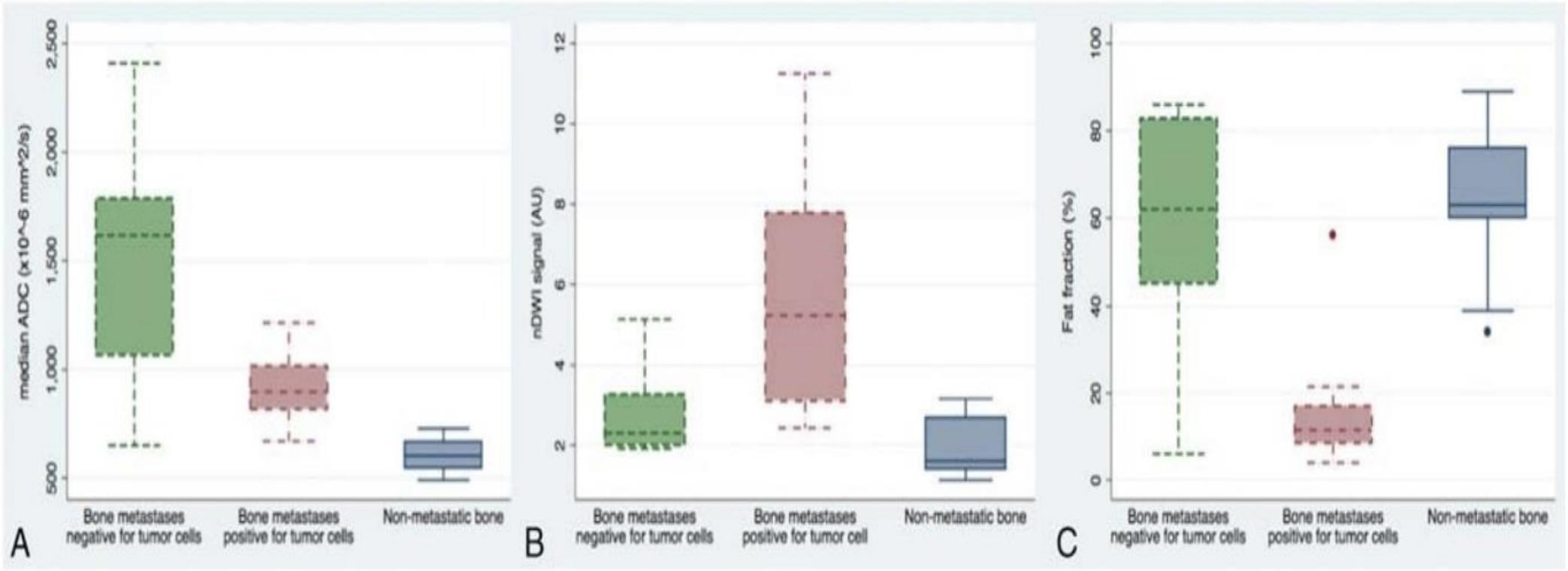


SE = 99%
SP = 98%
PPV = 98%
NPV = 96%
Accuracy = 98%

Parameters for bone response assessment[3]
DWI = diffusion weighted imaging
ADC = apparent diffusion coeffcient
FF% = fat fraction

1. Padhani AR., Eur Urol 2017

BONE RESPONSE ASSESSMENT



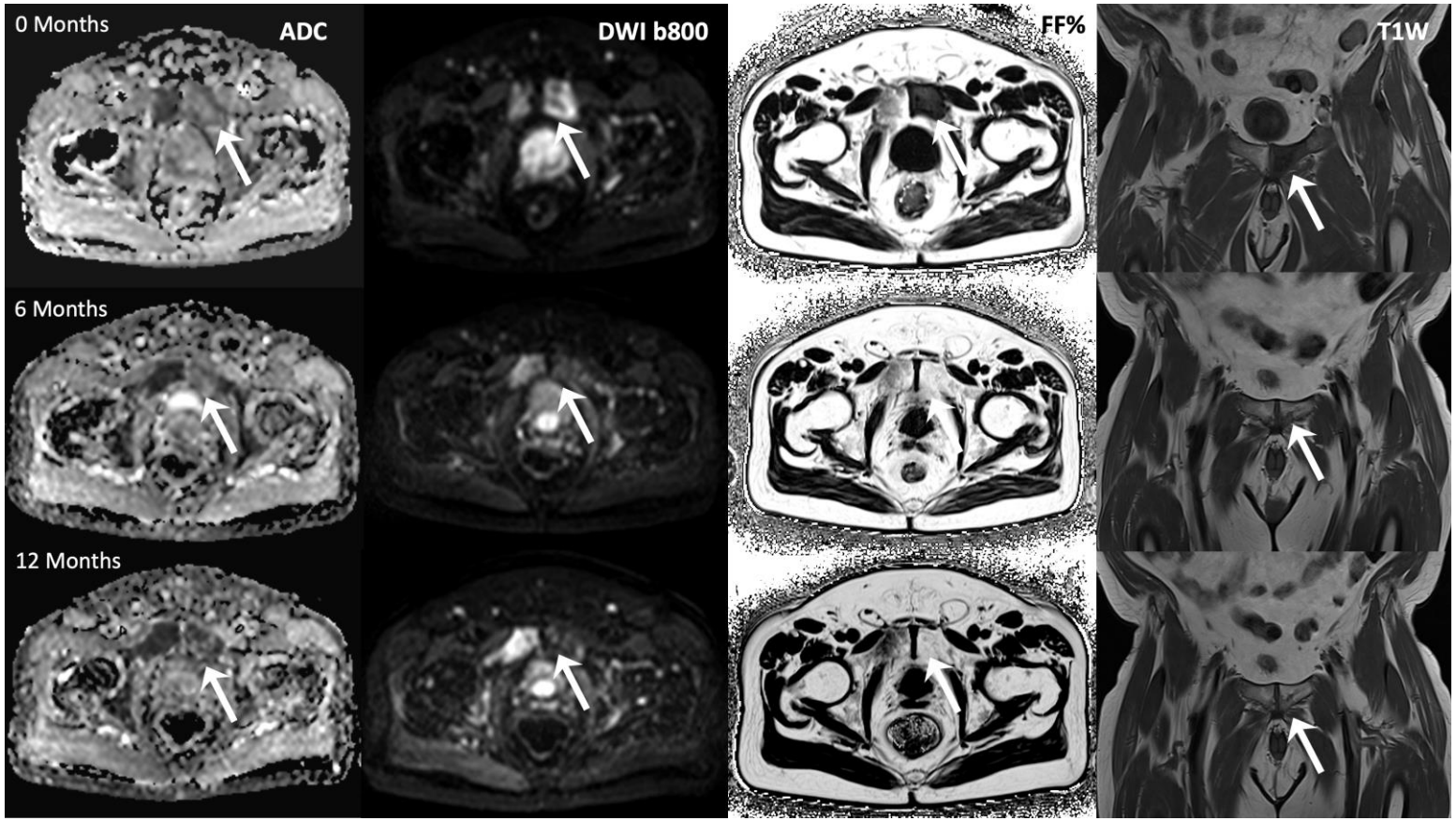
ADC

nDWI

FF%

Perez-Lopez R., Invest Radiol 2018

BONE RESPONSE ASSESSMENT



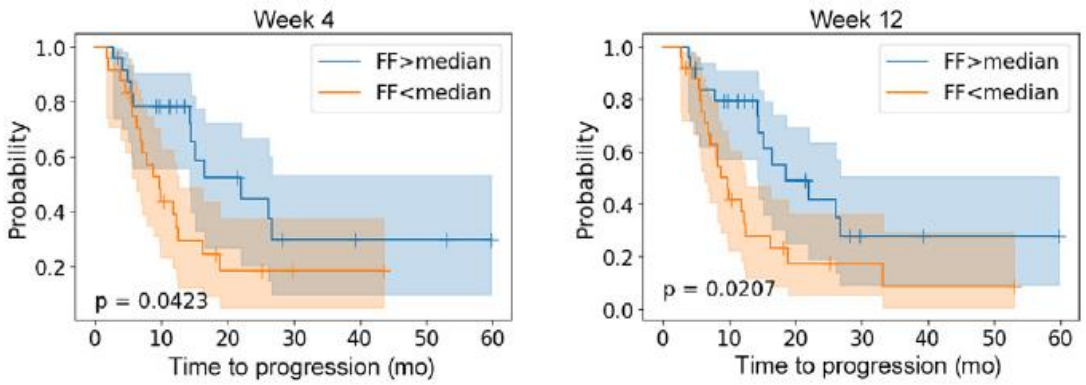
Example of a complete response on a bone lesion by WB-DW-MRI

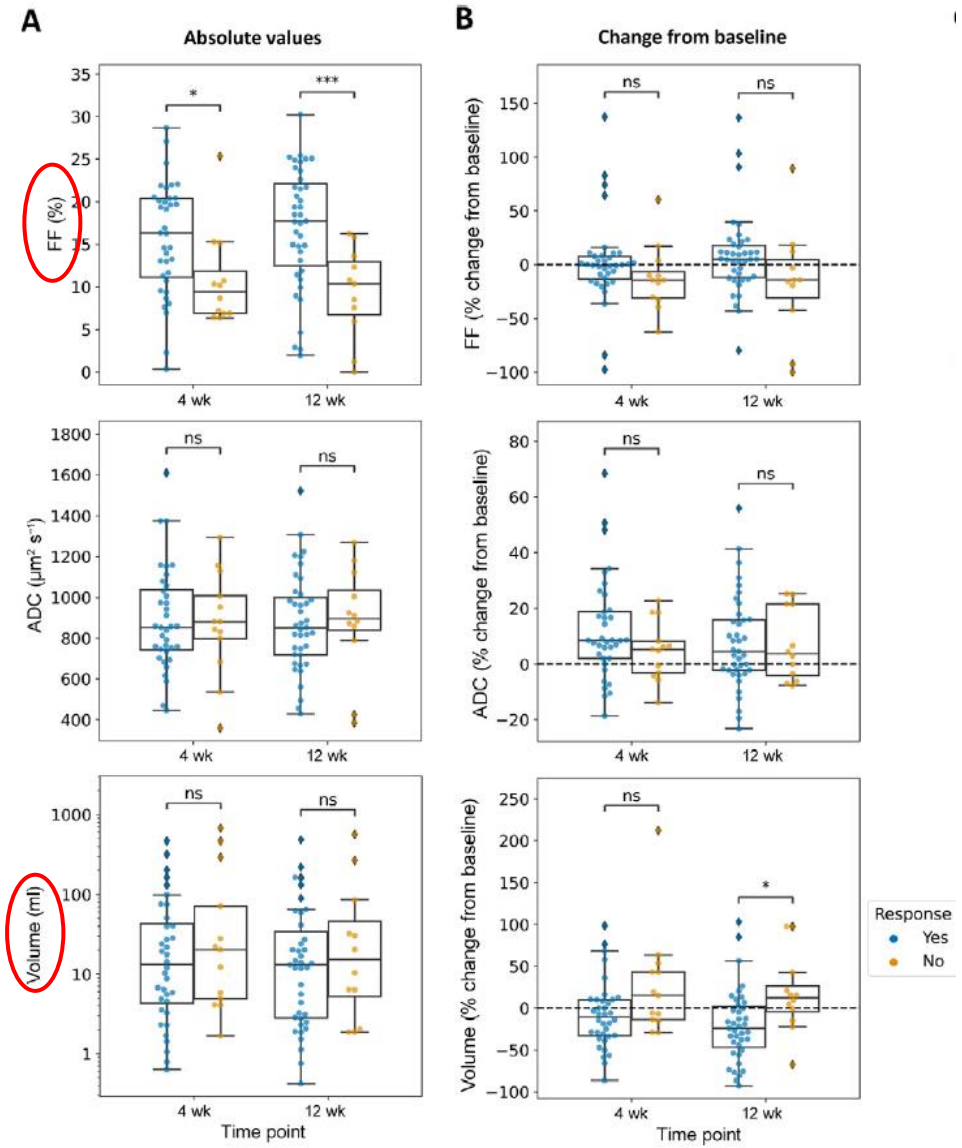
BONE RESPONSE ASSESSMENT - mCRPC

Research Letter

Whole-body Magnetic Resonance Imaging as a Treatment Response Biomarker in Castration-resistant Prostate Cancer with Bone Metastases: The iPROMET Clinical Trial

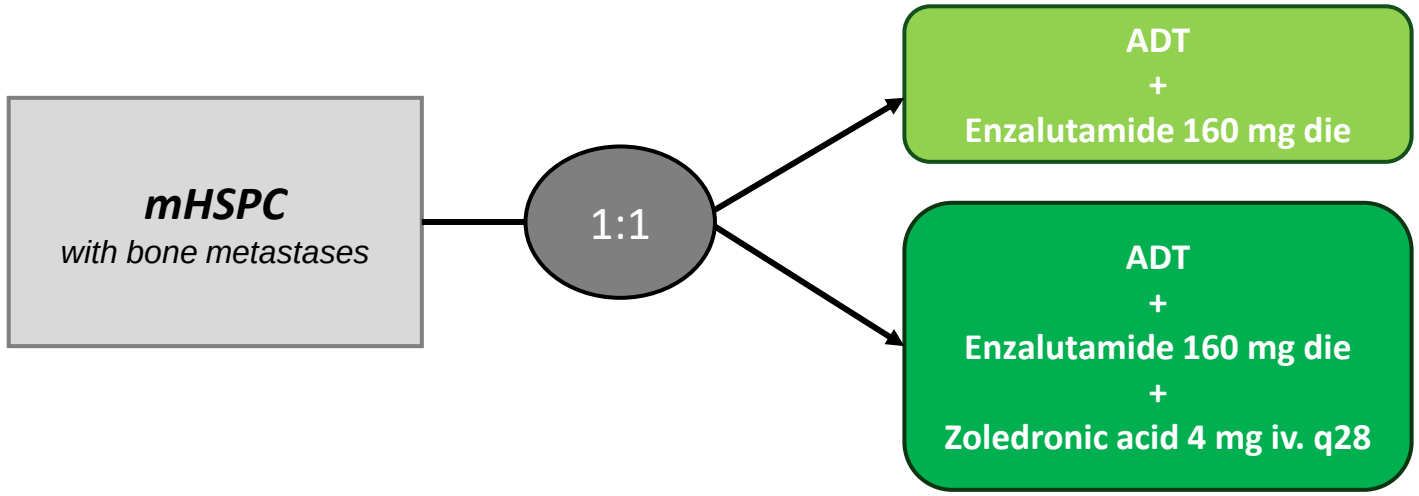
Alonso Garcia-Ruiz [a], Carlos Macarro [a], Francesca Zacchi [a,b,c], Rafael Morales-Barrera [a,b], Francesco Grussu [a], Irene Casanova-Salas [a], Francesco Sanguedolce [d,e], Macarena Gonzalez [a,b], Pablo Cresta-Morgado [a,b], Matias de Albert [b], Josep Garcia-Bennett [f], David Marmolejo [a,b], Jacques Planas [b], Sarai Roche [b], Richard Mast [b], Christina Zatse [a], Josep M Piulats [f,g], Bernardo Herrera-Imbroda [h], Lucas Regis [b], Laura Agundez [a], David Olmos [i], Nahum Calvo [f], Manuel Escobar [b], Joan Carles [a,b], Joaquin Mateo [a,b,], Raquel Perez-Lopez [a,*]*





Eur Urol 2024

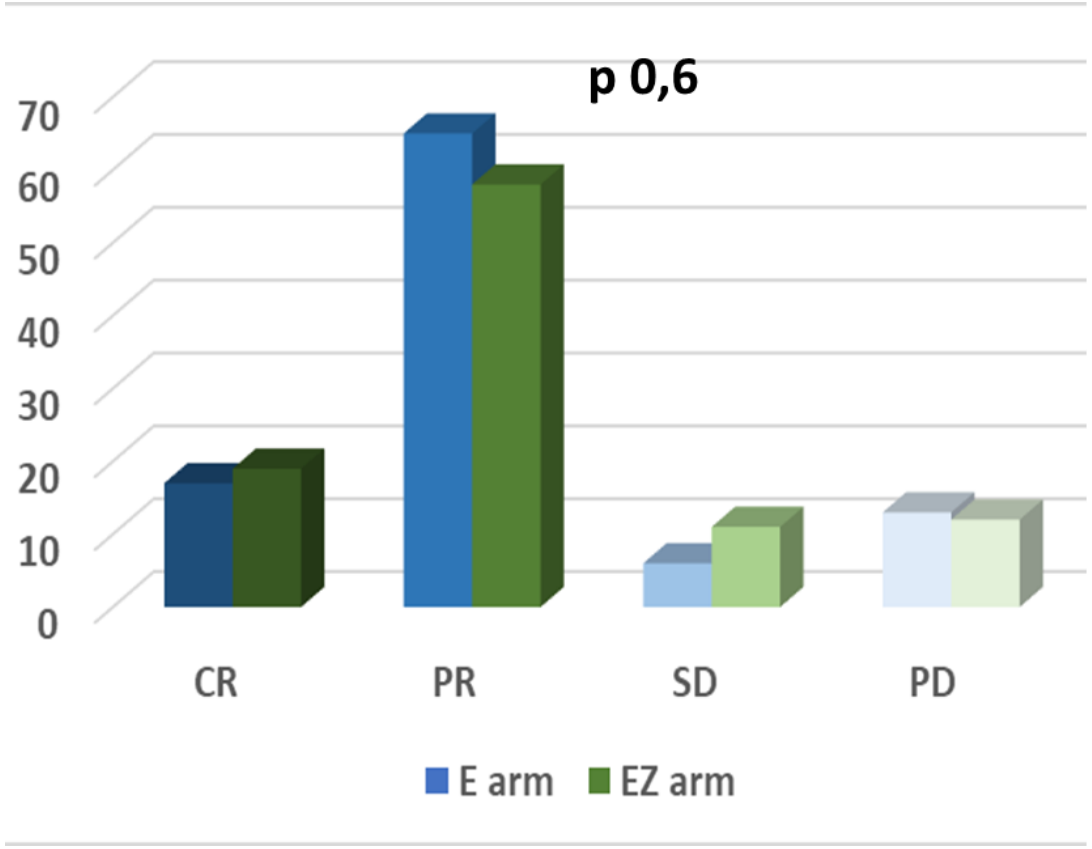
BONE RESPONSE ASSESSMENT - mHSPC

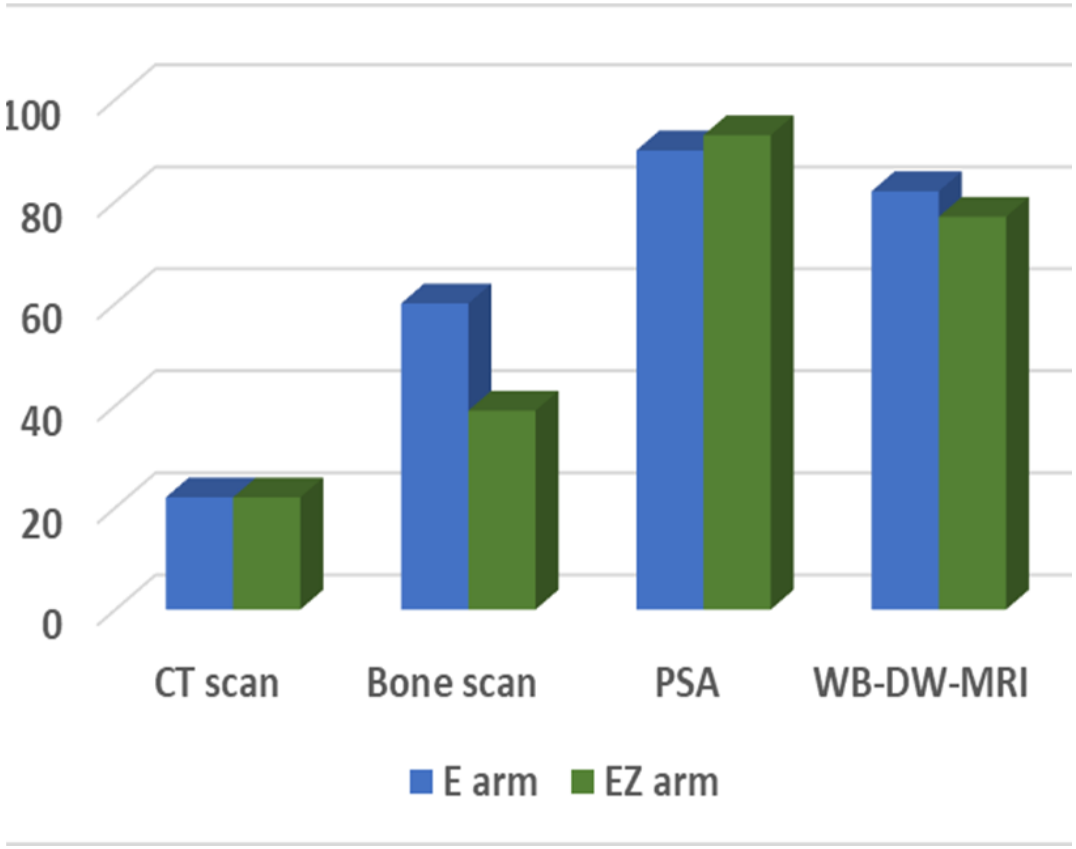


- Metastatic hormone-sensitive prostate cancer (mHSPC) with bone metastases
- Randomization 1:1 to enzalutamide vs enzalutamide + zoledronic acid
- Disease response assessment by WB-DW-MRI, CT scan and PSA at baseline and after 6-12 months, by bone scan at baseline and after 12 months

- **Primary objective**
  - Bone objective response rate (ORR) assessed by WB-DW-MRI
- **Secondary objectives**
  - Changes of bone health and body composition parameters assessed by dual energy X-ray absorptiometry (DXA) scan
  - Changes of bone metabolism markers
  - Quality of life (QoL)
  - Progression-free survival (PFS), overall survival (OS)

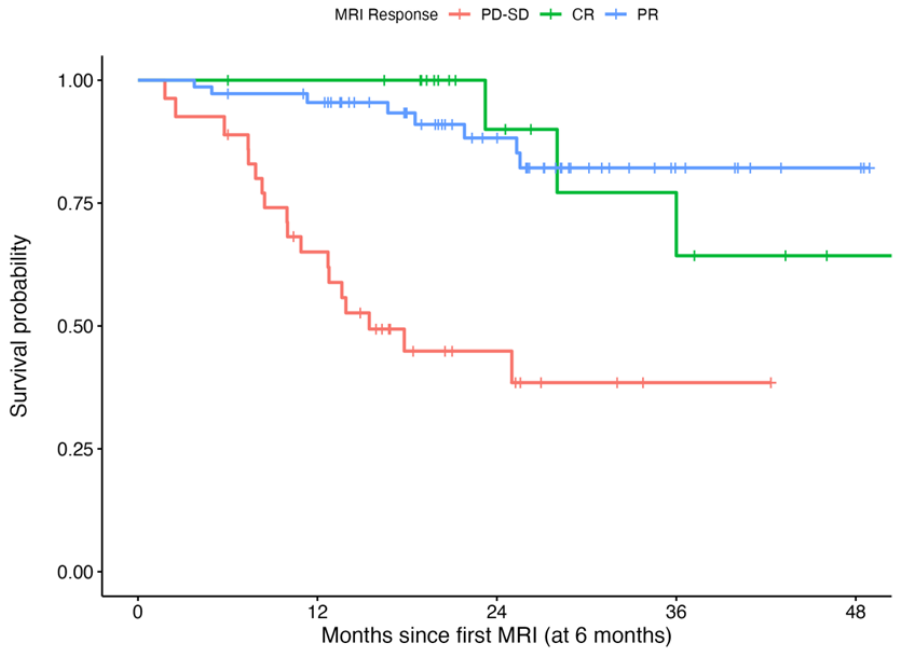
BONE RESPONSE ASSESSMENT - mHSPC





Dalla Volta A., ASCO GU 2023

BONE RESPONSE ASSESSMENT - mHSPC



“The corresponding response rates obtained in the 109 evaluable patients were 18.3% (CR), 62.4% (PR), 8.3% (SD), and 11% (PD). The overall response rate was 81% (95% CI: 73.6%-88.4%).”

“The clinical relevance of bone responses at WB-DW-MRI was reinforced by a significant association with overall survival within the PP population: complete response at WB-DW-MRI correlated with a reduced risk of death (HR 0.16; 95%CI 0.06-0.48; p<0.001) as well as partial response (HR 0.14; 95%CI 0.06-0.32; p<0.001), with respect to no response (CR/PR vs SD/PD: HR 0.15, 95% CI 0.07-0.30, p<0.001).”

Eur Urol, under submission

ARSI - BONE HEALTH

Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial

Christopher J Logothetis, Ethan Basch, Arturo Molina, Karim Fizazi, Scott A North, Kim N Chi, Robert J Jones, Oscar B Goodman, Paul N Mainwaring, Cora N Sternberg, Eleni Efstathiou, Dennis D Gagnon, Margaret Rothman, Yanni Hao, Cameron S Liu, Thian S Kheoh, Christopher M Haqq, Howard I Scher*, Johann S de Bono*

SRE rate per 100 patients-years of exposure (%)*	38·9%	65·1%
Radiation to bone (%)	24·0%	46·1%
Pathological fracture (%)	6·0%	4·0%
Surgery to bone (%)	1·7%	1·0%
Spinal cord compression (%)	7·3%	14·0%

Lancet Oncology 2012

ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer

Andrew J. Armstrong, MD, ScM[1]; Russell Z. Szmulewitz, MD[2]; Daniel P. Petrylak, MD[3]; Jeffrey Holzbeierlein, MD[4]; Arnauld Villers, MD[5]; Arun Azad, MBBS, PhD[6]; Antonio Alcaraz, MD, PhD[7]; Boris Alekseev, MD[8]; Taro Iguchi, MD, PhD[9]; Neal D. Shore, MD[10]; Brad Rosbrook, MS[11]; Jennifer Sugg, MS[12]; Benoit Baron, MS[13]; Lucy Chen, MD[12]; and Arnulf Stenzl, MD[14]

Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)

JCO 2019

Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu, M.D., Hirotsugu Uemura, M.D., Dingwei Ye, M.D., Kris Deprince, M.D., Vahid Naini, Pharm.D., Jinhui Li, Ph.D., Shinta Cheng, M.D., Margaret K. Yu, M.D., Ke Zhang, Ph.D., Julie S. Larsen, Pharm.D., Sharon McCarthy, B.Pharm., and Simon Chowdhury, M.D., for the TITAN Investigators*

Fracture†	33 (6.3)	7 (1.3)	24 (4.6)	4 (0.8)

NEJM 2019

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

Bone fracture¶	49 (7.5)	2.8	33 (5.1)	2.7

NEJM 2022

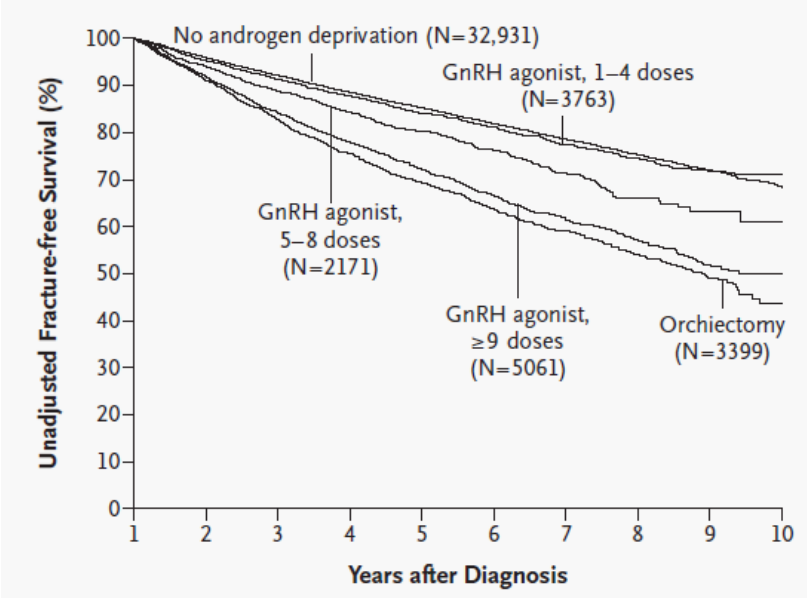
ARSI - BONE HEALTH

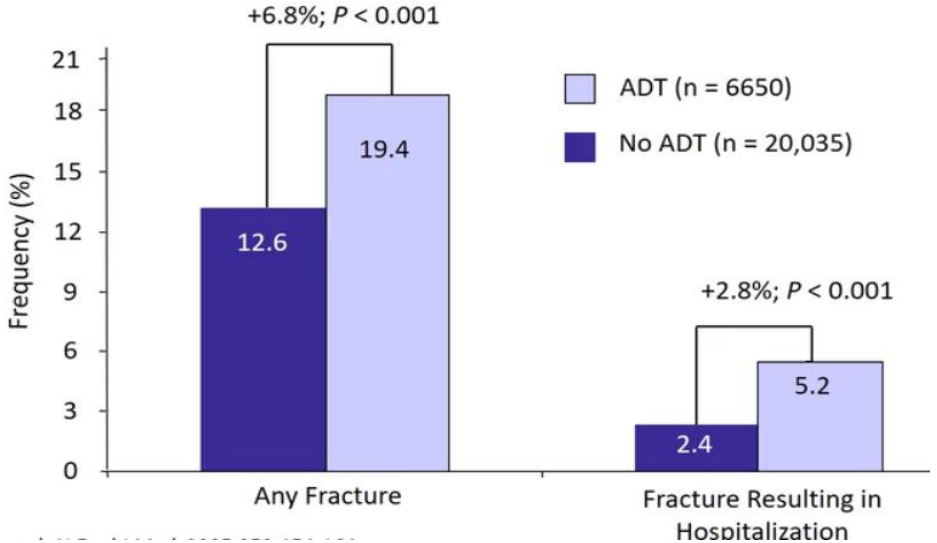
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Fracture after Androgen Deprivation for Prostate Cancer

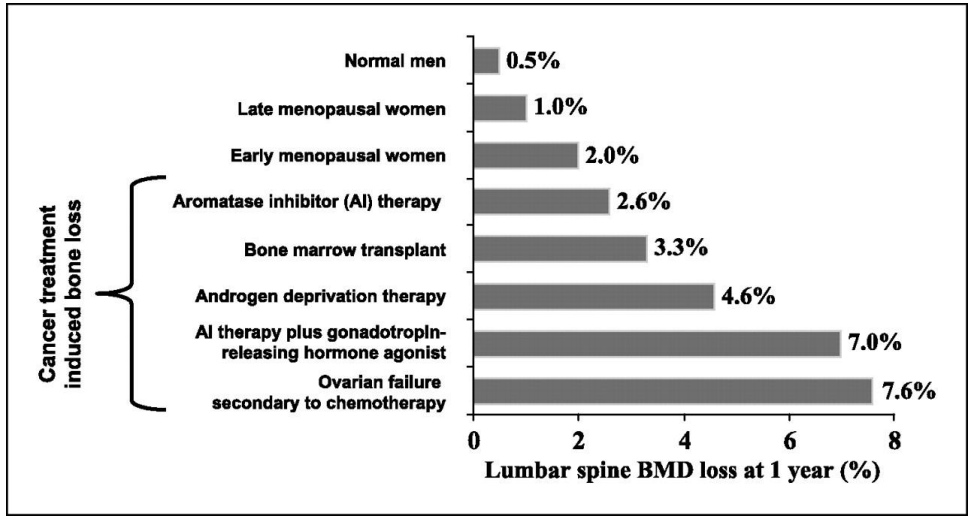
Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D., and James S. Goodwin, M.D.





Shahinian VB., NEJM 2005

ARSI - BONE HEALTH



Clinical Cancer Research

AACR American Association for Cancer Research

Angela Hirbe et al. Clin Cancer Res 2006;12:6309s-6314s

J. Clin. Med. **2019**, *8*, 113; doi:10.3390/jcm8010113

Article

Effect of Androgen-Deprivation Therapy on Bone Mineral Density in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis

Do Kyung Kim [1], Joo Yong Lee [2], Kwang Joon Kim [3], Namki Hong [4], Jong Won Kim [2], Yoon Soo Hah [1], Kyo Chul Koo [1], Jae Heon Kim [5] and Kang Su Cho [1,*]

A. Lumbar spine

Study or Subgroup	ADT Mean	ADT SD	ADT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Control: PCa								
Alibhai 2013	-2.12	7.2	80	1.05	4.7	80	24.2%	-3.17 [-5.05, -1.29]
Morote 2006	-4.8	5	31	-0.82	4.7	31	22.9%	-3.98 [-6.40, -1.56]
Subtotal (95% CI)			**111**			**111**	**47.1%**	**-3.48 [-4.96, -1.99]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 4.59 (P < 0.00001)								
Control: PCa or other urologic conditions								
Preston 2002	-0.2	0.8	39	1.1	0.6	39	26.5%	-1.30 [-1.61, -0.99]
Ziaran 2013	-13.28	1.8	95	-7.32	1.7	88	26.4%	-5.96 [-6.47, -5.45]
Subtotal (95% CI)			**134**			**127**	**52.9%**	**-3.63 [-8.19, 0.94]**
Heterogeneity: Tau² = 10.81; Chi² = 234.54, df = 1 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 1.56 (P = 0.12)								
Total (95% CI)			**245**			**238**	**100.0%**	**-3.60 [-6.72, -0.47]**
Heterogeneity: Tau² = 9.58; Chi² = 236.13, df = 3 (P < 0.00001); I² = 99%								
Test for overall effect: Z = 2.25 (P = 0.02)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%								

Mean Difference IV, Random, 95% CI

-20 -10 0 10 20

Favours [ADT] Favours [control]

C. Total hip

Study or Subgroup	ADT Mean	ADT SD	ADT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Control: PCa								
Alibhai 2013	-2.62	4.1	80	-1.02	4	80	24.7%	-1.60 [-2.86, -0.34]
Morote 2006	-3.76	4.7	31	-0.82	4.4	31	17.1%	-2.94 [-5.21, -0.67]
Subtotal (95% CI)			**111**			**111**	**41.7%**	**-1.92 [-3.05, -0.80]**
Heterogeneity: Tau² = 0.02; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%								
Test for overall effect: Z = 3.35 (P = 0.0008)								
Control: PCa or other urologic conditions								
Preston 2002	-1.5	1	39	0.8	0.5	39	30.1%	-2.30 [-2.65, -1.95]
Ziaran 2013	0	2.7	95	0	2.6	88	28.1%	0.00 [-0.77, 0.77]
Subtotal (95% CI)			**134**			**127**	**58.3%**	**-1.18 [-3.43, 1.08]**
Heterogeneity: Tau² = 2.55; Chi² = 28.50, df = 1 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.02 (P = 0.31)								
Total (95% CI)			**245**			**238**	**100.0%**	**-1.59 [-2.99, -0.19]**
Heterogeneity: Tau² = 1.67; Chi² = 29.53, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 2.22 (P = 0.03)								
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%								

Mean Difference IV, Random, 95% CI

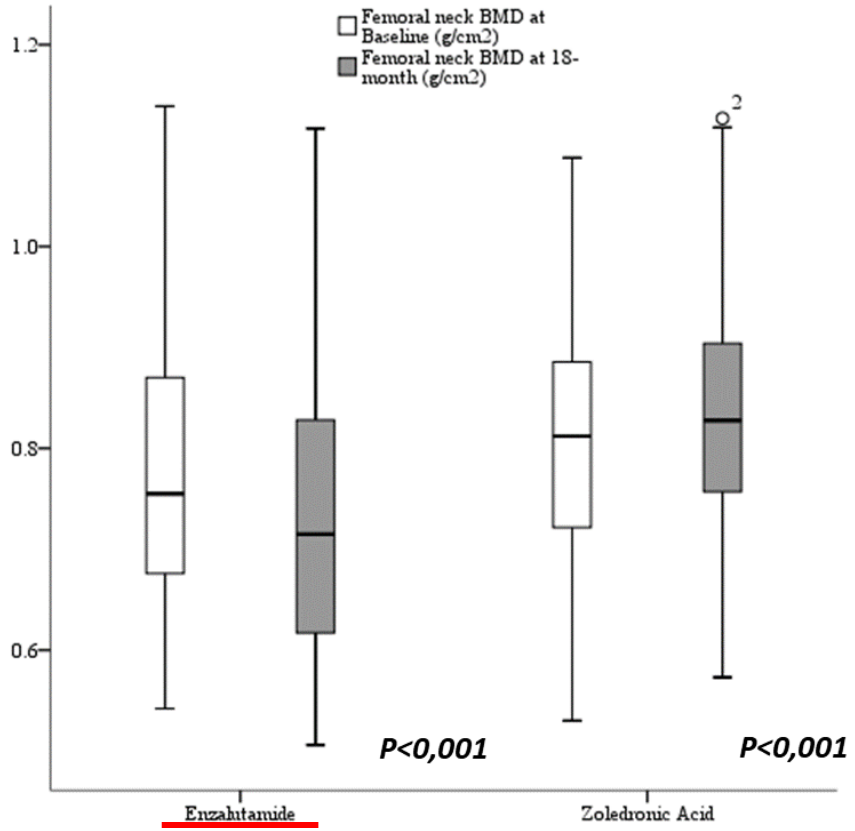
-4 -2 0 2 4

Favours [ADT] Favours [control]

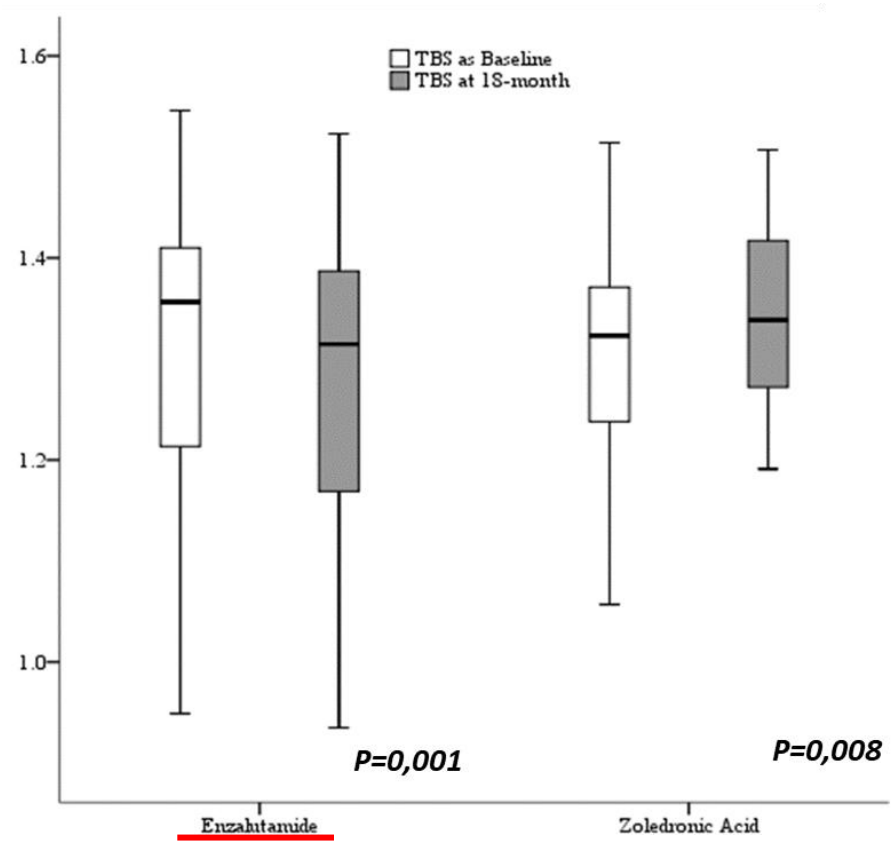
ARSI - BONE HEALTH

1785P Sistema Socio Sanitario Regione Lombardia ASST Spedali Civili

Changes in bone mineral density, trabecular bone score and body composition in metastatic hormone-sensitive prostate cancer patients randomized to receive androgen deprivation + enzalutamide +/- zoledronic acid. The BonEnza study.



BMD



TBS

Dalla Volta A,. ESMO 2023

ARSI

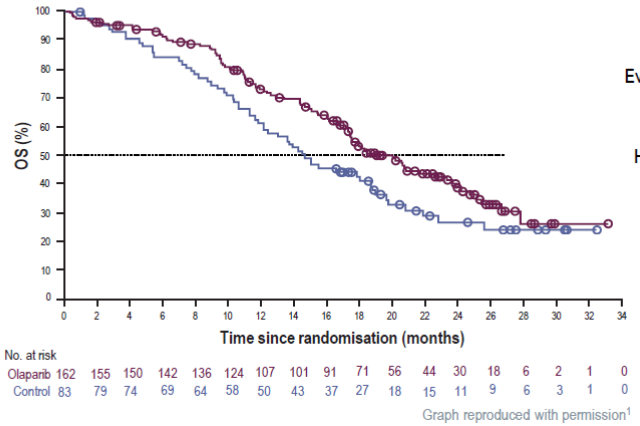
- Androgen receptor signaling inhibitors (ARSI) improve **survival** outcomes of metastatic prostate cancer patients, both in the castration resistant setting (mCRPC) and in the hormone-sensitive setting (mHSPC)
- ARSI offer significant benefit in terms of **bone response rates**, prevention of skeletal-related events (**SREs**) and **pain relief**
- Caveat: ARSI have a potential impact on **bone health**, leading to an increased risk of fragility fractures

These data support the use of ARSI in the management of advanced prostate cancer with bone metastases

PARP-INHIBITORS

PROfound phase 3 trial: Olaparib improved OS (in cohort A)

BRCA1, *BRCA2* and/or *ATM* mCRPC (final prespecified analysis)



	Olaparib (N = 162)	Control (N = 83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50-0.97); *P* = 0.0175*	

*0.047 alpha spent at the final OS analysis. Median follow-up duration for censored patients was 21.9 months in the olaparib arm and 21.0 in the control arm.

Graph reproduced with permission[1]

Olaparib should be considered after novel androgen receptor axis inhibitors (with or without prior taxane treatment) for patients with mCRPC and ***BRCA1/2*** **alterations** [I, B; ESMO-MCBS v1.1 score: 3].

Fizazi K., ESMO 2023

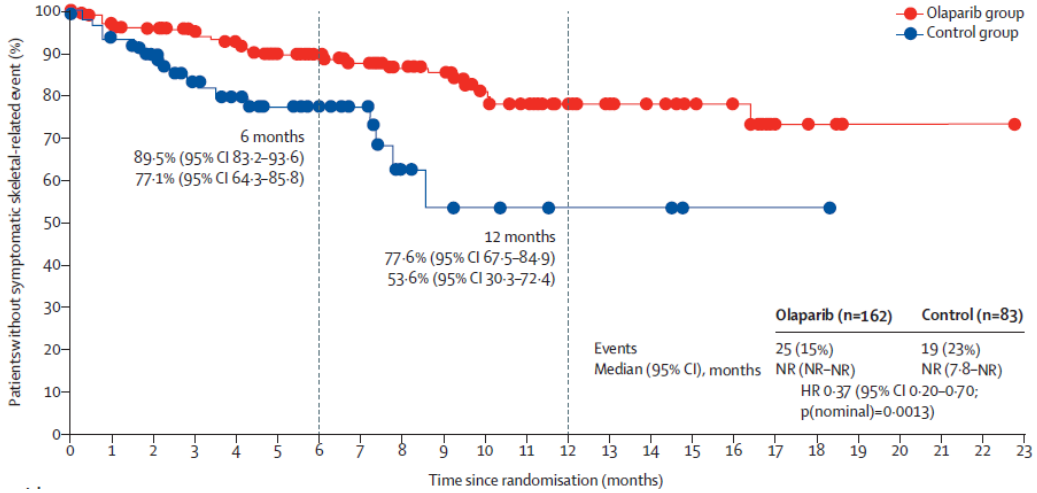
ESMO guidelines eUpdate 2023

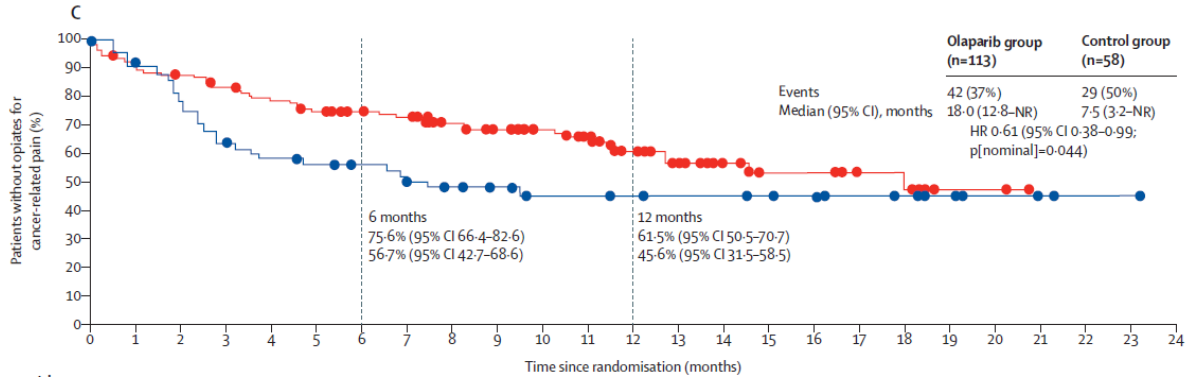
OLAPARIB - mCRPC

Pain and health-related quality of life with olaparib versus physician's choice of next-generation hormonal drug in patients with metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations (PROfound): an open-label, randomised, phase 3 trial

Antoine Thiery-Vuillemin, Johann de Bono, Maha Hussain, Guilhem Roubaud, Giuseppe Procopio, Neal Shore, Karim Fizazi, Gabriel dos Anjos, Gwenaelle Gravis, Jae Young Joung, Nobuaki Matsubara, Daniel Castellano, Arnold Degboe, Chris Gresty, Jinyu Kang, Allison Allen, Christian Poehlein, Fred Saad

Metastases at baseline‡		
Bone only	57 (35%)	23 (28%)
Visceral (lung or liver)	46 (28%)	32 (39%)
Other	49 (30%)	23 (28%)





Lancet Oncol. 2022

PARP-INHIBITORS + ARSI

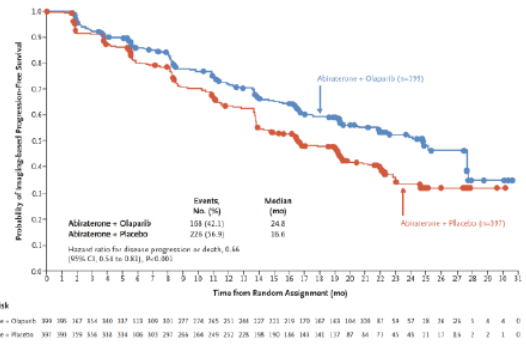
MADRID 2023 ESMO congress

ARPi + PARPi trials in 1L mCRPC

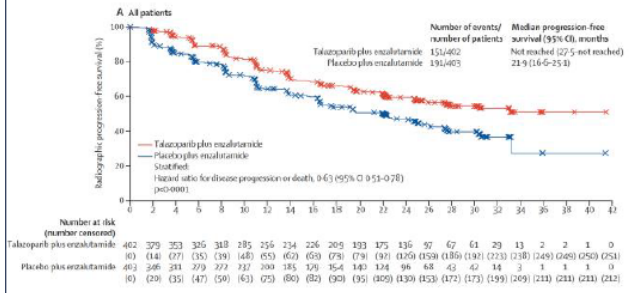
(prior ARPi for mHSPC or nmCRPC underrepresented)

rPFS benefit reported in pts unselected for HRR alterations, except in MAGNITUDE

rPFS PROPEL: AAP +/- Olaparib

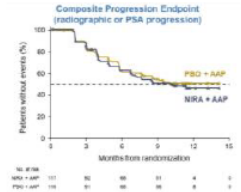


rPFS TALAPRO2: Enza +/- Talazoparib

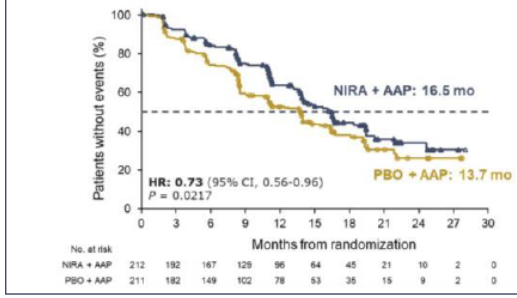


rPFS MAGNITUDE: AAP +/- Niraparib

COHORT 2 Non-HRRm



COHORT 1 HRRm



Clarke et al, NEJM Evidence 2022; Agarwal et al, Lancet 2023; Chi et al, JCO 2023

TALAZOPARIB + ENZALUTAMIDE - mCRPC

Article https://doi.org/10.1038/s41591-023-02704-x

First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial

Disease site		
Bone (including with soft tissue component)	175 (88)	158 (79)
Lymph node	82 (41)	94 (47)
Visceral (lung)	23 (12)	26 (13)
Visceral (liver)	9 (4)	6 (3)
Other soft tissue	23 (12)	20 (10)

	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)	Hazard Ratio	P value (Two-Sided)
Median duration of response* (95% CI) — mo	20.3 (12.2–NR)	14.8 (6.6–25.8)		
PSA response ≥50%† — n/N (%)	171/198 (86)	125/199 (63)		<0.0001
(95% CI)	(81–91)	(56–70)		
Time to initiation of subsequent antineoplastic therapy				
Patients with use — no. (%)	44 (22)	85 (43)		
Median time to use (95% CI) — mo	NR (NR–NR)	18.8 (15.4–NR)	0.40	<0.0001
Time to first symptomatic skeletal event				
Patients with event — no. (%)	36 (18)	45 (23)		
Median time to first event (95% CI) — mo	NR (33.9–NR)	NR (32.9–NR)	0.69	0.09

Fizazi K., Nature Medicine 2024

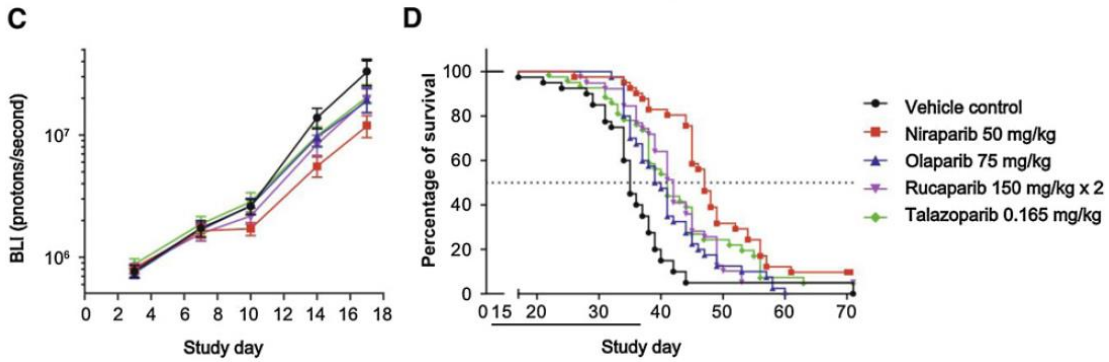
NIRAPARIB

Niraparib Shows Superior Tissue Distribution and Efficacy in a Prostate Cancer Bone Metastasis Model Compared with Other PARP Inhibitors

Linda A. Snyder[1], Rajendra Damle[1], Shefali Patel[2], Jared Bohrer[2], Anna Fiorella[2], Jenny Driscoll[1], Rebecca Hawkins[1], Christopher F. Stratton[3], Carol D. Manning[1], Kanaka Tatikola[4], Volha Tryputsen[5], Kathryn Packman[6], and Rao N.V.S. Mamidi[7]

ABSTRACT

Patients with prostate cancer whose tumors bear deleterious mutations in DNA-repair pathways often respond to PARP inhibitors. Studies were conducted to compare the activity of several PARP inhibitors *in vitro* and their tissue exposure and *in vivo* efficacy in mice bearing PC-3M-luc-C6 prostate tumors grown subcutaneously or in bone. Niraparib, olaparib, rucaparib, and talazoparib were compared in proliferation assays, using several prostate tumor cell lines and in a cell-free PARP-trapping assay. PC-3M-luc-C6 cells were approximately 12- to 20-fold more sensitive to PARP inhibition than other prostate tumor lines, suggesting that these cells bear a DNA damage repair defect. The tissue exposure and efficacy of these PARP inhibitors were evaluated *in vivo* in PC-3M-luc-C6 subcutaneous and bone metastasis tumor models. A steady-state pharmacokinetic study in PC-3M-luc-C6 tumor-bearing mice showed that all of the PARP inhibitors had favorable subcutaneous tumor exposure, but niraparib was differentiated by superior bone marrow exposure compared with the other drugs. In a PC-3M-luc-C6 subcutaneous tumor efficacy study, niraparib, olaparib, and talazoparib inhibited tumor growth and increased survival to a similar degree. In contrast, in the PC-3M-luc-C6 bone metastasis model, niraparib showed the most potent inhibition of bone tumor growth compared with the other therapies (67% vs. 40%–45% on day 17), and the best survival improvement over vehicle control [hazard ratio (HR), 0.28 vs. HR, 0.46–0.59] and over other therapies (HR, 1.68–2.16). These results show that niraparib has superior bone marrow exposure and greater inhibition of tumor growth in bone, compared with olaparib, rucaparib, and talazoparib.



Molecular Cancer Therapeutics 2022

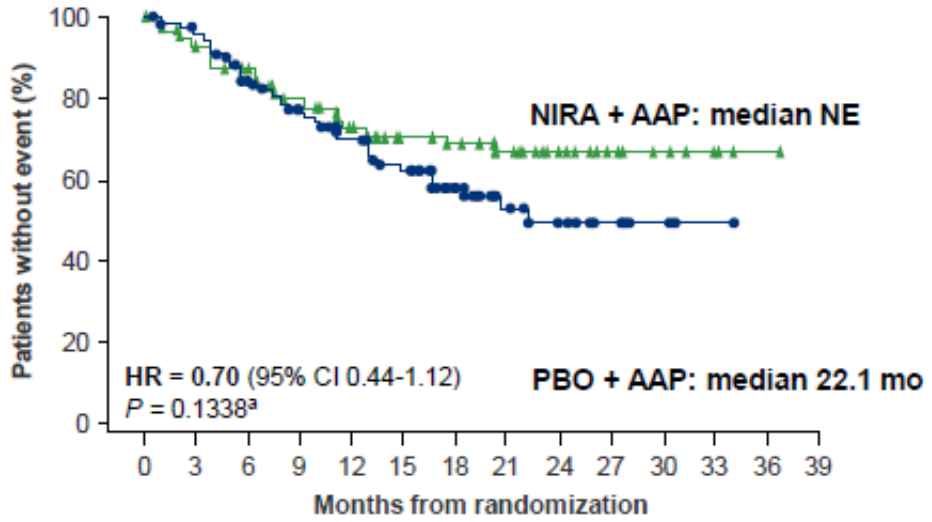
NIRAPARIB + ABIRATERONE - mCRPC

Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

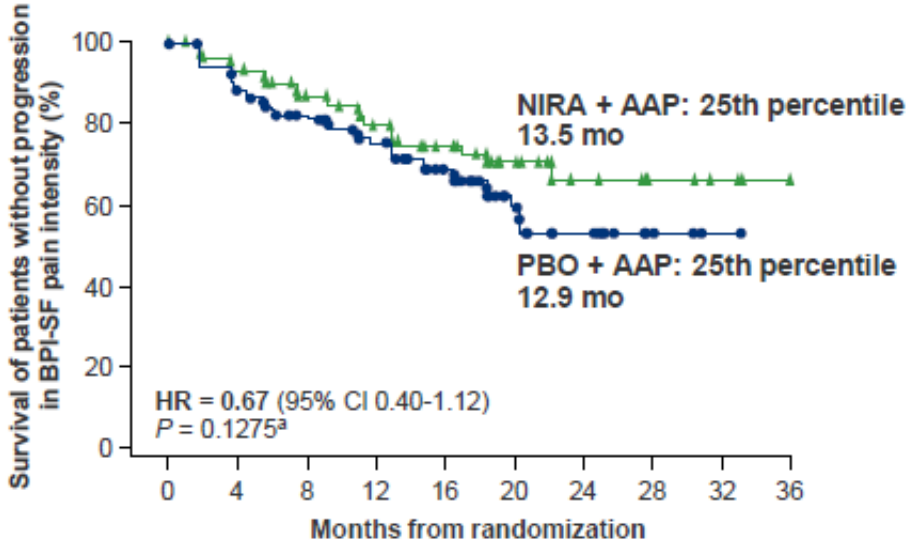
Kim N. Chi, MD[1]; Dana Rathkopf, MD[2]; Matthew R. Smith, MD[3]; Eleni Efstathiou, MD[4]; Gerhardt Attard, MD[5]; David Olmos, MD[6]; Ji Youl Lee, MD[7]; Eric J. Small, MD[8]; Andrea J. Pereira de Santana Gomes, MD[9]; Guilhem Roubaud, MD[10]; Marniza Saad, MD[11]; Bogdan Zurawski, MD[12]; Valerii Sakalo, MD[13]; Gary E. Mason, MD[14]; Peter Francis, MD[15]; George Wang, MS, MAS[14]; Daphne Wu, PhD[16]; Brooke Diorio, PhD[17]; Angela Lopez-Gitlitz, MD[16]; and Shahneen Sandhu, MD[18]; on behalf of the MAGNITUDE Principal Investigators

Metastatic site involvement at study entry, No. (%)			
Bone	183 (86.3)	170 (80.6)	353 (83.5)
Lymph node	113 (53.3)	95 (45.0)	208 (49.2)
Visceral	51 (24.1)	39 (18.5)	90 (21.3)
Adrenal gland	3 (1.4)	7 (3.3)	10 (2.4)
Liver	18 (8.5)	13 (6.2)	31 (7.3)
Lung	27 (12.7)	18 (8.5)	45 (10.6)
Other soft tissue	6 (2.8)	15 (7.1)	21 (5.0)

A



B



JCO 2023

PARP-INHIBITORS

- PARP-inhibitors improve **survival** outcomes of metastatic castration resistant prostate cancer patients (mCRPC) harbouring homologous recombination repair (HRR)/BRCA mutations
- PARP-inhibitors may offer significant benefit in terms of prevention of skeletal-related events (**SREs**) and **pain relief** in mCRPC patients harbouring HRR/BRCA mutations

These data support the use of PARP-inhibitors in the management of mCRPC with bone metastases harbouring HRR/BRCA mutations

UNIVERSITÀ DEGLI STUDI DI BRESCIA

Dott. Marco Bergamini

Università degli Studi di Brescia

Oncologia Medica ASST Spedali Civili di Brescia

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Grazie per l'attenzione!!!