

Imaging bone (flare) responses in APC

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APCCC 2019

#ICIS2019, Verona, It



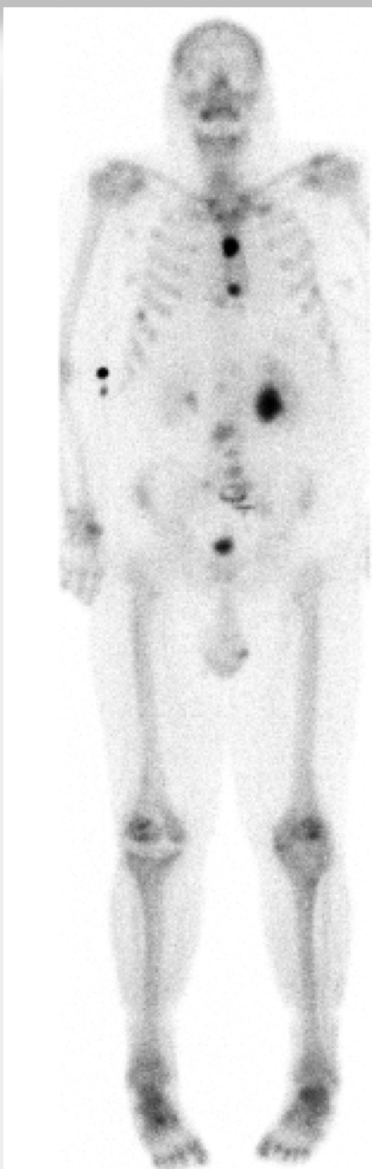
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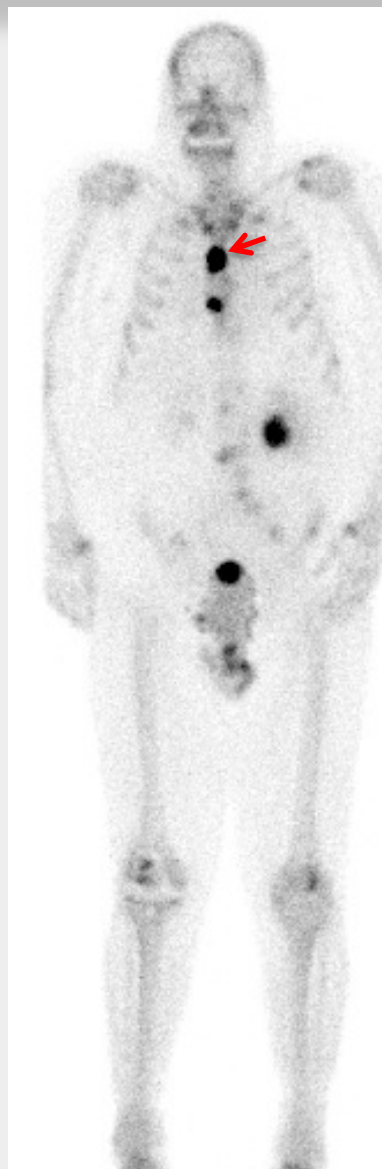
Presentation may include discussions of the off-label use of drugs, equipment and software. I am active on twitter @ProfPadhani

BS/CT scans lead to
poor confidence
for knowing the
'true' clinical states
& assessing
therapy benefits
for bone disease in
APC with precision
oncology
implications

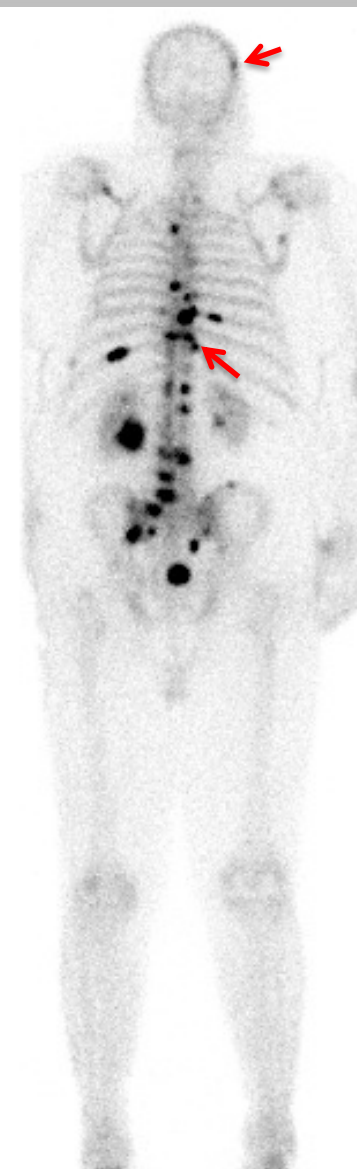
- **Limited conventional imaging tools**
 - Unable to accurately predict metastatic disease presence and extent
 - Unable to identify who is not benefiting early after starting treatment
 - Limited ability to depict heterogeneity of biologic behavior of bone disease in advancing disease
- **Consequences for precision oncology**
 - Late detection & volume underestimation of metastatic disease (inaccurate tumor volume estimates | inaccurate risk allocations); misdirects therapy approaches
 - Fail to rapidly detect primary & secondary resistance; impedes patient progress to alternate Rx; increases costs
 - Heterogeneity of response is increasingly important for predicting patient outcomes



December 2011



February 2012



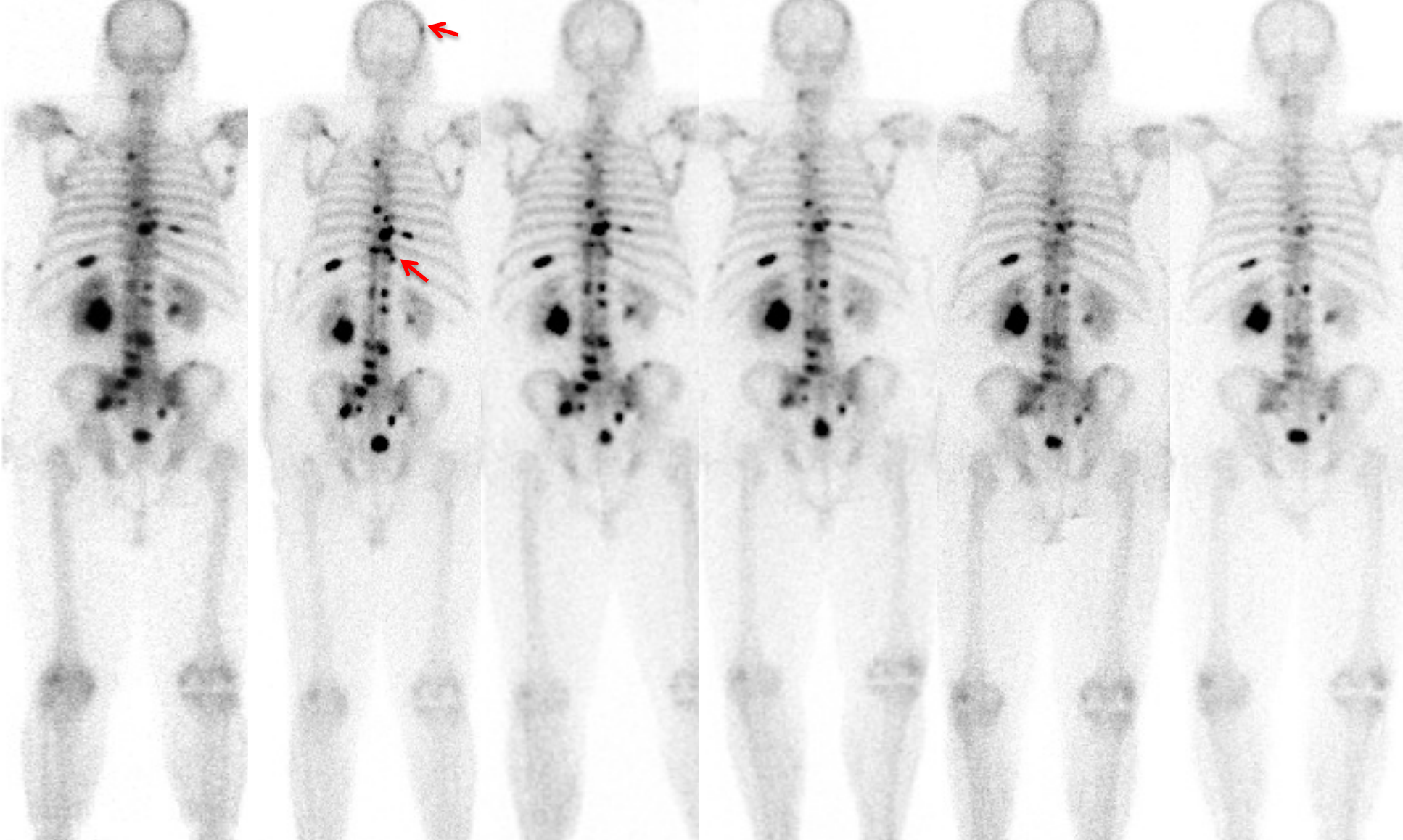
New lesions
'unconfirmed'
On 1st follow-
up study

Images courtesy Courtesy Nina Tunariu & Johann de Bono: ICR, London

53 YO, mCRPC ; rising PSA (41 to 52ng/ml) on Enzalutamide; new lesions - unconfirmed

Unconfirmed new bone scan lesions

- ≈ 20-25% of patients with enzalutamide/abiraterone (PREVAIL/AFFIRM/AA-302)
- New bone scan lesions on the first follow-up scan may represent
 1. **True progression**
 2. **Tumor ‘momentum’** – temporary worsening disease before delayed ADT response
 3. Early favorable osteoblastic reaction (**bone scan flare** or pseudo-progression)
- **PCWG 2+2 Rule**: new focal bone scan lesions that develop in the flare period (8-12 weeks) should be confirmed with the documentation of additional new lesions on the next follow-up scan (in the absence of other signs of progression)



Scintigraphic/healing flare \approx 15-30% within 3 months when there is clinical benefit

Images courtesy Nina Tunariu & Johann de Bono: ICR, London

December 2011


February 2012

..... Rx Enzalutamide continued →

November 2012

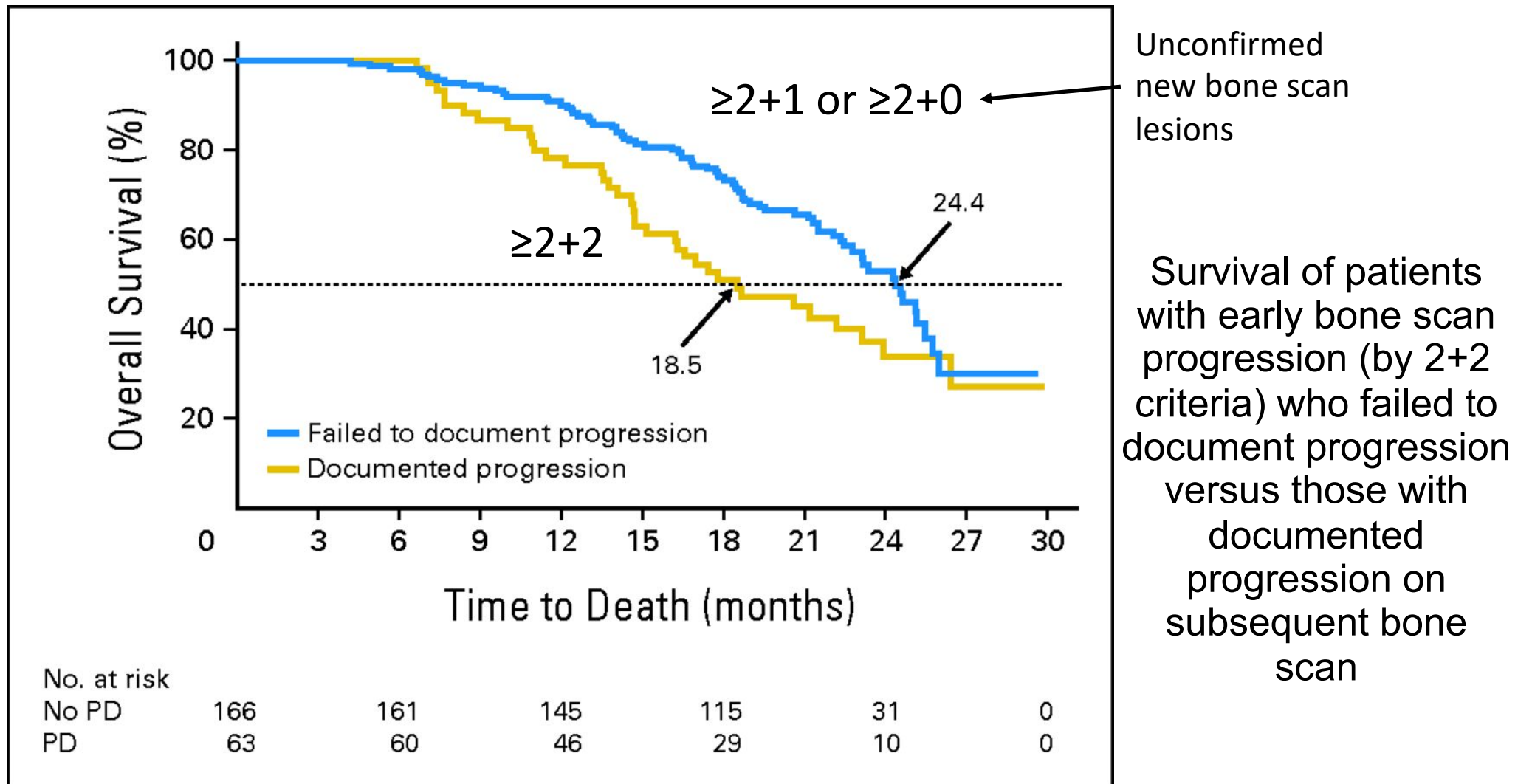
Imaging bone flare reactions in APC

- Development of new focal bone lesion(s) on the 1st follow-up bone scan (unconfirmed) in the absence of clinical progression, often represents a favorable response to treatment (pseudoprogression)



Morris MJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol. 2015;33(12):1356-63	✓
Rathkopf DE, et al. Radiographic Progression-Free Survival as a Clinically Meaningful End Point in Metastatic Castration-Resistant Prostate Cancer: The PREVAIL Randomized Clinical Trial. JAMA Oncol. 2018; 4(5):694-701.	✓
Armstrong AJ, et al. The Clinical Impact of New Unconfirmed Bone Scan Lesions in Men with Metastatic 2 Castration-Resistant Prostate Cancer Treated with Enzalutamide. JAMA Oncol 2019 [in-press]	?

Radiographic progression with abiraterone Rx is associated with poorer survival (COU-AA-302 study)



Morris MJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol. 2015;33(12):1356-63

Unconfirmed BS lesions on enzalutamide for mCRPC without prior docetaxel (PREVAIL) or after docetaxel (AFFIRM)

Figure 3. Kaplan-Meier Estimates of (A) OS and (B) rPFS in PREVAIL

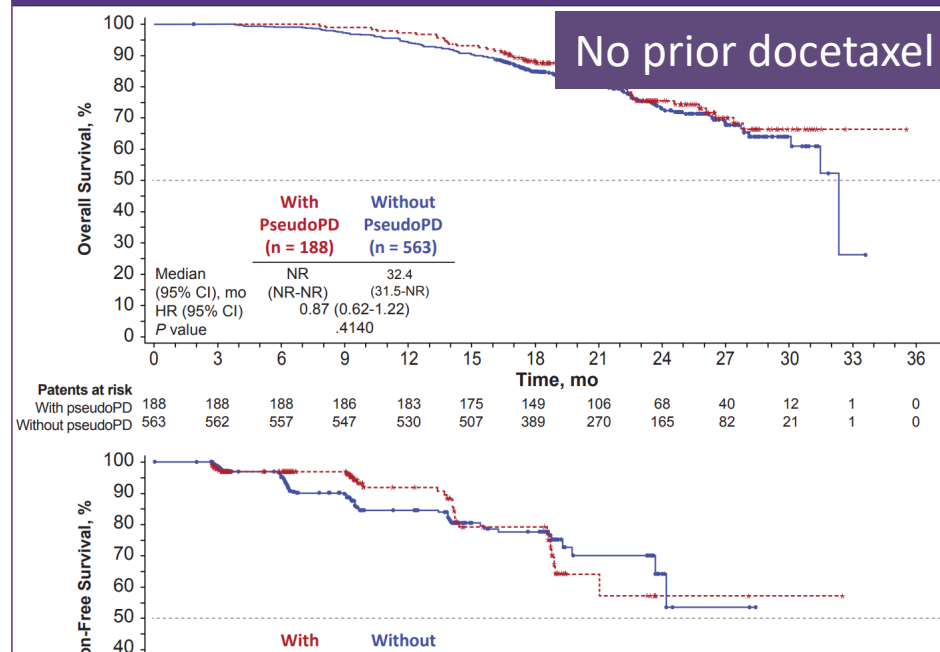
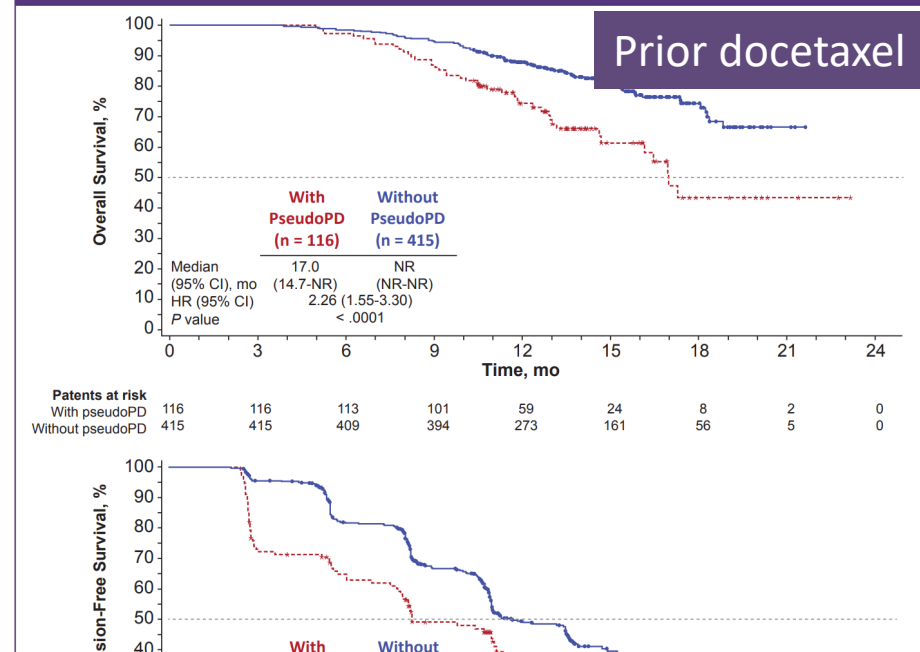


Figure 5. Kaplan-Meier Estimates of (A) OS and (B) rPFS in AFFIRM



New bone scan lesions in chemotherapy-naïve men may reflect early treatment response to enzalutamide (avoid premature discontinuation)

New BS lesions in post-docetaxel men may reflect true bone scan progression (need direct functional imaging of bone metastasis activity)

Armstrong AJ, et al. The Clinical Impact of New Unconfirmed Bone Scan Lesions in Men with Metastatic 2 Castration-Resistant Prostate Cancer Treated with Enzalutamide. JAMA Oncol 2019 [in-press]; ASCO 2019 JCO 37(7_suppl):183-183

Strategies to over-come limitations of BS imaging flare



BS – 2+2 rule (PCWG) – protocol directed



Clinical (including
PSA/morphological soft tissue
assessments CT scans)



Functional imaging

Heterogeneity between clinical and radiographic tumor response – how common?

mHSPC

- Symptoms & PSA are usually sufficient monitoring tools⁴
- PSA-discordant progression (clinical & imaging progression in the absence of a PSA rise) in 30-45% on ADT/Docetaxel (tumor volume dependent)⁶

mCRPC

- Symptoms & PSA are commonly used¹, but are increasingly considered inadequate^{4,5}
- PSA-discordant progression 21-30% can develop radiographic progression without clinical/PSA progression to abiraterone and enzalutamide^{2,3}

¹RADAR II guidelines – Crawford ED, Urology 2017; 104:150-159; ²Morris MJ, J Clin Oncol. 2015; 20;33:1356-63; ³Bryce AH, et al. Prostate Cancer Prostatic Dis 2017 [epub]; ⁴Gillessen S, et al. Euro Urol. 2018; 73(2):178-211; ⁴Fitzpatrick JM, et al. Eur J Cancer 2014; 50:1617-27; ⁴Scher HI, et al. J Clin Oncol. 2016; 34:1-38; ⁴EAU 2017 Guidelines; ⁵Padhani AR, et al. Eur Urol 2017; 71:81-92; ⁶Bryce A, ASCO 2018: abstr 5046

Imaging flare responses in APC

(in the absence of clinical evidence of progression)

Modality	Mech	Therapy	Key APC references
Bone scan (BS)	Osteoblastic reaction	ADT/Abiraterone/ Enzalutamide/ Radium-223	Ryan, CJ, et al. Clin Cancer Res 2011; 17:4854-4861 Keizman D, et al. Prostate Cancer Prostatic Dis. 2017; 20:289-293 Morris MJ, et al. J Clin Oncol. 2015;33(12):1356-63. Rathkopf DE, et al. JAMA Oncol. 2018; 4(5):694-701. Armstrong AJ, et al. JAMA Oncol. 2019 [in-press]
NaF PET/CT	Osteoblastic reaction	ADT/Abiraterone	Case reports
CT	Osteoblastic reaction	ADT/Abiraterone	C. Messiou, et al. Acta Radiol, 2011; 52: 557-561
PSMA PET/CT	PSMA upregulation	ADT/Abiraterone/ Enzalutamide	Aggarwal R, et al. Eur Urol Oncol. 2018; 1:78-82. Zukotynski KA, et al. Clin Nucl Med. 2018 Mar;43(3):213-216.
PET/CT – other tracers	Non-specificity of tracer	Choline	U. De Giorgi, et al. Oncotarget, 5 (2014), pp. 12448-12458
MRI – morphology	Marrow edema	Docetaxel/ Radium 223	Personal experience
MRI - diffusion	-	-	Not described (yet!)

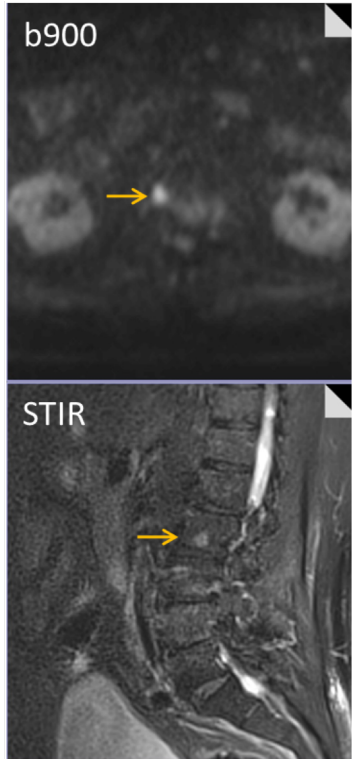
Date of mCRPC Rx Enzalutamide. 2^o resistance confirmed using PCWG

Oligo-progression

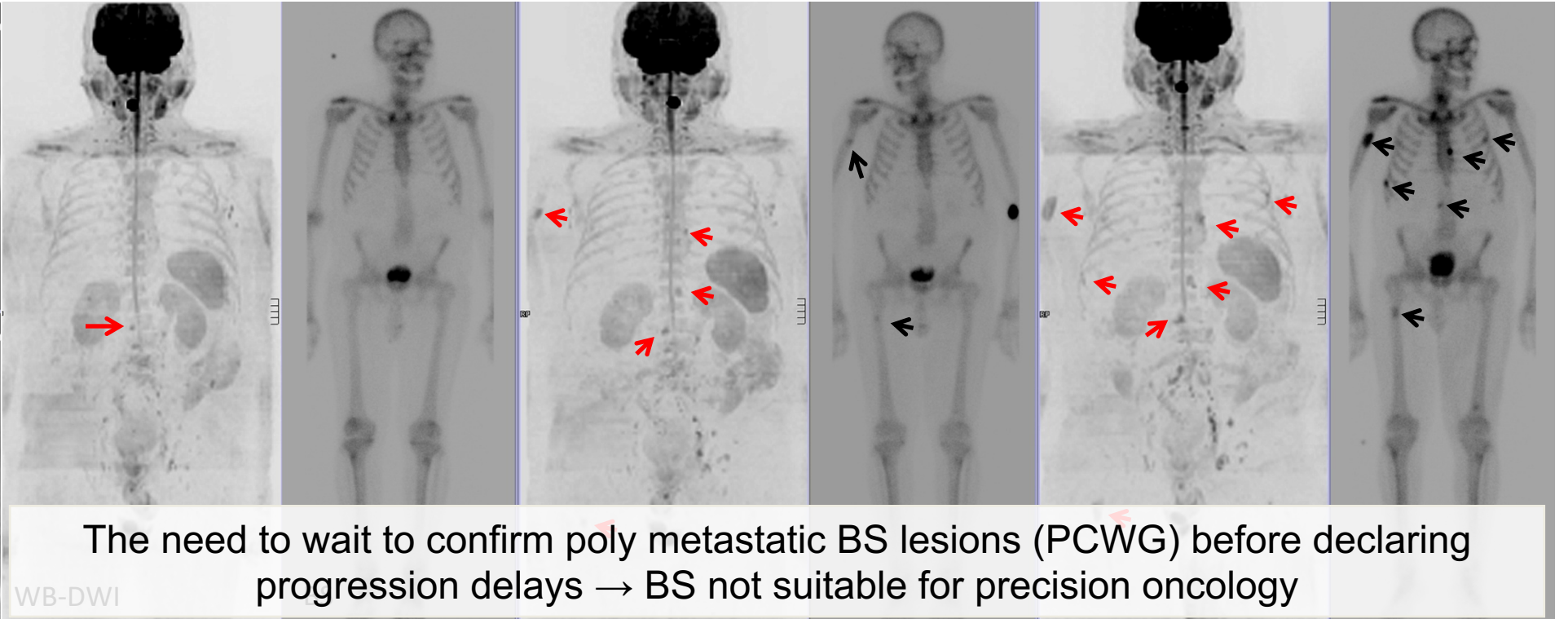
Recorded date of progression

Poly-metastatic progression

Screening PSA 45.5	Week 25 PSA 0.3	Week 37 PSA 0.4	Week 49 PSA 1.5
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Retroperitoneal nodes on DWI,
No bone lesions on BS/CT/MRI



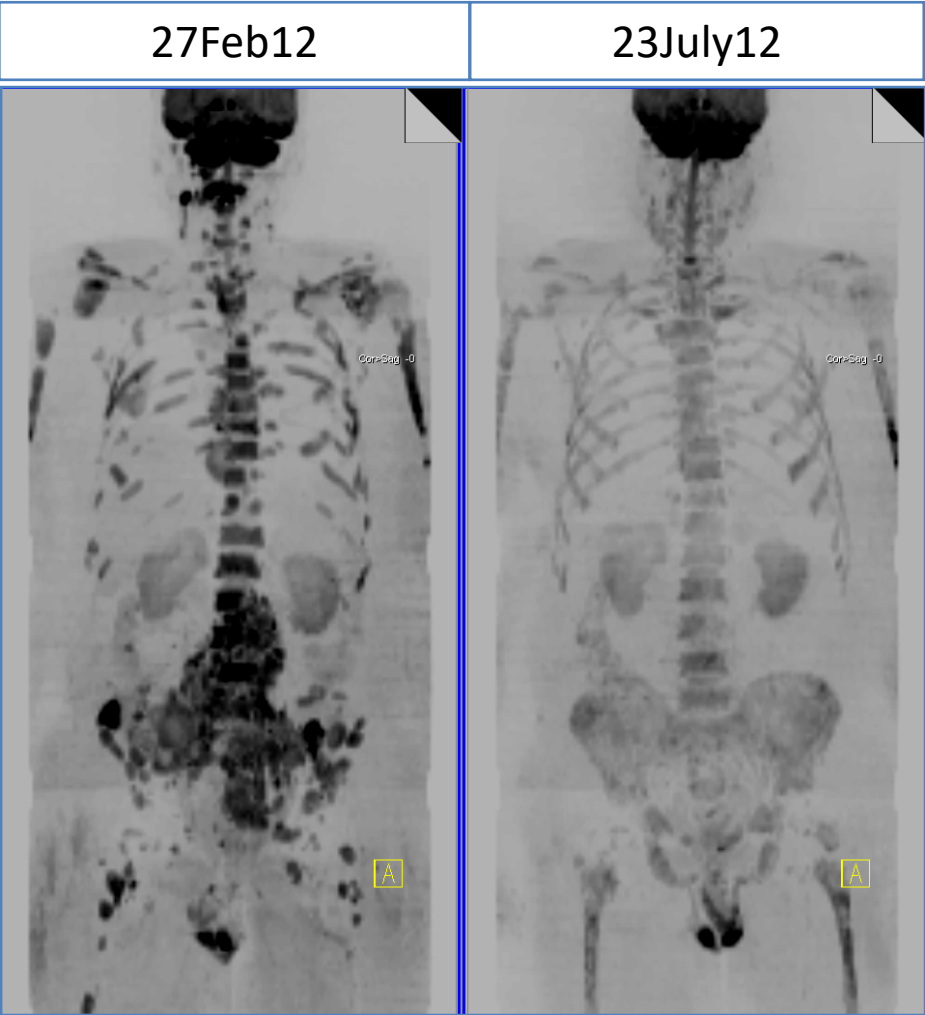
Retroperitoneal nodes improved.
WB-MRI = 1 new bone metastasis
BS = no lesions

Retroperitoneal nodes worse.
WB-MRI = 5 bone lesions
BS = 2 lesions (outside flare period; needs confirmation)

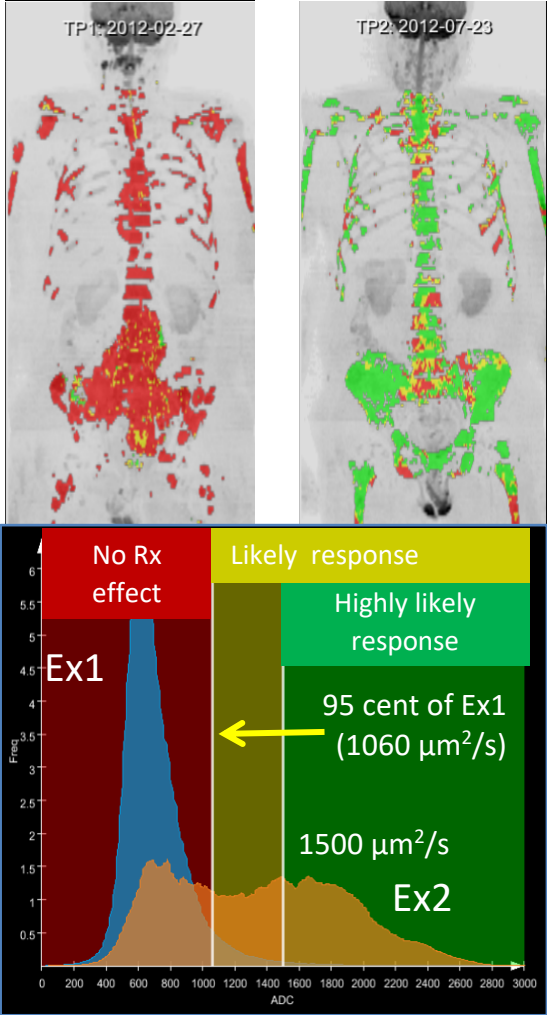
Retroperitoneal nodes progressing. New lymphoedema.
WB-MRI = 7 bone lesions
BS = 7 lesions (1 on posterior projection)

The need to wait to confirm poly metastatic BS lesions (PCWG) before declaring progression delays → BS not suitable for precision oncology

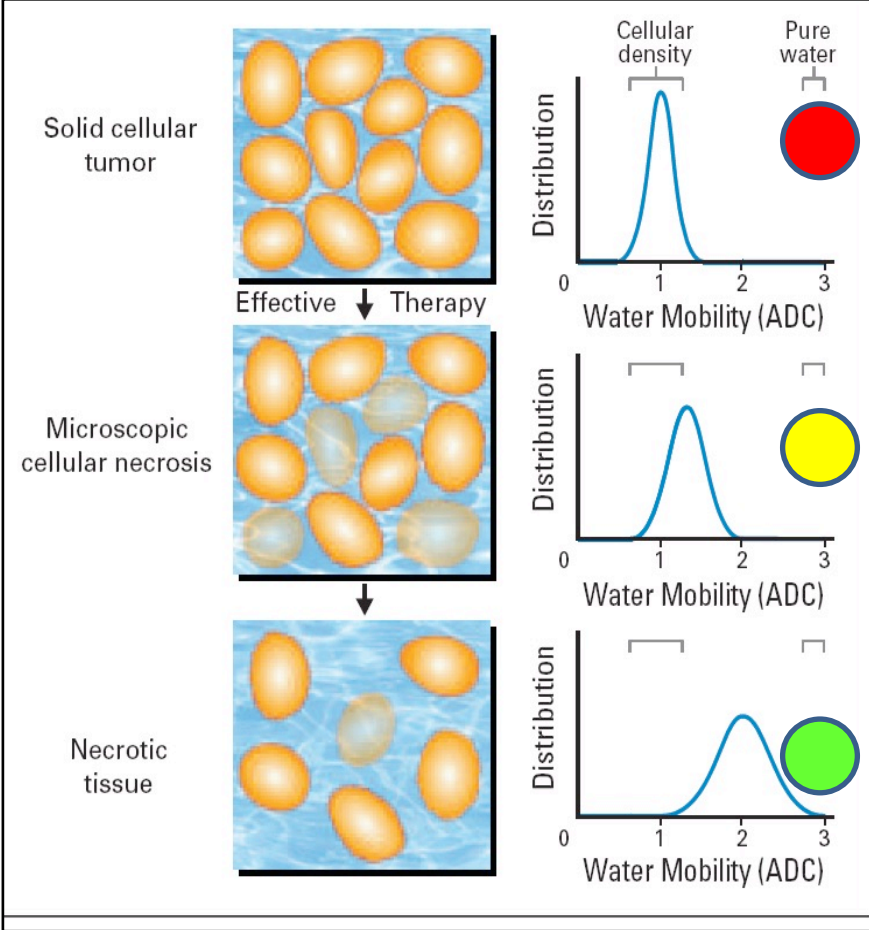
DWI: cellular viability habitats can be spatially mapped



Metastatic prostate cancer (x4 docetaxel, goserelin & prednisone)

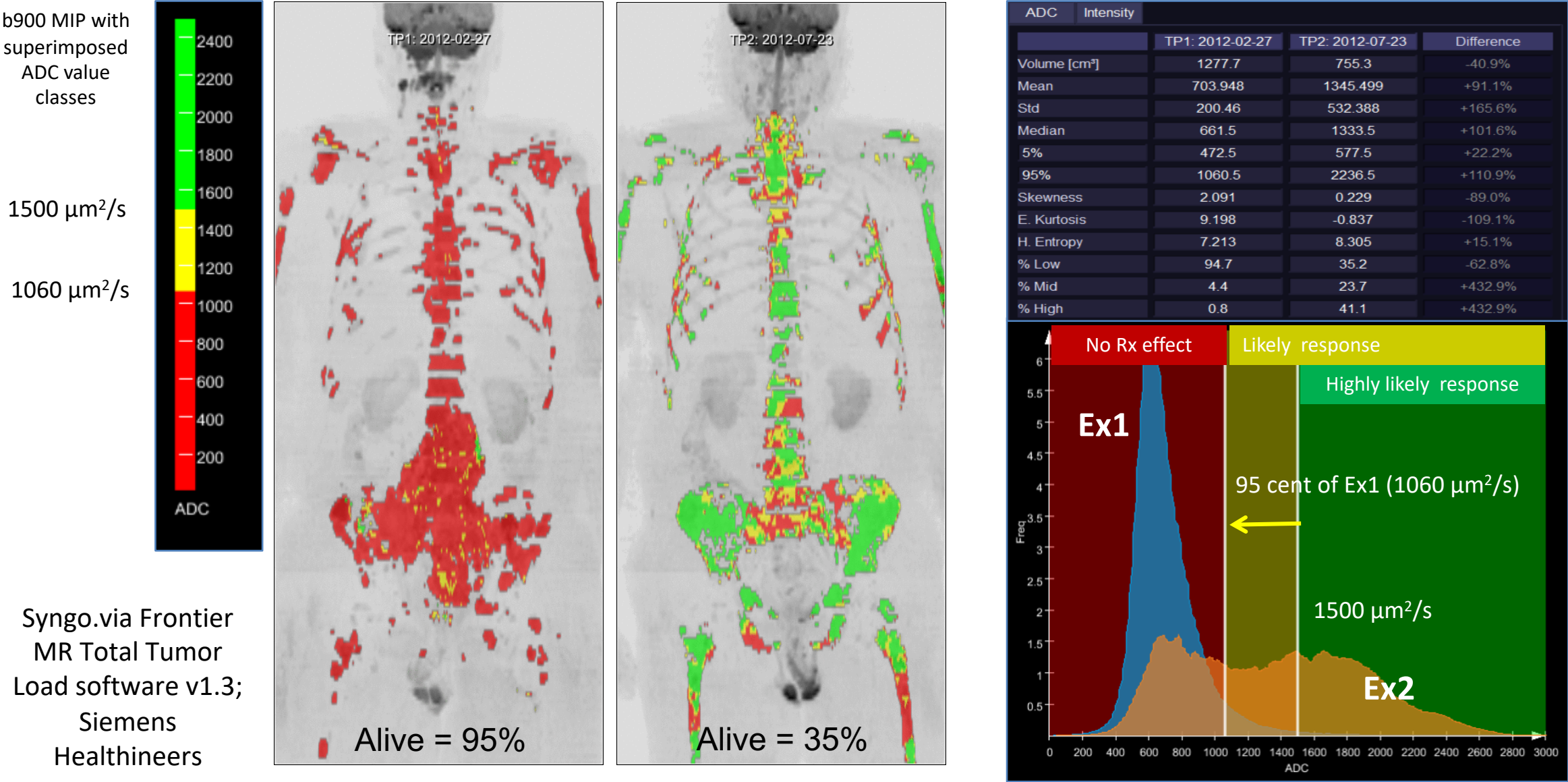


Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers



Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

Viability habitats: mapped & quantified (ADC distribution/spatial heterogeneity)



Viability habitats: mapped & quantified (ADC distribution/spatial heterogeneity)

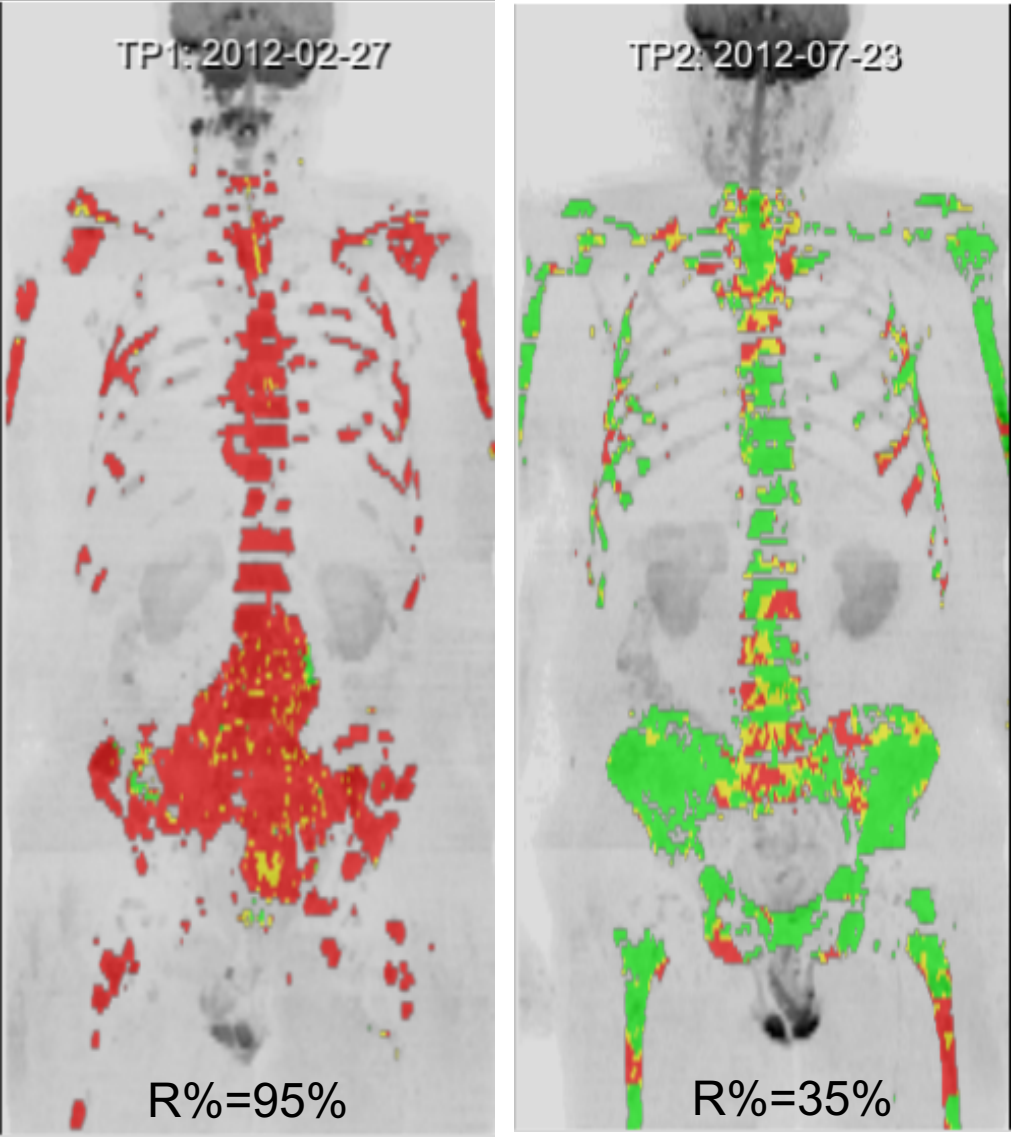
b900 MIP with superimposed ADC value classes

1500 $\mu\text{m}^2/\text{s}$

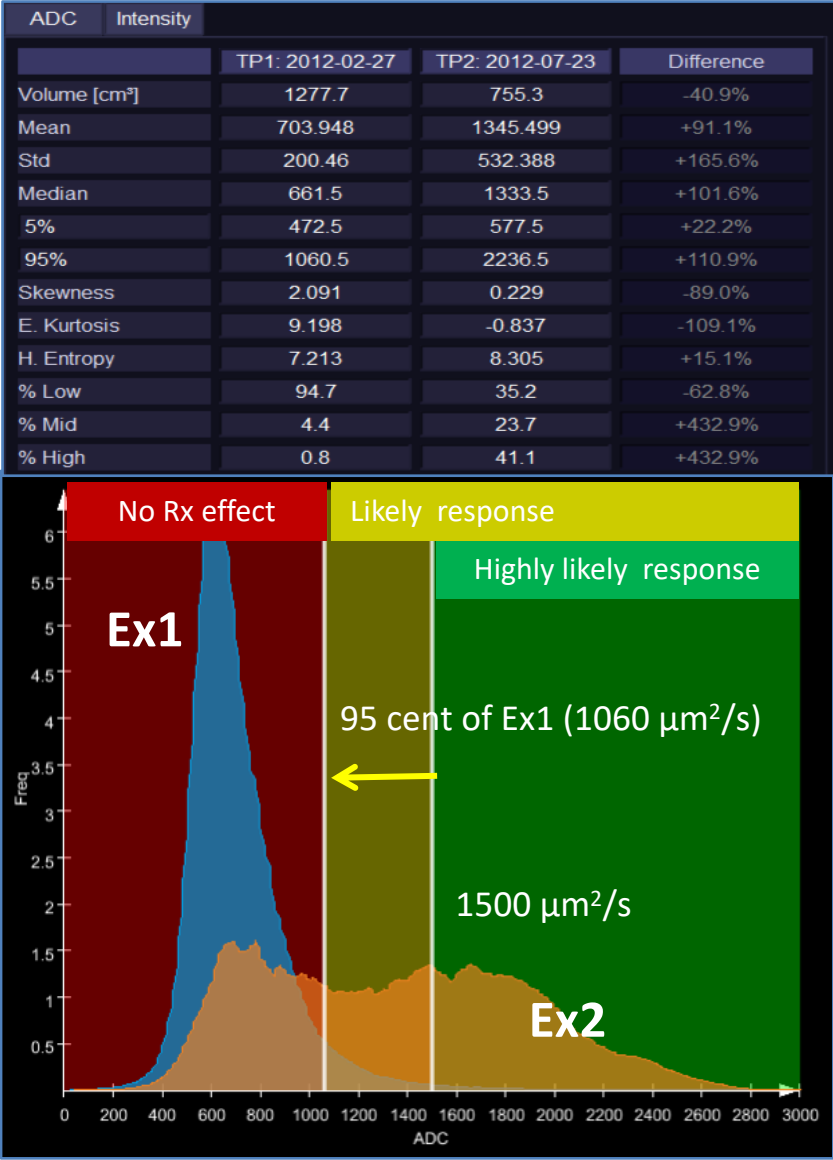
1060 $\mu\text{m}^2/\text{s}$

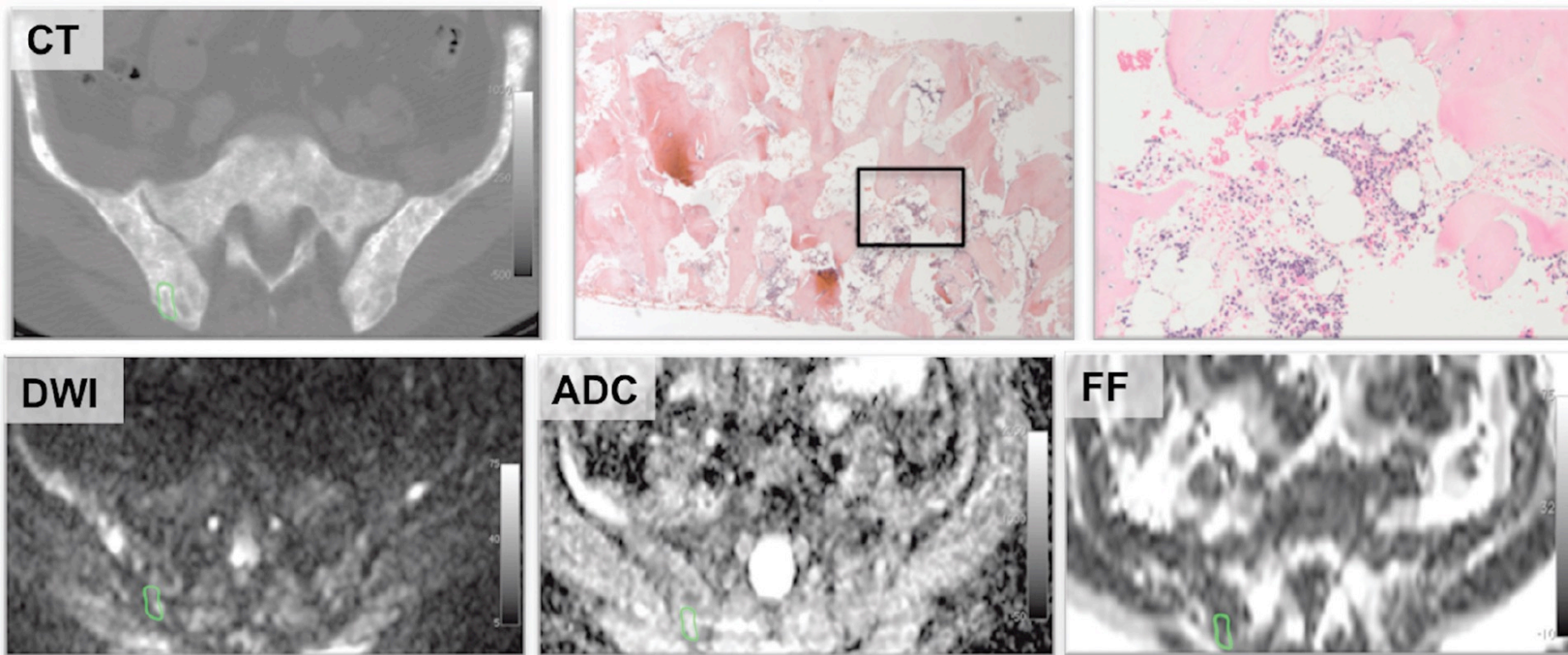
ADC

Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers



Metastatic prostate cancer (x4 docetaxel, ADT & prednisone)





Cellular infiltrate

- Lower ADC
- High DWI signal
- Lower rF%

Radiology • Volume 00, Number 00, Month 2017

Perez-Lopez R, et al. Multiparametric MRI of Prostate Cancer Bone Disease: Correlation With Bone Biopsy Histological and Molecular Features. *Invest Radiol* 2018 Feb;53(2):96-102

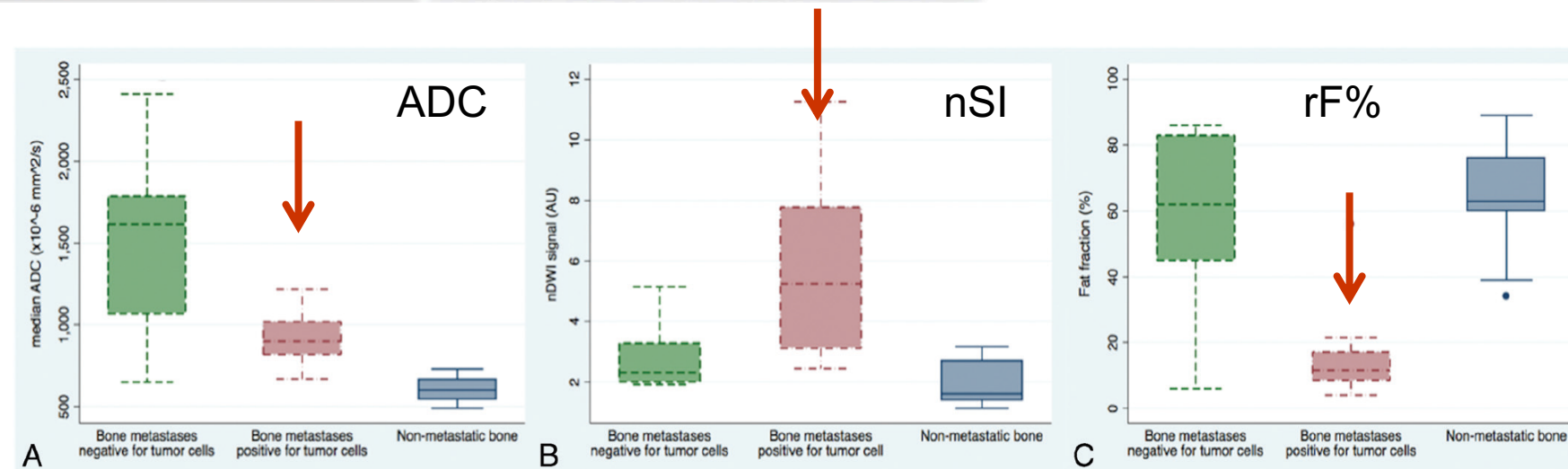


FIGURE 1. Box plots of the distribution of (A) median ADC, (B) median nDWI signal intensity, and (C) median swFF of the bone marrow in patients with bone metastases and bone biopsy negative for tumor cells (green), bone metastases and bone biopsy positive for tumor cells (red), and no bone metastases (blue).

Circulating Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition

Jane Goodall, Joaquin Mateo, Wei Yuan, Helen Mossop, Nuria Porta, Susana Miranda, Raquel Perez-Lopez, David Dolling, Dan R. Robinson, Shahneen Sandhu, Gemma Fowler, Berni Ebbs, Penny Flohr, George Seed, Daniel Nava Rodrigues, Gunther Boysen, Claudia Bertan, Mark Atkin, M. Semini Sumanasuriya, Pasquale Rescigno, Zafeiris Zafeiriou, Adam Sharp, Nina Tunariu, Diletta Bianchini, Alex Suzanne Carreira, and Johann S. de Bono

Published OnlineFirst April 27, 2017; DOI: 10.1158/2159-8290.CD-17-0261

DOI: 10.1158/2159-8290.CD-17-0261 Published June 2017


[Article](#)
[Figures & Data](#)
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[PDF](#)

- Somatic mutations in DNA repair pathways in mCRPC ≈20-25%
- Rx options include PARP inhibitors, platinum chemotherapy, immunotherapy
- cfDNA for sequencing & Rx selection, therapy monitoring, resistance mechanism
- **Imaging:** localisation of biopsy site before & at therapy resistance, monitoring Rx response

Response and Resistance to PARP Inhibition in cfDNA

RESEARCH ARTICLE

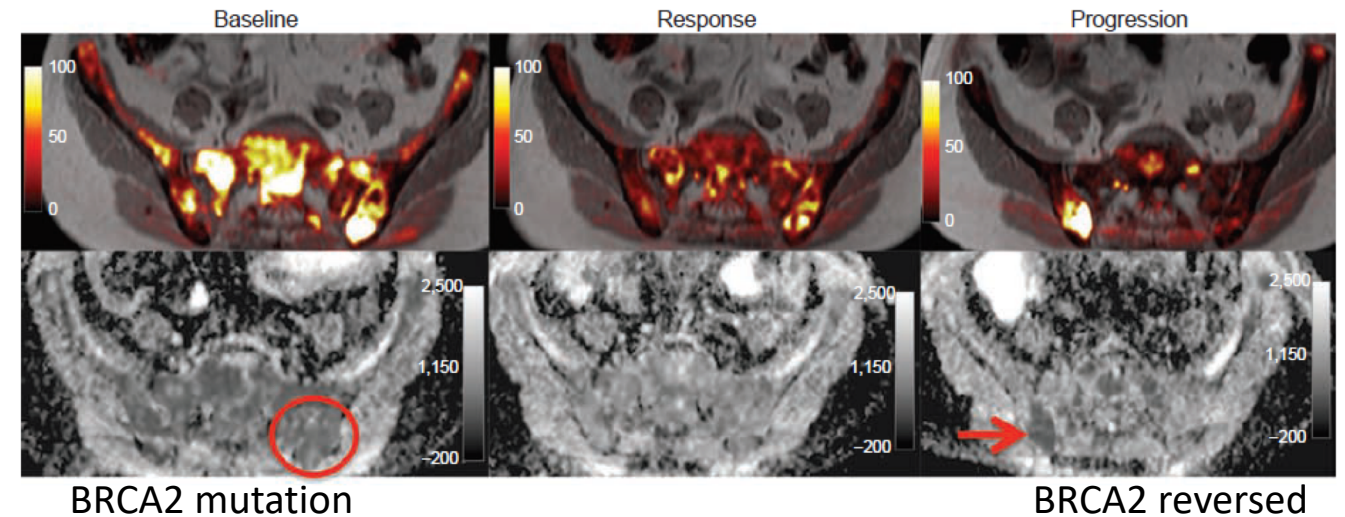
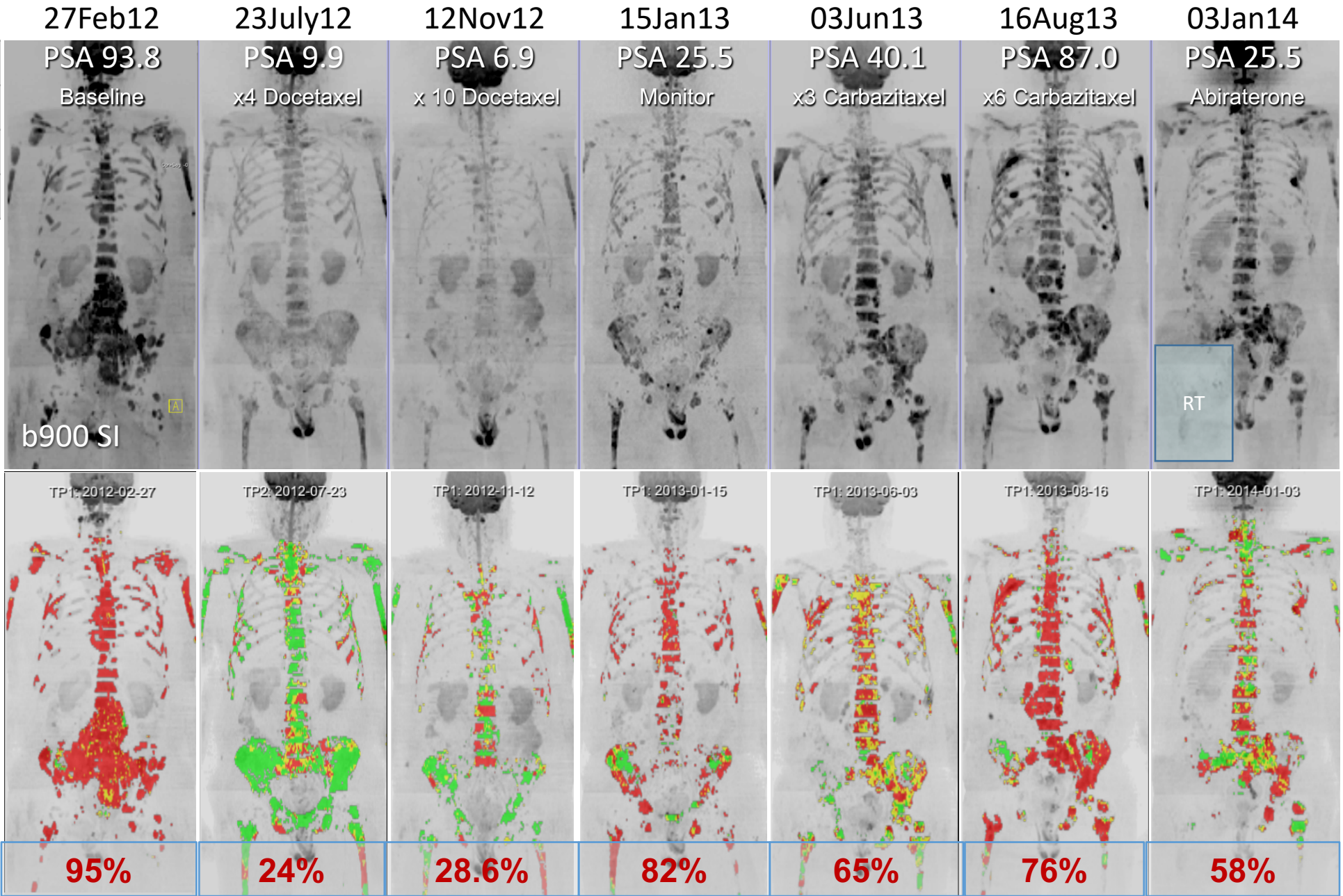
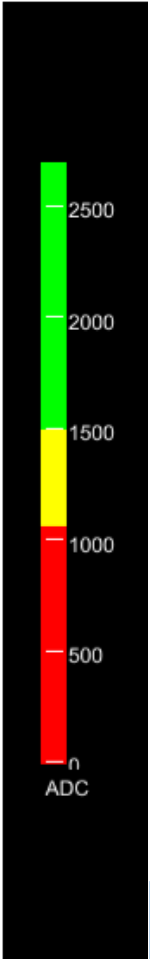


Figure 4. Single-site disease progression after 9 months of response to therapy in the right hemipelvis visualized by diffusion-weighted whole-body MRI. Top, fusion of the T1-weighted imaging and diffusion-weighted imaging; bottom, apparent diffusion coefficient (ADC) maps. Areas of high signal on diffusion-weighted imaging and low ADC values indicate tumor bone marrow infiltration. Left, baseline MRI scan, showing diffuse tumor infiltration in the pelvic bone. The first trial biopsy was taken from the left iliac bone (red circle) and identified a deleterious *BRCA2* mutation with LOH. After 12 weeks of therapy (middle), there was a major response to therapy reported. After 9 months (right), the MRI identified a focal area of tumor relapse in the right iliac bone, which was biopsied (red arrow). Next-generation sequencing of this biopsy confirmed a *de novo* mutation in *BRCA2* restoring the open reading frame.

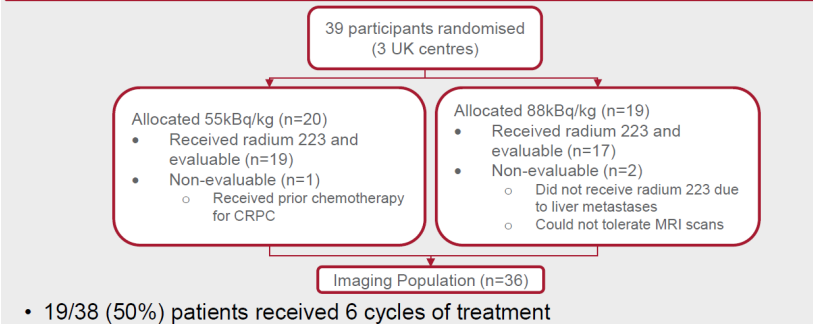
ADC classes	
<div></div>	Alive
<div></div>	Dying
<div></div>	Dead



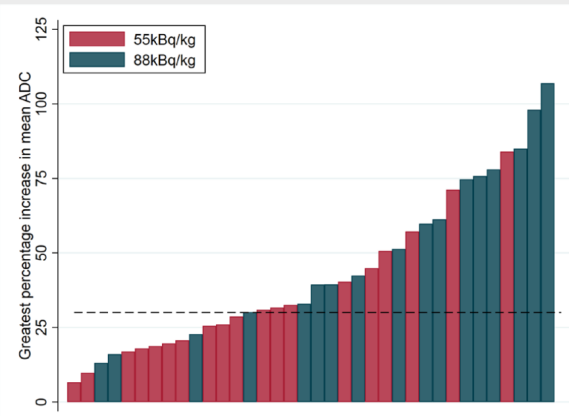
ADC classes Syngo.via Frontier MR Total Tumor Load software v1.3; Siemens Healthineers; WIP

Radium-223: Disease response and fracture assessment by whole body diffusion-weighted MRI in mCRPC

Results: Consort diagram and compliance



Results: Per patient WB DWMRI Response

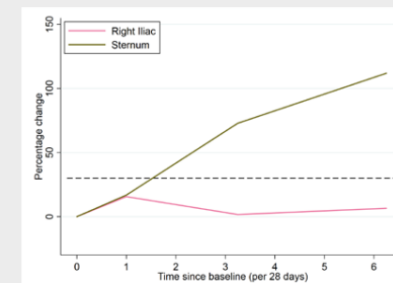
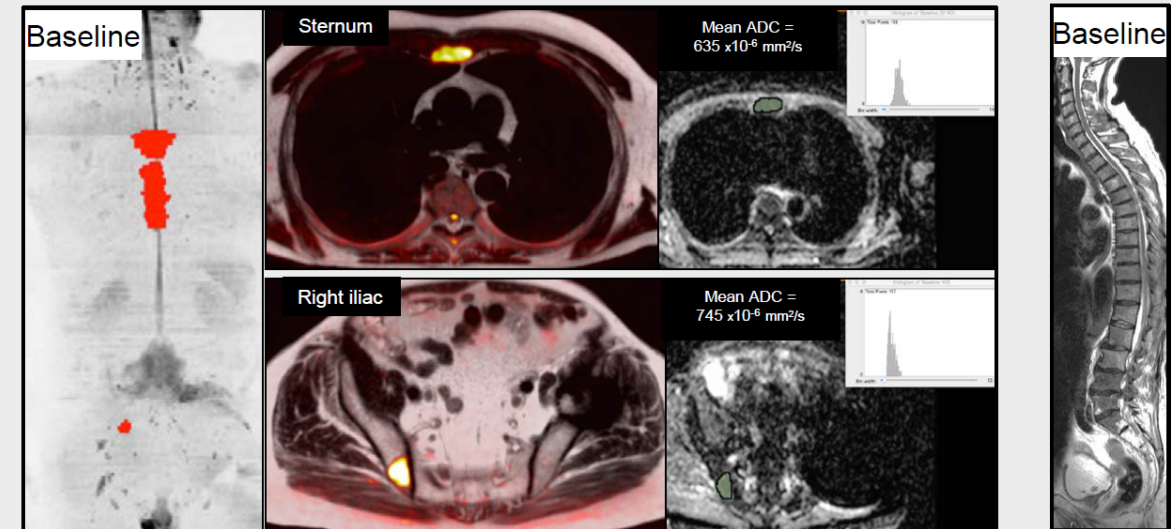


- 23/36 (64%; 95% CI: 46-79%) patients had a WB-DWMRI response
- 14/17 (82%) patients who received 88kBq/kg had a WB-DWMRI response compared to 9/19 (47%) who received 55kBq/kg; Fisher exact p-value=0.04

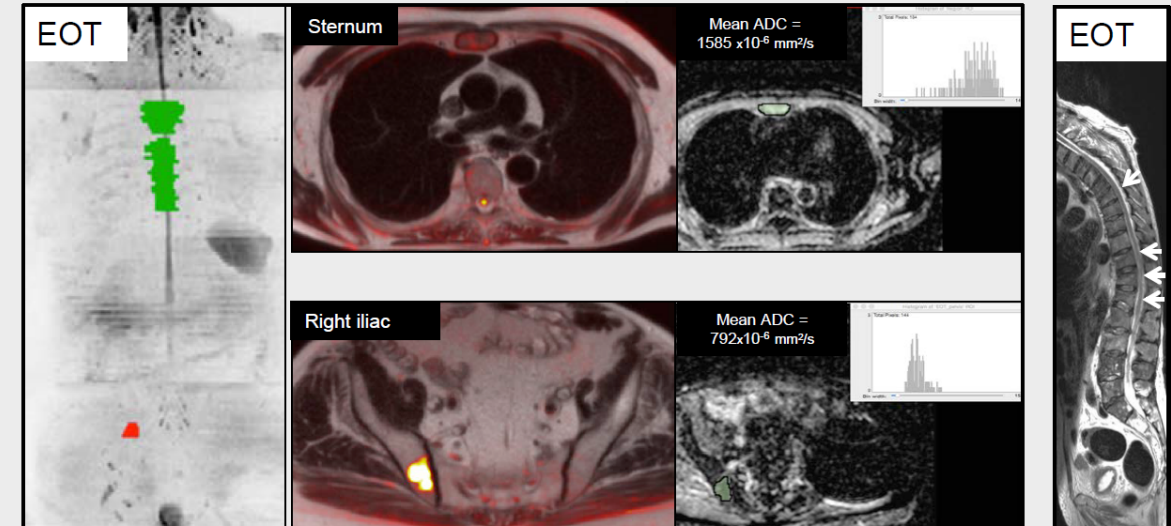
Parker CC, et al. *JCO* 36, no. 15_suppl (May 20, 2018) 5024-5024.

Marked heterogeneity between lesions and patients at both Ra-223 doses

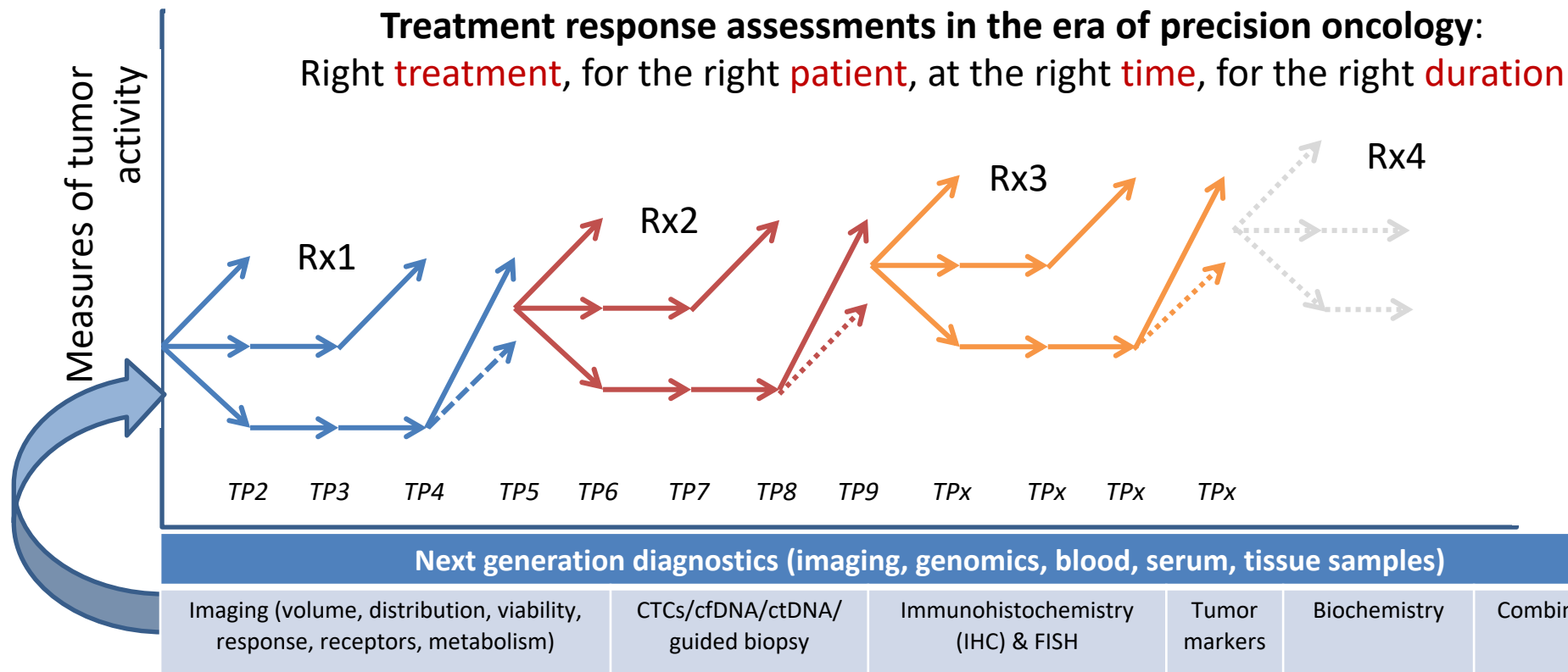
Results: WB-DWMRI Images



- Baseline and EOT MRI images showing significant increase in ADC (+149%) in keeping with response in the sternal lesion and no significant change (+6%) in keeping with lack of response in the right iliac bone lesion.
- In a different patient, new vertebral compression fractures in uninvolved bone are seen at EOT.



NextGen
Imaging
promotes
Precision
Oncology
Trials

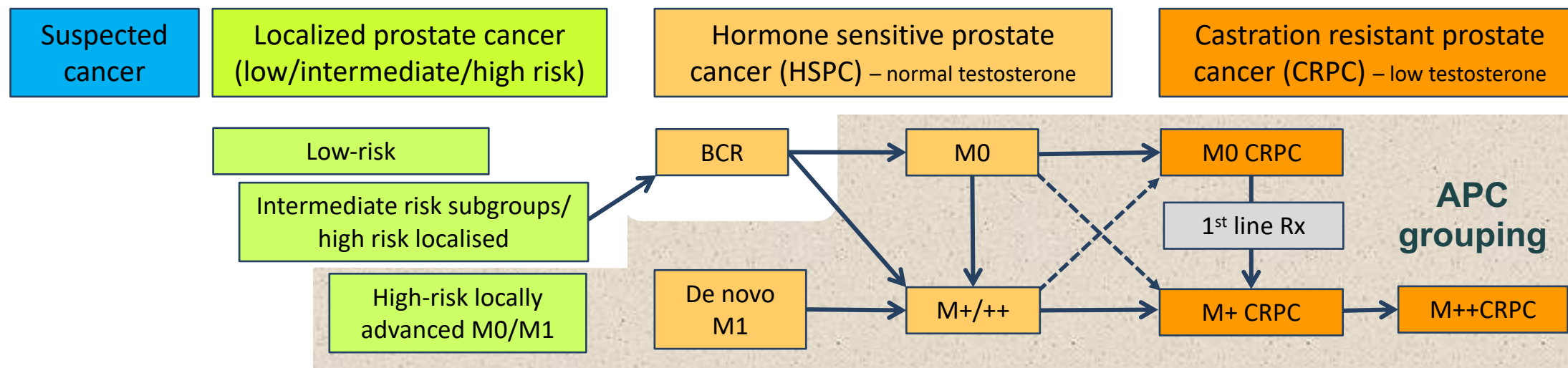


Prognostic or
predictive
genomic tests
poised for clinical
decision making
in APC

@MarkRubin
GU-ASCO2019

MSI, Mismatch repair (MMR) gene mutation	Immunotherapy (FDA approved)
DNA Repair Status. 'BRACAness' assays for BRCA1/2/ATM, PALB2 - mutations/loss or HR signatures	useful for platinum or PARPi
Loss of AR (AR-v7, mutations)	Lack of response to AR directed therapy
cfDNA/ctDNA	Prognostic value
PTEN loss	AKT inhibitor responses with AR inhibitors
CDK12 loss	Cell cycle checkpoint inhibitors
Loss of TP52/RB1	Short duration of response to AR directed therapies; possible response to platinum
CTC heterogeneity	Response to docetaxel vs AR directed therapies
Neuroendocrine tumor	Platinum chemotherapy
PSMA expression	PSMA directed therapies

Which NextGen Imaging method & when?



(mp)MRI for detection, staging & local restaging

PET/CT for oligometastases detection and restaging for Rx decisions

@ProfPadhani

WB-MRI/DWI for poly-metastatic disease staging & treatment monitoring

Take home points: Time to move on to NextGen Imaging

Don't rely on CT/BS for (bone) metastatic assessments

Next generation imaging PET-CT (various tracers) & whole-body MRI/DWI can detect bone metastases with high sensitivity; early detection of metastases & therapy resistance can have positive precision oncology therapy implications

NextGen imaging can positively assess therapy response and early failure, unlike bone scans which only identify late tumor progression. Accurate therapy assessments & heterogeneity can promote the development and clinical use of targeted therapies

NextGen imaging directed therapy survival benefits in APC has not been evaluated, but methods are ready for clinical trials incorporation*

*Padhani AR, et al. METastasis Reporting And Data System for Prostate cancer (MET-RADS-P): Practical guidelines for acquisition, interpretation, and reporting of Whole-body MRI based evaluations of multiorgan involvement in advanced prostate cancer. Eur Urol. 2017 Jan;71(1):81-92.

*Fendler WP, et al. (68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.