Discussion on Ryan et al:

Association of rPFS with OS in patients with mCRPC

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THE ROYAL MARSDEN

ICR The Institute of Cancer Research 1909 2009

Financial disclosure

- The inhibitor of androgen synthesis, abiraterone acetate, was developed at The Institute of Cancer Research and is licensed to Cougar Biotechnology/J&J.
- I am included in The ICR co-inventors' reward scheme of abiraterone acetate.
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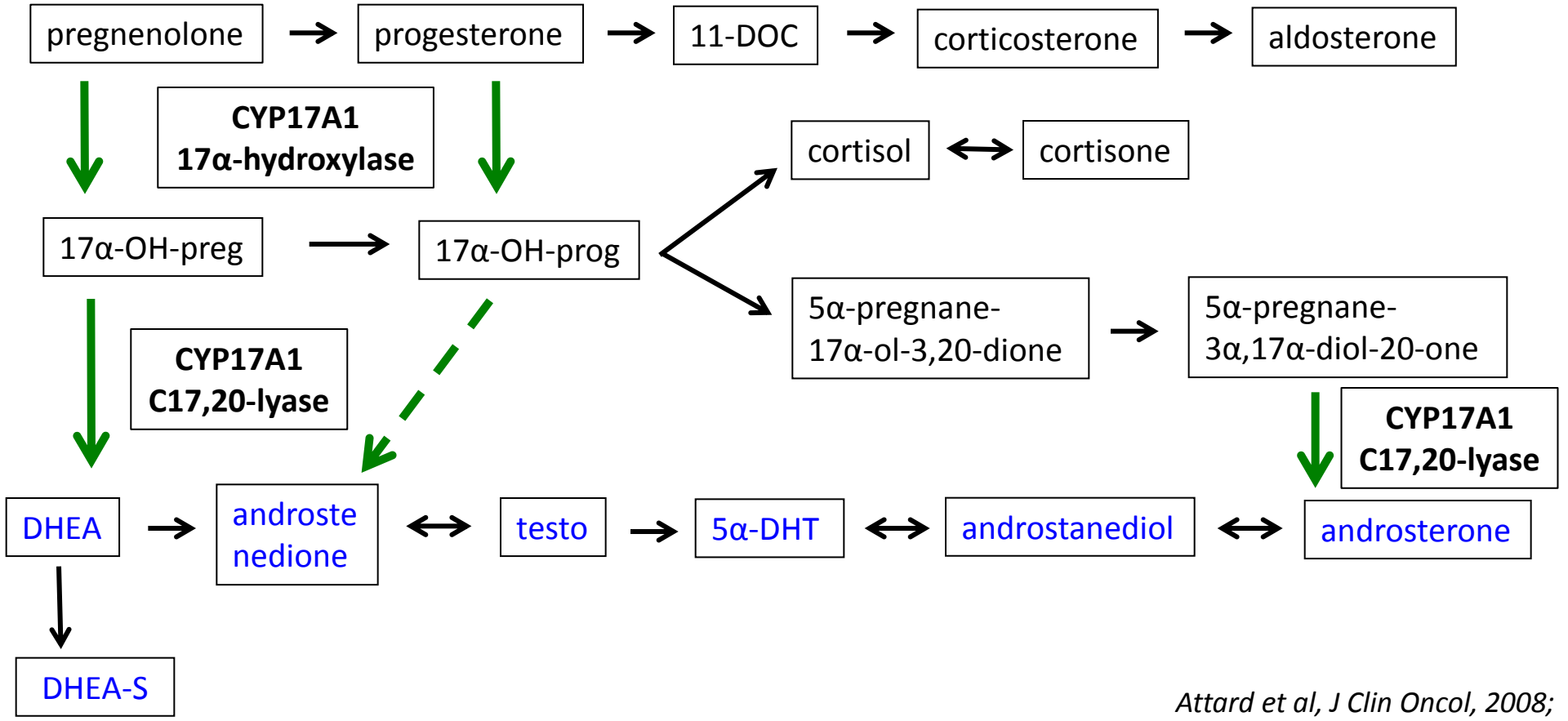
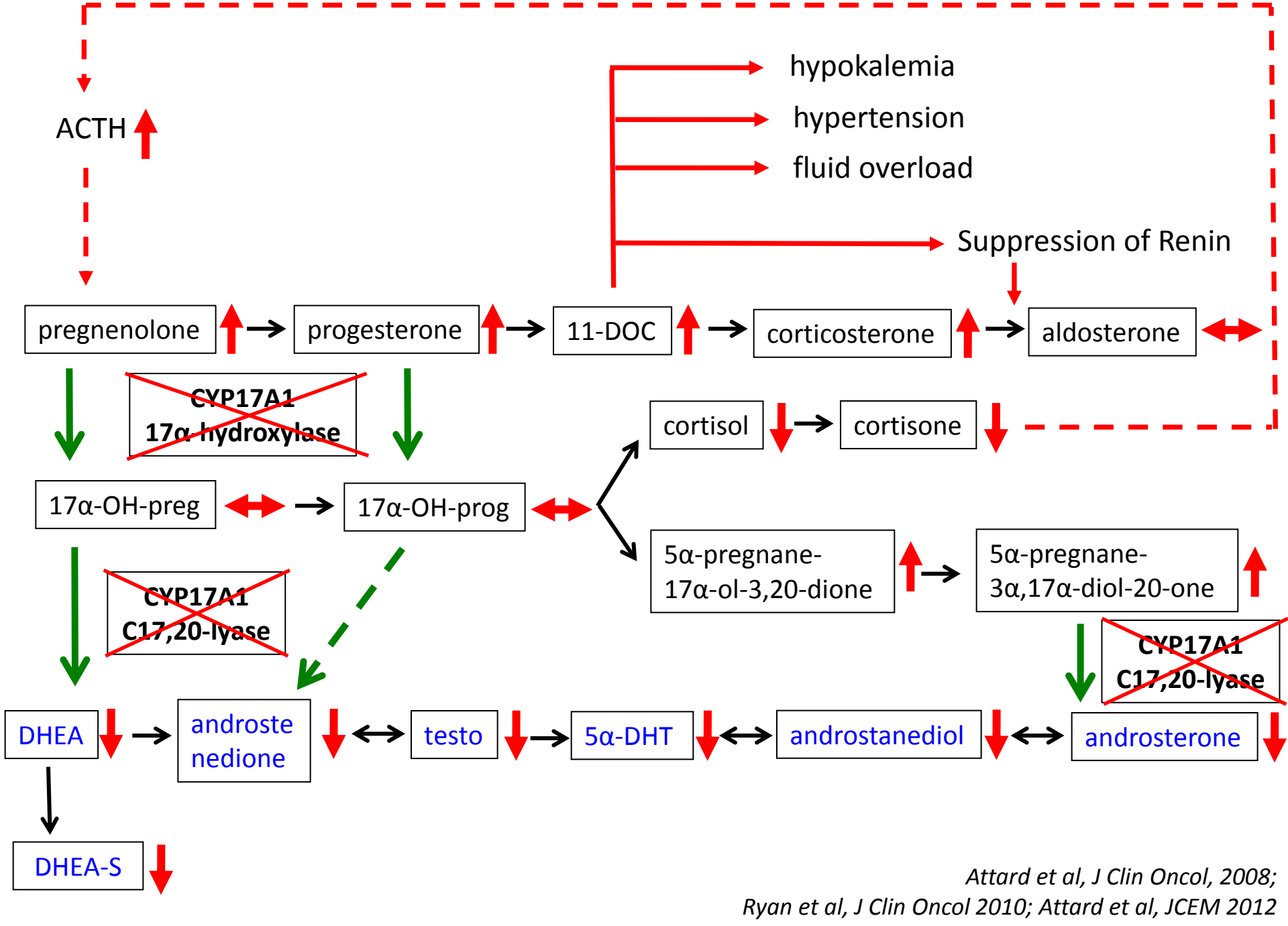
- I have received honoraria and travel support from Sanofi Aventis, Jannsen, Veridex, Ipsen, Millenium Pharmaceuticals, Ventana/Roche

Mechanism of action of abiraterone in humans



Attard et al, J Clin Oncol, 2008;
Ryan et al, J Clin Oncol 2010; Attard et al, JCEM 2012



Attard et al, J Clin Oncol, 2008;
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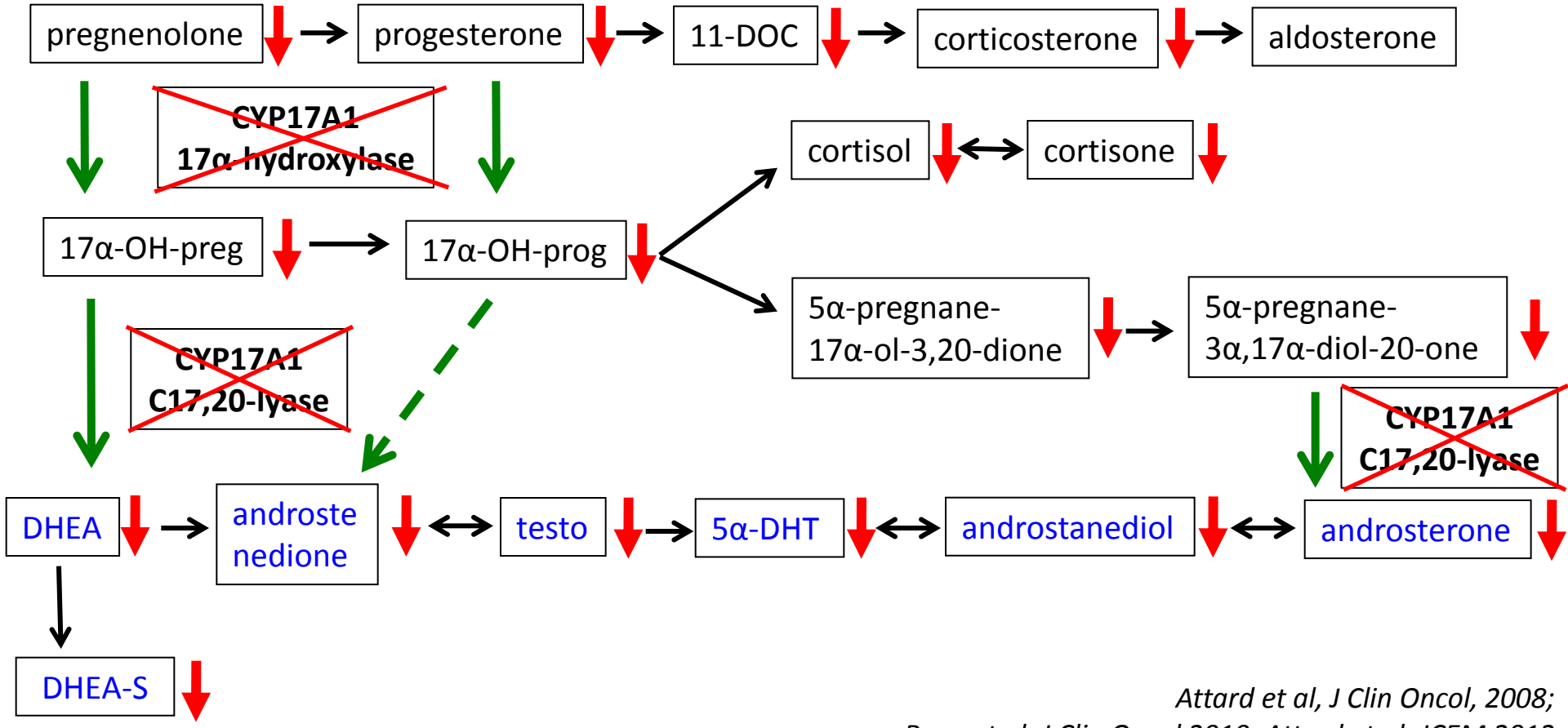
Addition of exogenous glucocorticoids suppresses the ACTH drive

…although sometimes incompletely



Attard et al, J Clin Oncol, 2008;
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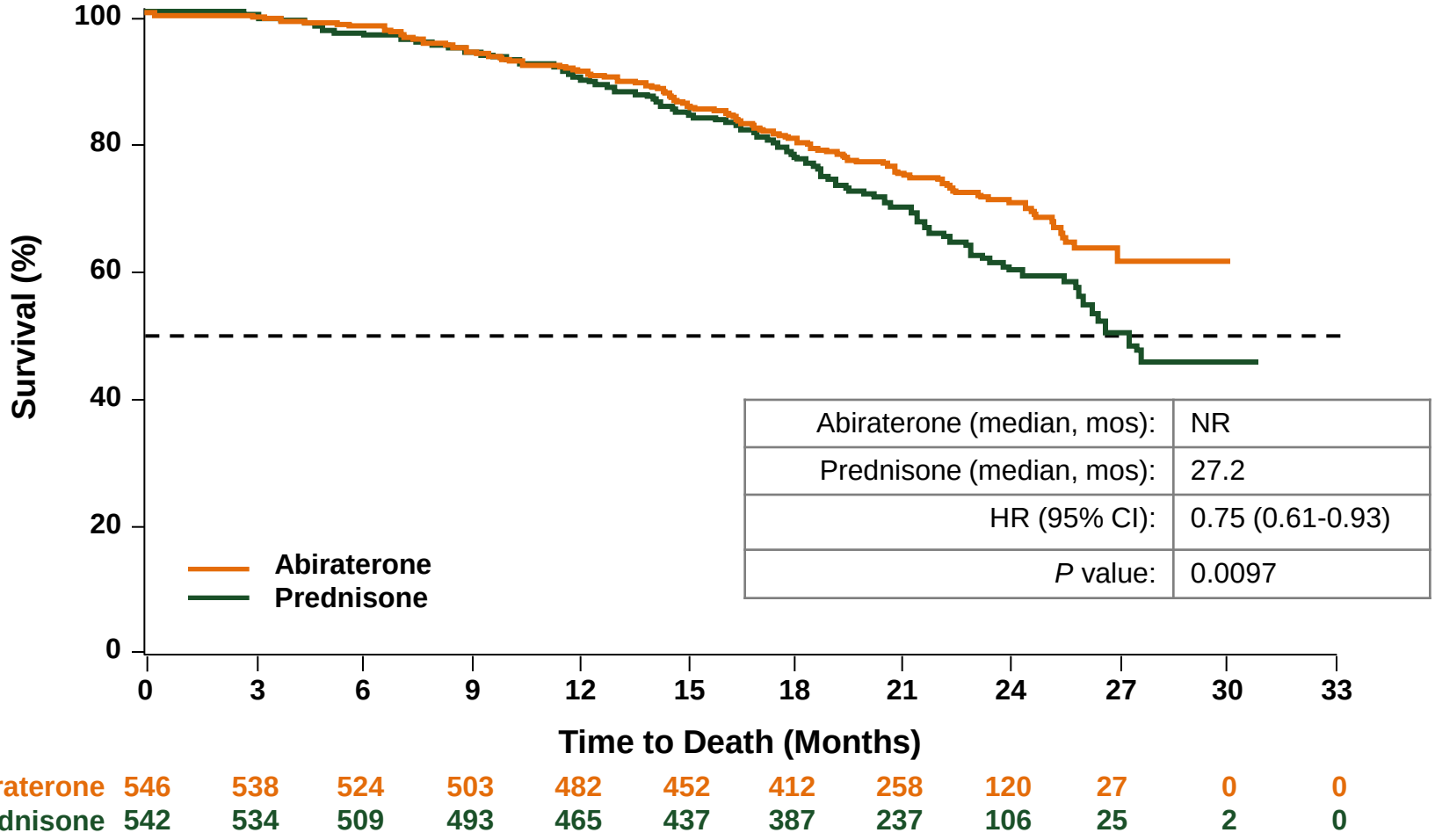
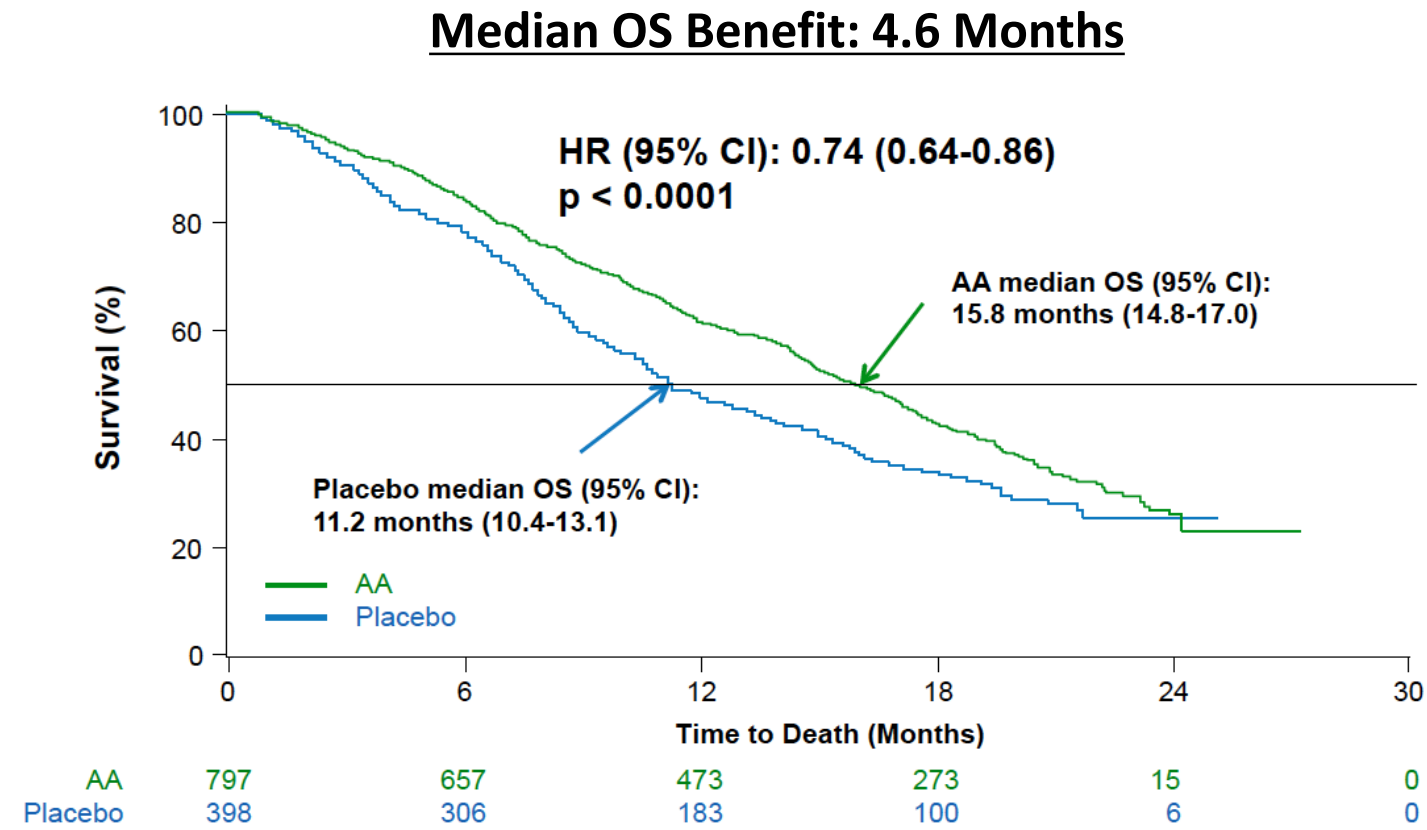
Strong Trend in OS Primary End Point in chemotherapy naïve mCRPC



Data cutoff 12/20/2011.

Prespecified significance level by O'Brien-Fleming Boundary = 0.0008.

OS benefit with abiraterone in chemotherapy-treated CRPC patients



- Median duration of follow-up: 20.2 months
- Median duration of treatment: AA, 8 months vs placebo, 4 months

Fizazi et al. ESMO 2011; abstract 7000 (oral presentation)

Chemotherapy naïve vs chemotherapy treated

Study	Number of events	Duration of follow-up (months)	Survival (months, 95%CI) abiraterone vs placebo	HR (95% CI)	P value
301 interim analysis	534	12.8	14.8 vs. 10.9	0.65 (0.54 - 0.77)	<0.001
301 final analysis	775	20.2	15.8 vs 11.2	0.74 (0.64-0.86)	<0.0001
302 interim analysis	311	22.3	NR vs 27.2	0.75 (0.61-0.93)	0.0097

de Bono et al, NEJM, 2011; Fizazi et al. ESMO 2011; abstract 7000 (oral presentation)

- Can 1 or 2 chemotherapy regimens change a CYP17A1 inhibitor into an effective drug from a relatively ineffective one?

….Unlikely….

- The AR is a well validated target pre and post-chemotherapy
- Phase II and III evidence suggests greater activity pre-chemotherapy with abiraterone compared to post-chemotherapy
- Subsequent docetaxel or abiraterone or enzalutamide is likely to prove more effective in the placebo arm compared to the abiraterone arm

Therapies administered after participation in 302

	AA + P (n = 546) n (%)	Placebo + P (n = 542) n (%)
No. with selected subsequent therapy for mCRPC	242 (44.3)	327 (60.3)
Docetaxel	207 (37.9)	287 (53.0)
Cabazitaxel	45 (8.2)	52 (9.6)
Ketoconazole	39 (7.1)	63 (11.6)
Sipuleucel-T	27 (4.9)	24 (4.4)
Abiraterone acetate*	26 (4.8)	54 (10.0)

*Prior to unblinding (e.g. not per protocol)

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Can rPFS be used as a primary/co-primary end-point in Phase III studies?

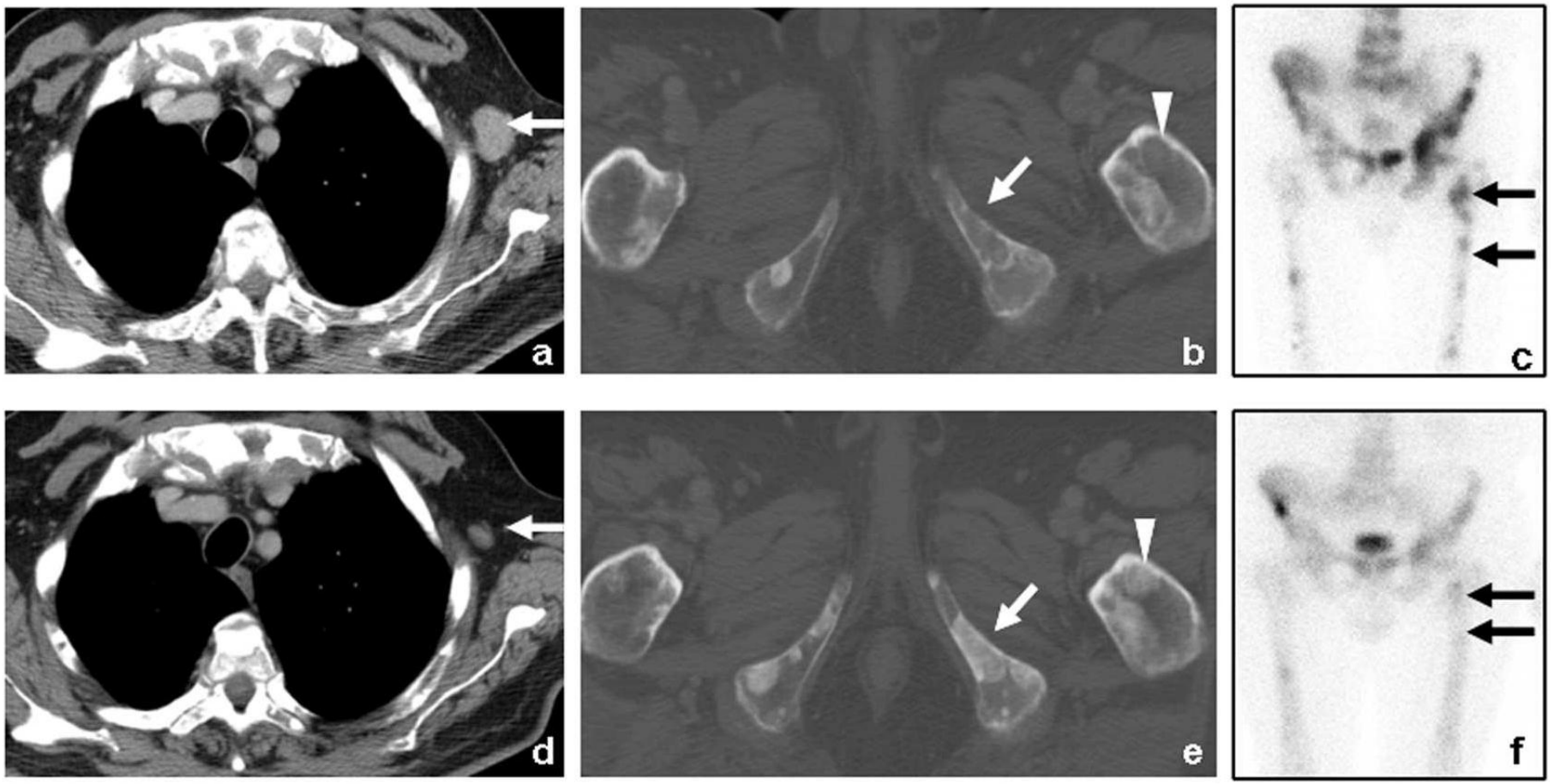
- a correlate is not necessarily a surrogate
- a surrogate endpoint cannot solely be correlated with clinical outcome (OS), but *must also fully capture the net effect of treatment on the clinical outcome*
- Is this association specific to abiraterone/targeting of AR?

PFS is a surrogate end-point of OS in advanced colorectal cancer

- 10 randomised clinical trials in colorectal adenocarcinoma evaluating 5-FU-based treatment (>4000 patients)
- Surrogate threshold effect of 0.86 to 0.77 – if a new treatment reduced the hazard of tumour progression by 23%, it was very likely to produce a survival benefit
- PFS may not capture effect of targeted therapies/novel cytotoxics

Buyse et al, J Clin Oncol 25, 5218-5224 (2007)

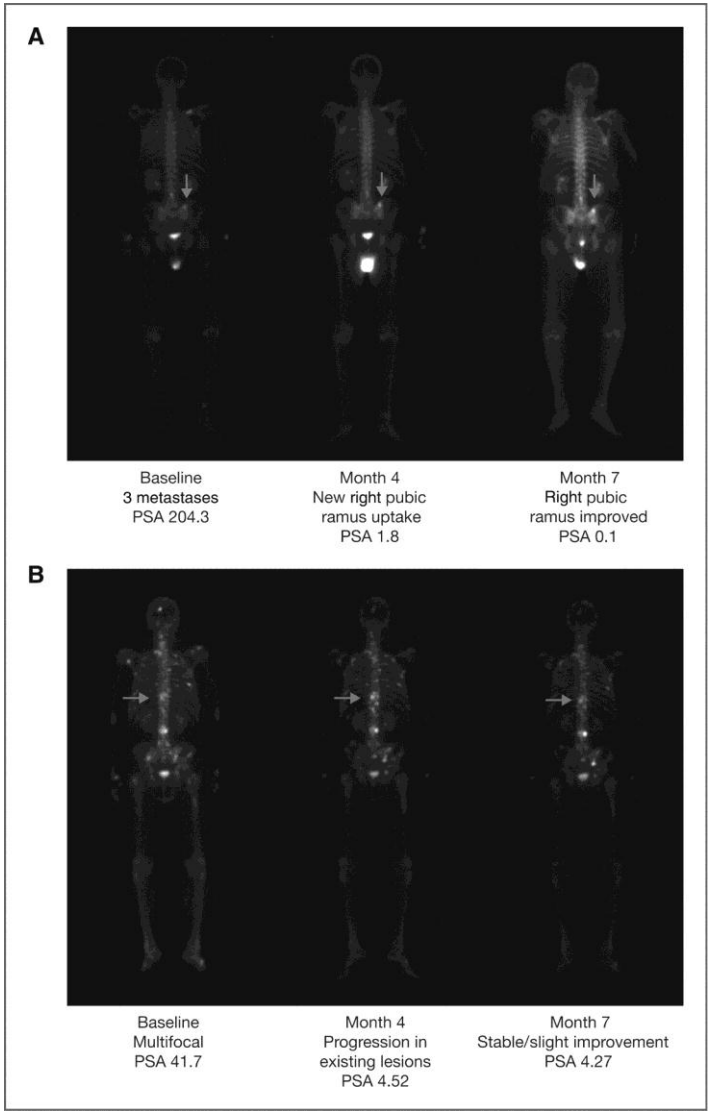
Bone flare within 3 months of starting abiraterone



PSA decline from 271 to 58 ng/ml

Messiou et al, Acta Radilogica, 2011 Jun 1;52(5):557-61.

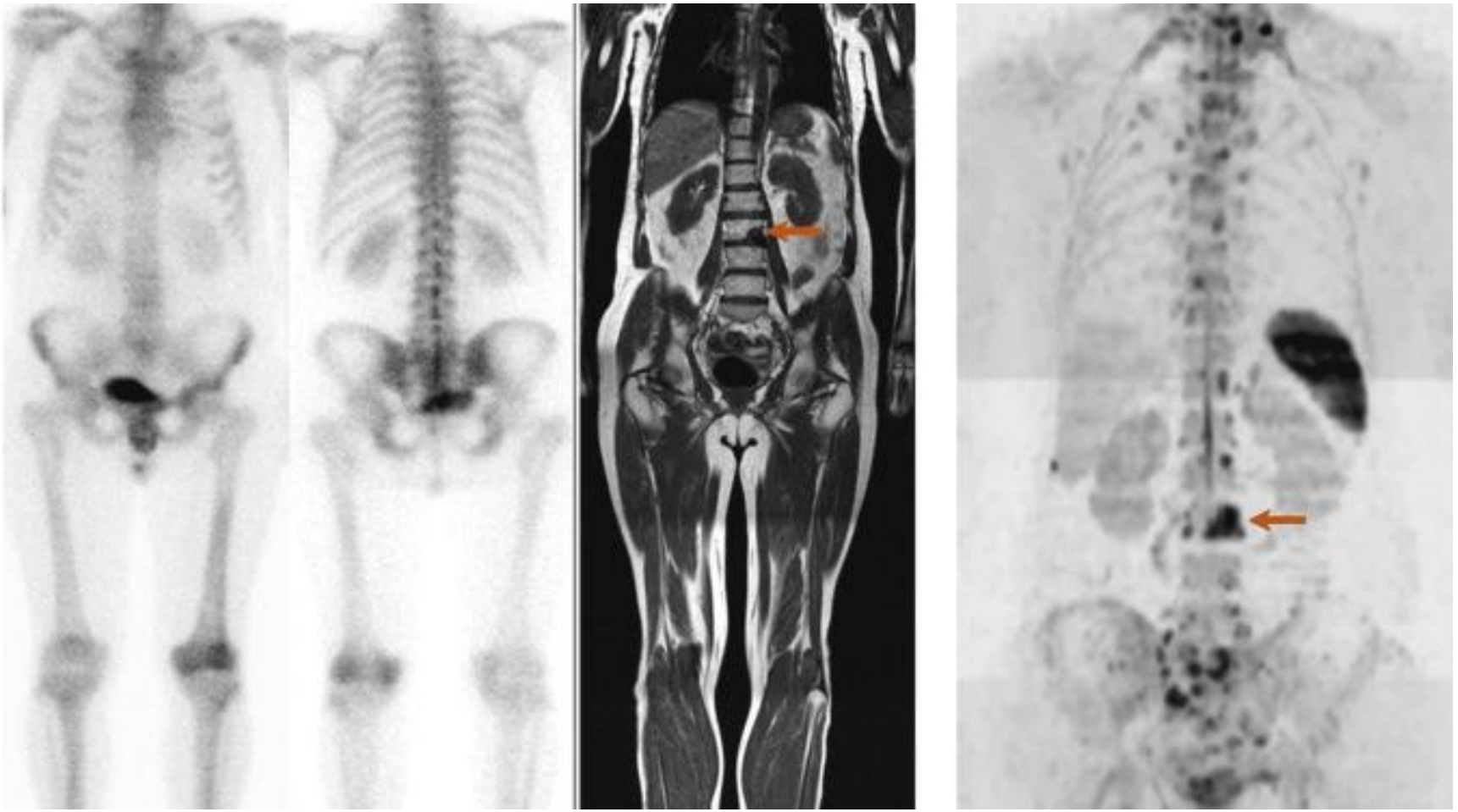
Bone flare within 3 months of starting abiraterone



Ryan et al, Clin Cancer Res 2011 17(14) 4854-61

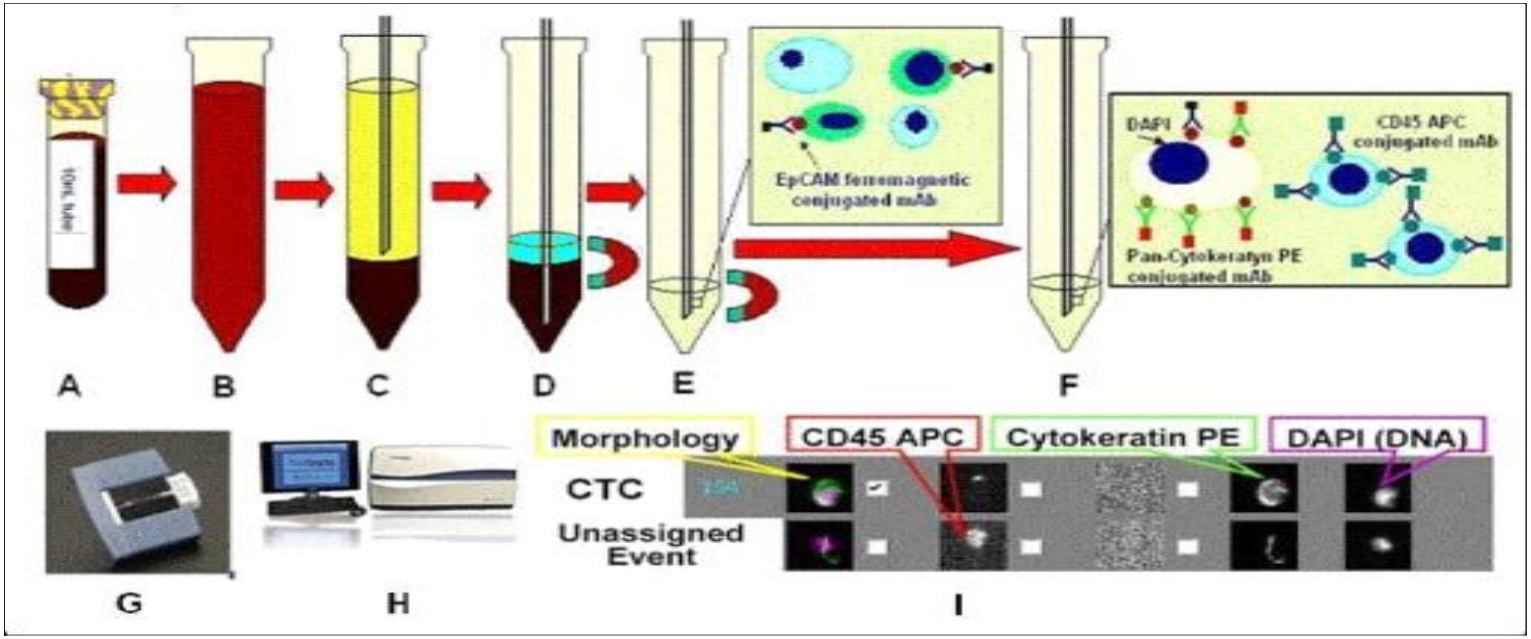
- Should all Phase III studies include a week 8 bone scan? For eg Cabozantinib??
- Interesting that 12% had a bone flare with pred (vs 31% with abi)
- What is the proportion of patients who progressed by bone scan versus RECIST?
- Is 2+2 definition accurate/feasible in patients with >100 hot spots on bone scan? Will automation/BSI improve accuracy? Inter-reader variability?

Can whole-body dw-MRI replace/supplement Bone and CT scans?



Lecouvet et al, Eur Urol. 2012 Jul;62(1):68-75.

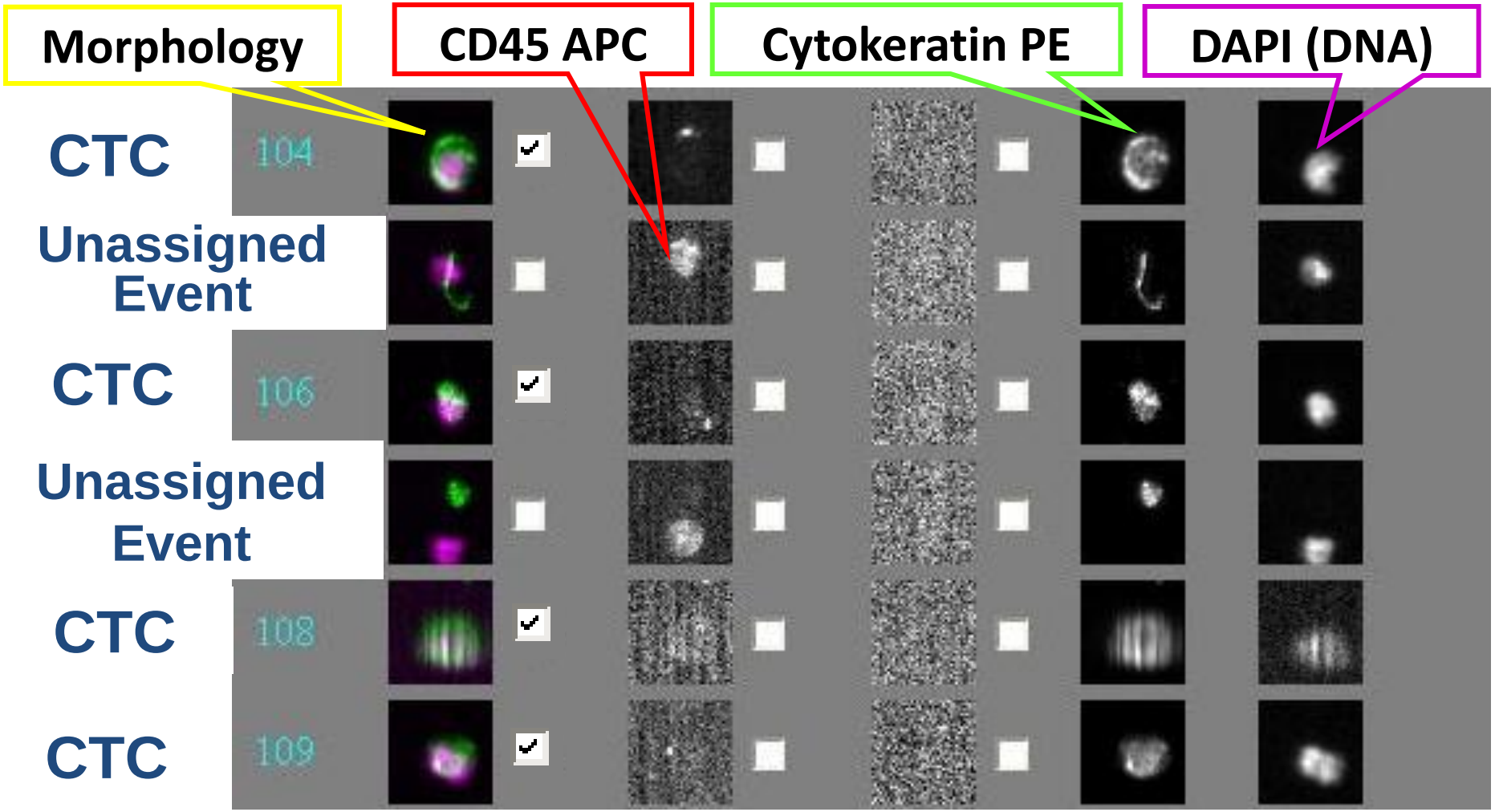
Circulating tumour cell enumeration
Veridex CellSearch®



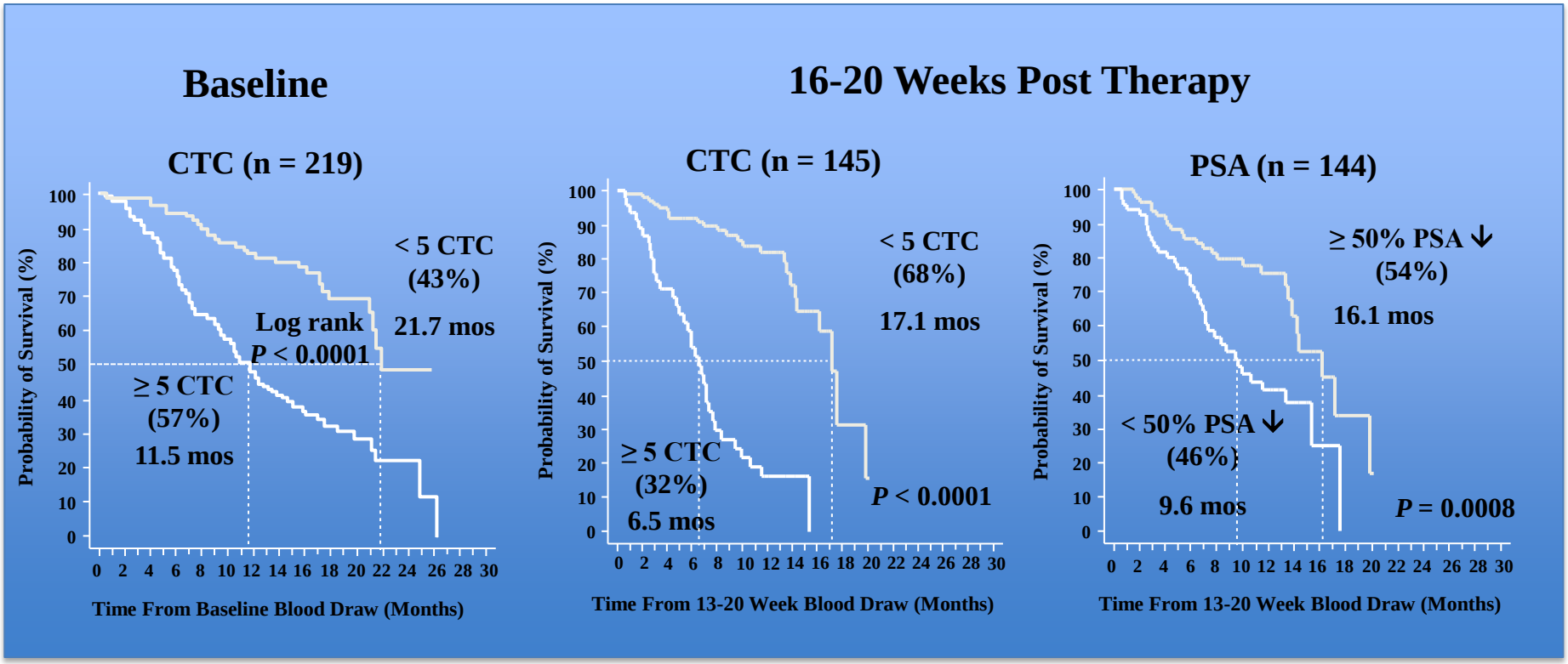
- Analytically Valid and FDA Cleared (Breast, Colorectal, and Prostate)
- Sample must be analysed within 96 hours
- Immunomagnetic selection by anti-EpCAM MAB bound to ferrofluids
- Immunofluorescence for CTC identification

Tibbe AG et al, Nature Biotechnology, 1999

Identification of CTC



In Chemotherapy-Treated Patients, CTC Number Is Prognostic For Survival Pre-treatment and More Prognostic Post-treatment Than a > 50% Decline in PSA



The results lead to a 510K clearance, but did not establish surrogacy as an efficacy-response biomarker

de Bono JS, et al. Clin Cancer Res. 2008;14:6302.

The Treatment Effect of Abiraterone on Survival could be explained by a Biomarker Panel including CTC and LDH

Baseline CTC ≥ 5		
	Week 12 (n = 321, CPE = 0.71 [SE = 0.014])	
Model Factors	**HR (95% CI)**	**p Value**
Treatment	**1.030 (0.773, 1.372)**	**0.8371**
LDH_FC	1.252 (1.047, 1.497)	0.0135
LDH_BL	**3.036 (2.276, 4.048)**	**<0.0001**
CTC Conversion	**0.386 (0.284, 0.527)**	**<0.0001**
CTC_BL	1.135 (0.987, 1.306)	0.0747

Landmark analysis; CTC Conversion: Baseline ≥ 5 and post-baseline < 5;
BL, Baseline; FC, Fold change defined as post-baseline/baseline value.

Scher et al, ASCO 2011