Androgens and prostate cancer: insights from abiraterone acetate and other novel agents

Ian Davis

Ludwig Institute for Cancer Research

Austin Health, Melbourne, Australia

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Prostate cancer

- Most common cancer in Australia:
  - 14.5% of all cancers (colorectal 13.5%, breast 12.8%)
  - Estimated 17,444 new cases in 2006
  - 2938 deaths in 2007
  - Highest incidence in the world
- Marked variation globally, most common in “developed” countries
- Global estimates:
  - 14% (903,500) of the total new cancer cases in 2008
  - 6% (258,400) of cancer deaths in males in 2008
- US estimates:
  - 230,900 new cases in 2004
  - 29,900 deaths
  - 1/6 men will get it
  - 1/32 will die of it

http://www.cancervic.org.au/
Jemal A et al. (2011). http://dx.doi.org/10.3322/caac.20107
AIHW data 2010

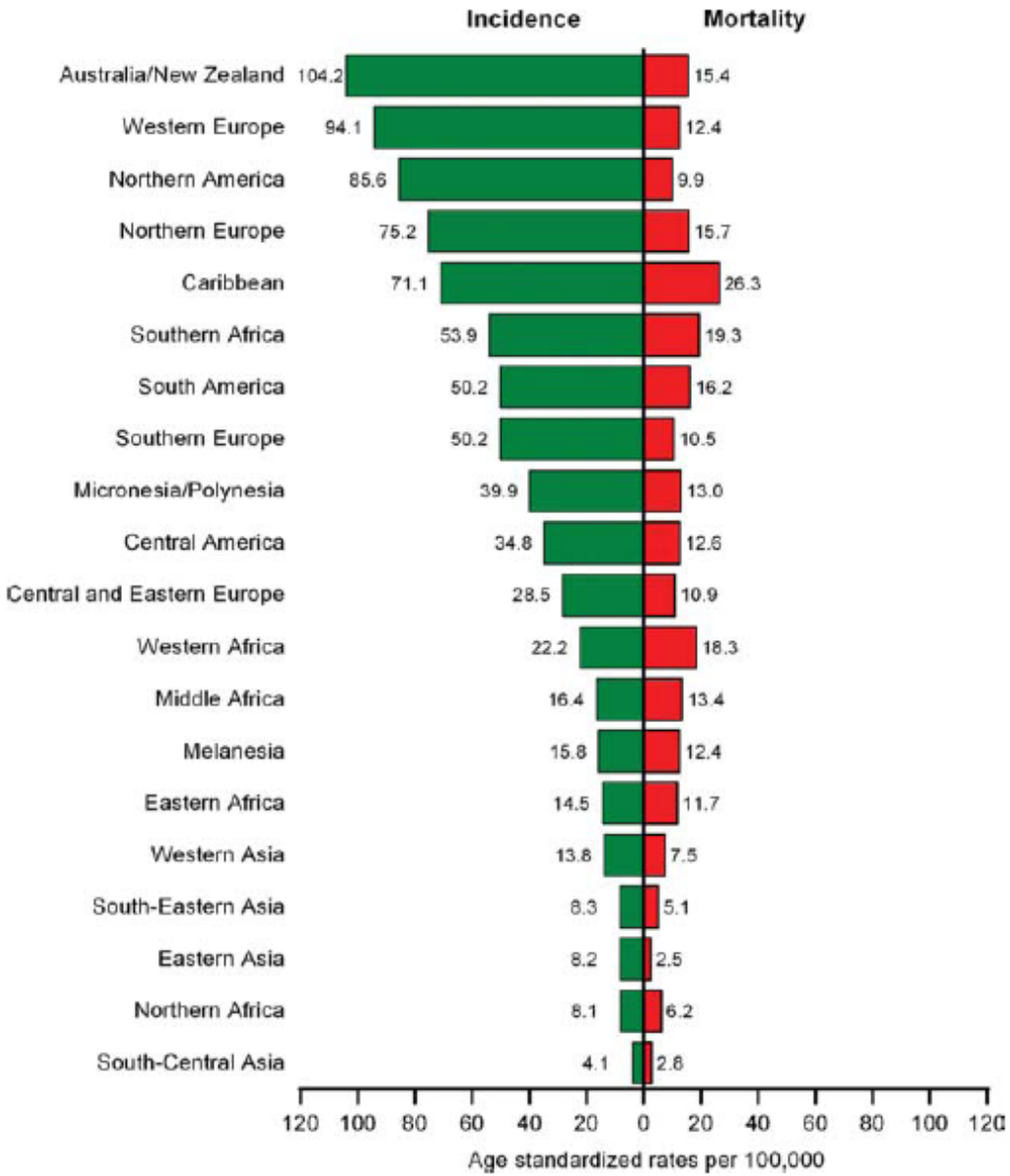


FIGURE 7. Age-Standardized Prostate Cancer Incidence and Mortality Rates by World Area. Source: GLOBOCAN 2008.

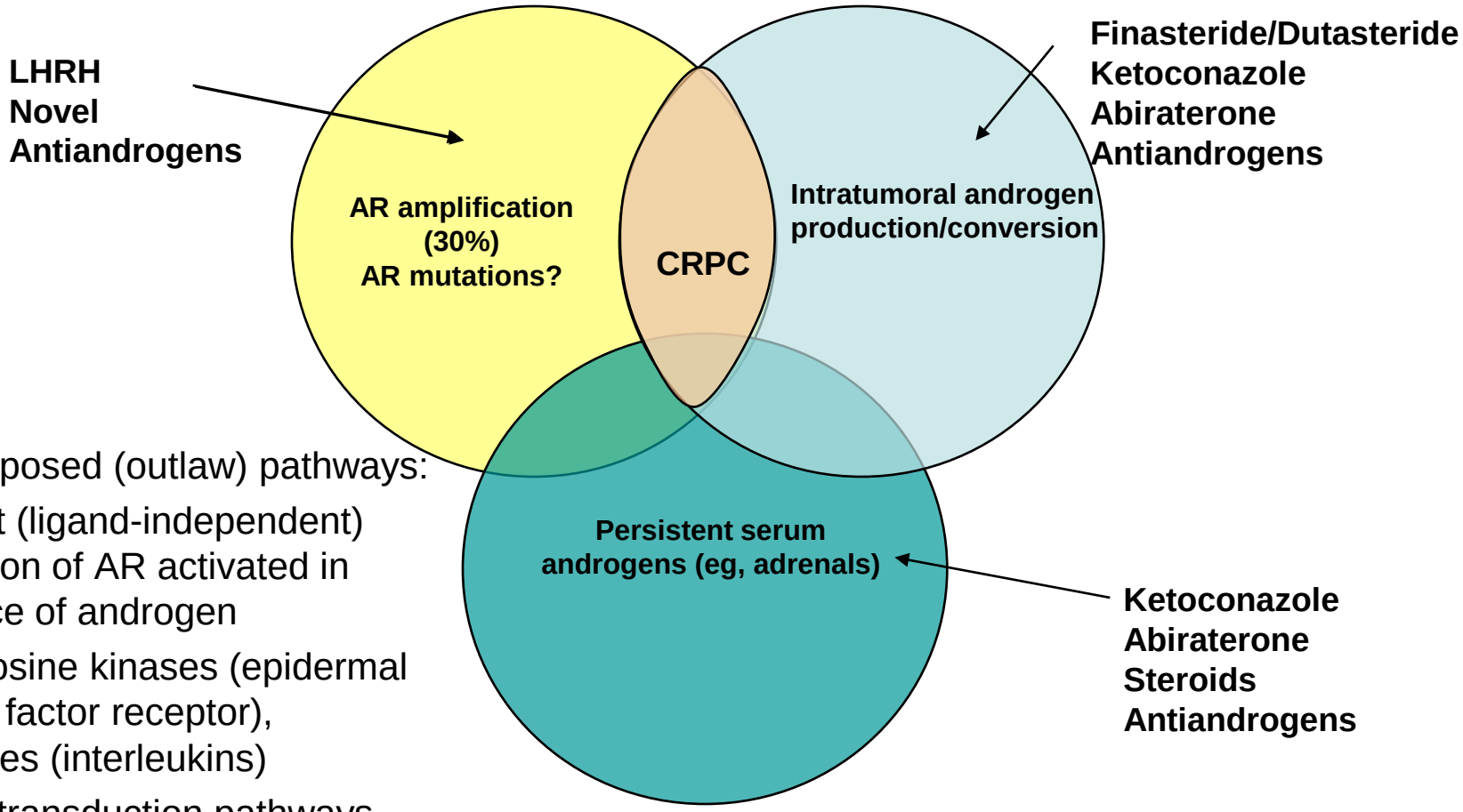
Jemal A et al. (2011). CA: A Cancer Journal for Clinicians. http://dx.doi.org/10.3322/caac.20107

CRPC and androgen receptor (AR)

- CRPC remains driven by ligand-dependent AR activation
  - Tumor cells can generate their own androgens
  - Enzymes involved in steroidogenesis are increased
  - Paracrine production and de novo synthesis of testosterone and dihydrotestosterone
- Enhanced survival/growth:
  - Increased number of androgen receptors (ARs)
  - Increased production of coactivators and decreases corepressors, which sensitize the AR to androgens
  - Mutations in the AR may sensitize it to other androgen and nonandrogen ligands

Attard et al, Cancer Cell, 2009; Locke et al, Cancer Res, 2008; Holzbeierlein et al, Am J Pathol, 2004; Gregory CW et al. Cancer Res. 2001;61:2892-2898. Chen CD et al. Nature Med. 2004;10(1):33-39;Pienta KJ, Bradley D. Clin Cancer Res. 2006;12(6):1665-1671.

Androgen Resistance: Overlapping mechanisms

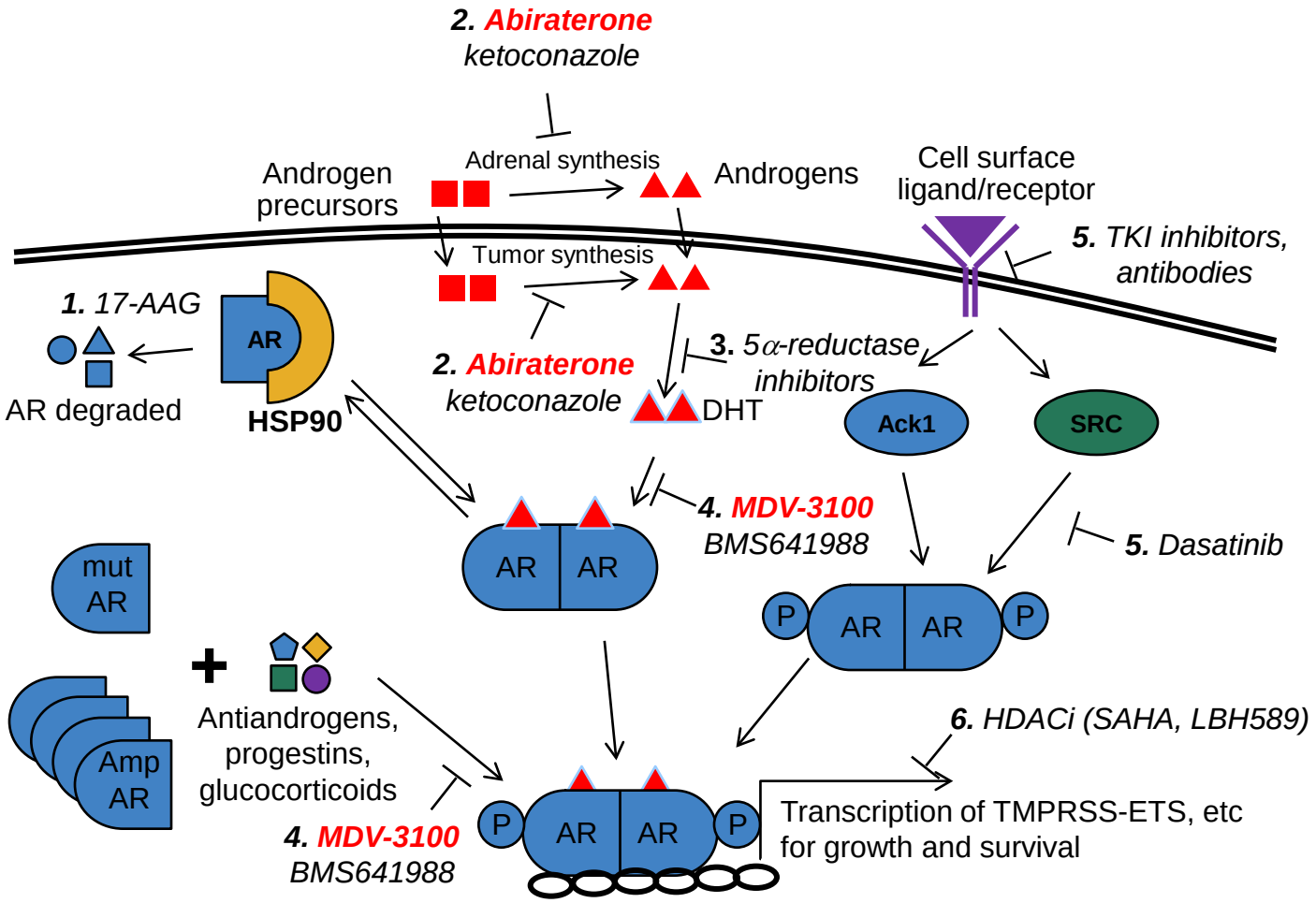


Other proposed (outlaw) pathways:

- Indirect (ligand-independent) activation of AR activated in absence of androgen
- Via tyrosine kinases (epidermal growth factor receptor), cytokines (interleukins)
- Signal transduction pathways nuclear factor-κB
- Apoptotic pathways

Modified from: Van Allen EM, Ryan CJ. *Curr Opinion Urol*. 19:315-321. Bonkoff H, Berges R. *Prostate.* 2010;70:100-112.

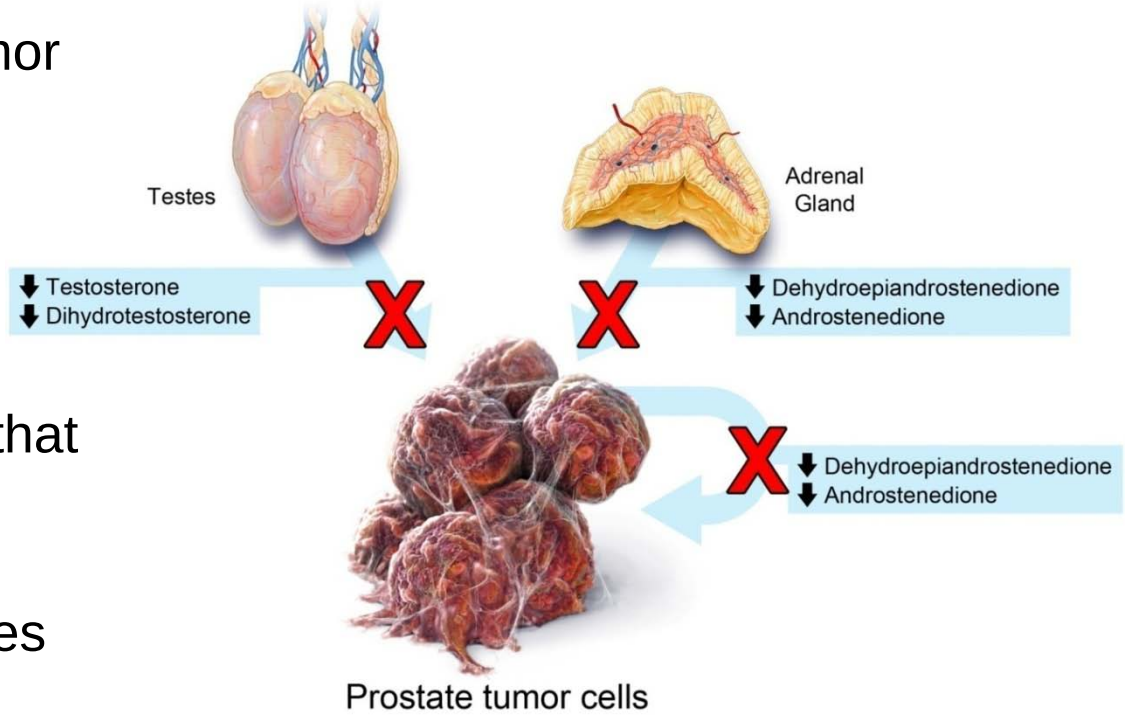
Multiple mechanisms of action: points of targeted intervention in AR pathways



From: Chen Y et al. *Curr Opin Pharmacol.* 2008;8:440-448.

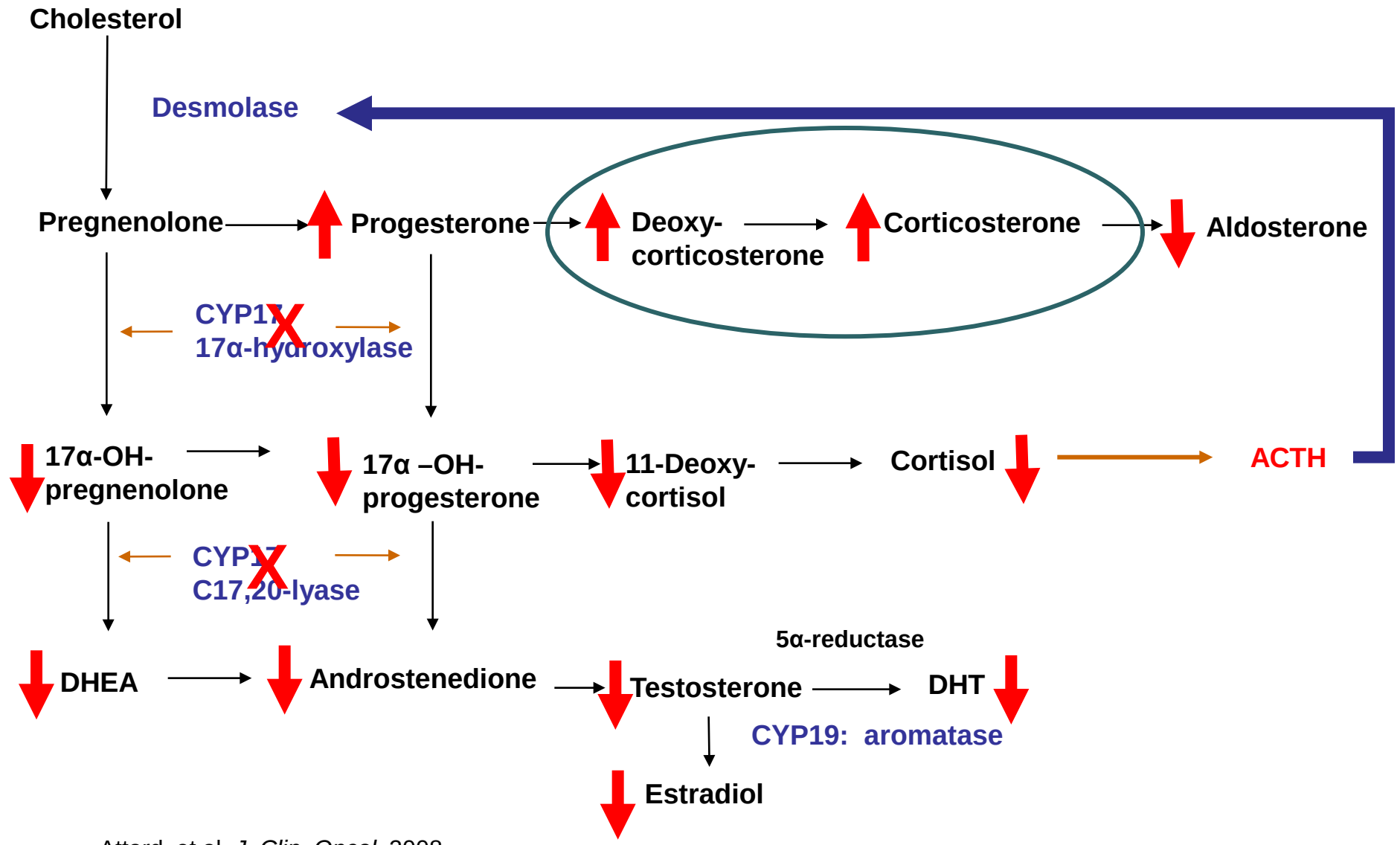
Abiraterone acetate: androgen biosynthesis inhibitor

- Androgens produced at 3 critical sites lead to tumor proliferation:
  - Testes
  - Adrenal gland
  - Prostate tumor cells
- Abiraterone inhibits biosynthesis of androgens that stimulate tumor cell growth
- PSA and radiographic responses in phase 2 studies of CRPC
  - Chemo-naïve and post-chemo patients



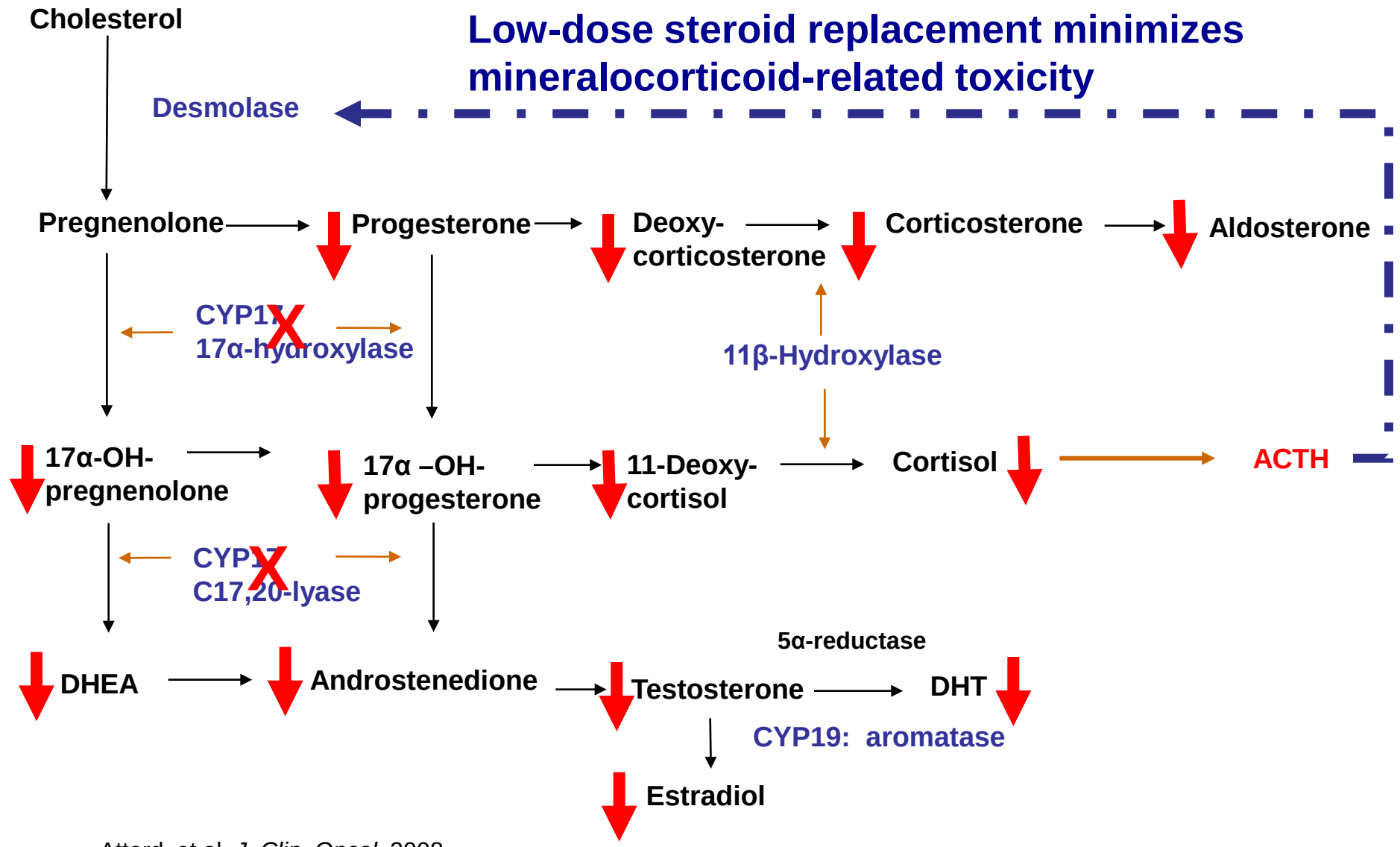
Attard G et al, *J Clin Oncol*, 2008; Attard G et al. *J Clin Oncol*. 2009; Reid AH et al. *J Clin Oncol*. 2010; Ryan C et al, *J Clin Oncol*, 2009; Danila D et al, *J Clin Oncol*, 2010.

Steroid Synthesis



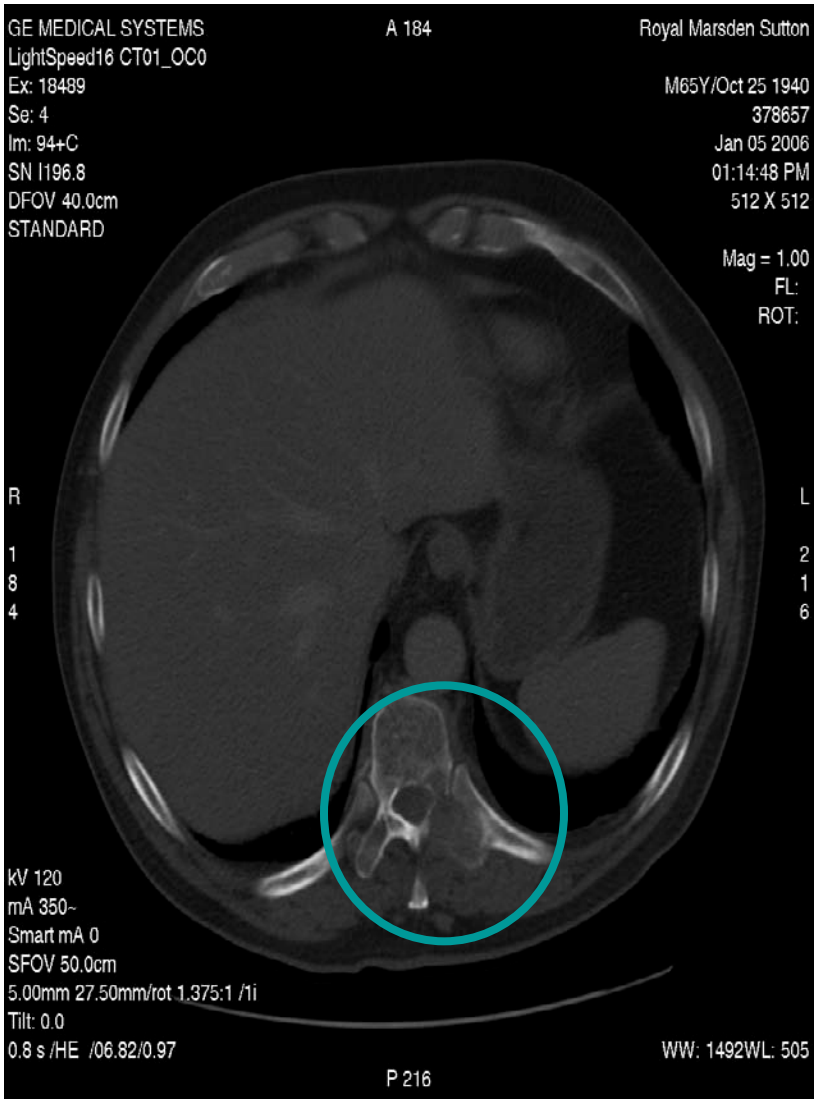
Attard, et al, *J. Clin. Oncol*. 2008

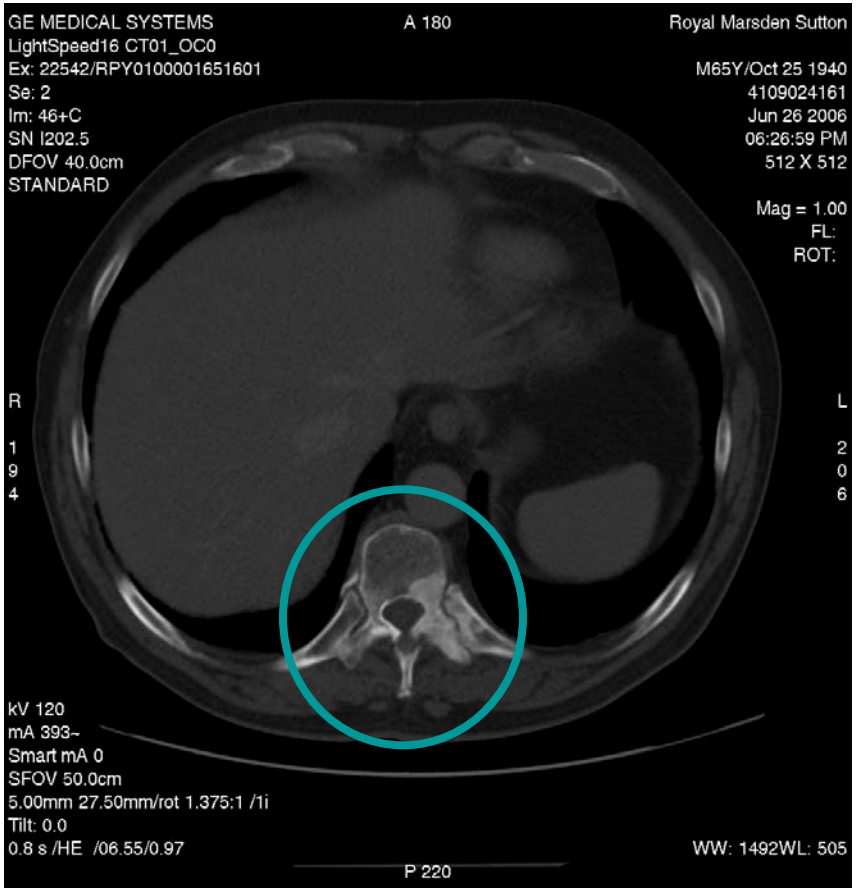
Steroid Synthesis



Attard, et al, *J. Clin. Oncol*. 2008

Study 001 Phase 1, Chemo-Naïve CRPC: Improves Bone Disease and Resolution of Pain

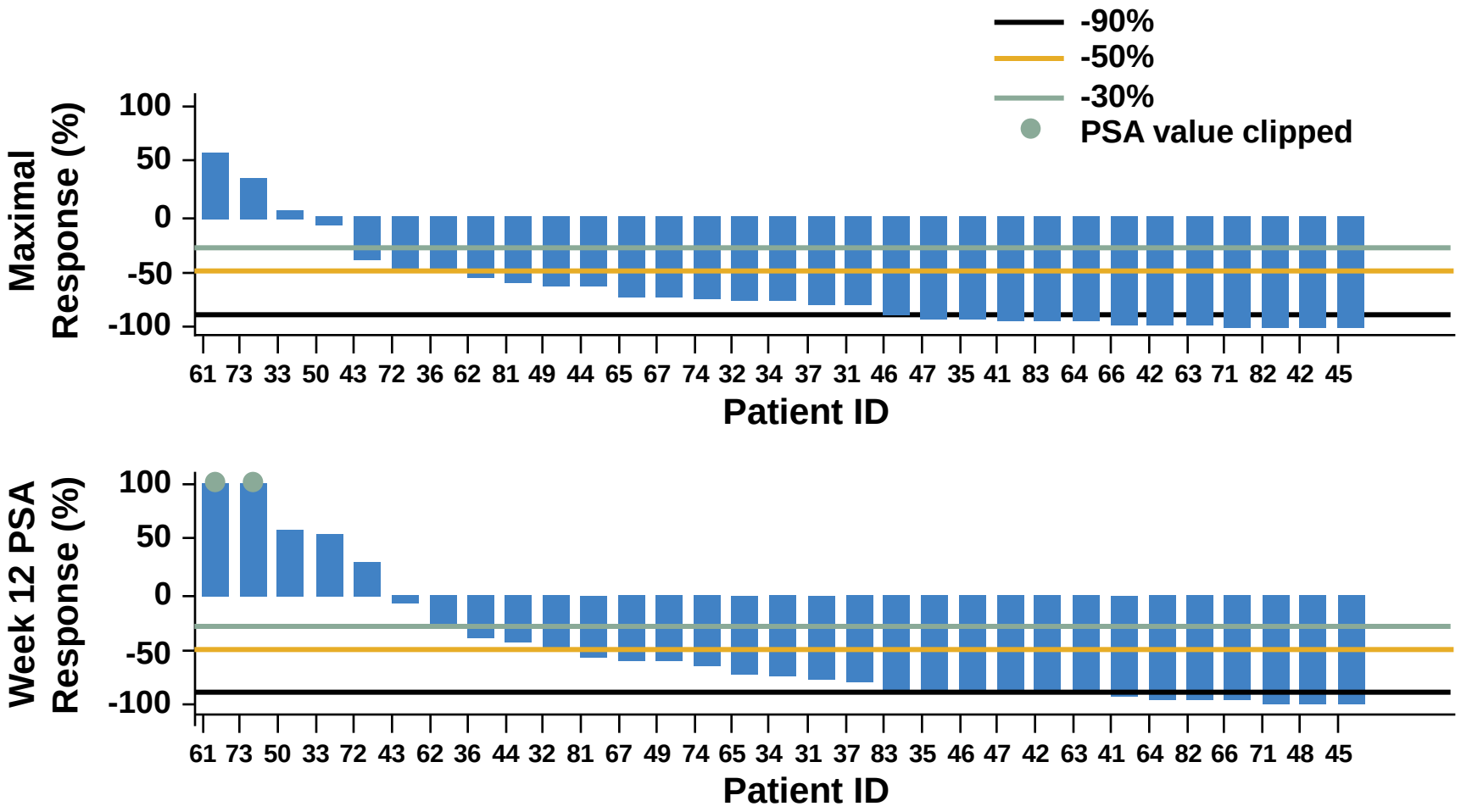




Patient on abiraterone acetate treatment for more than 12 months

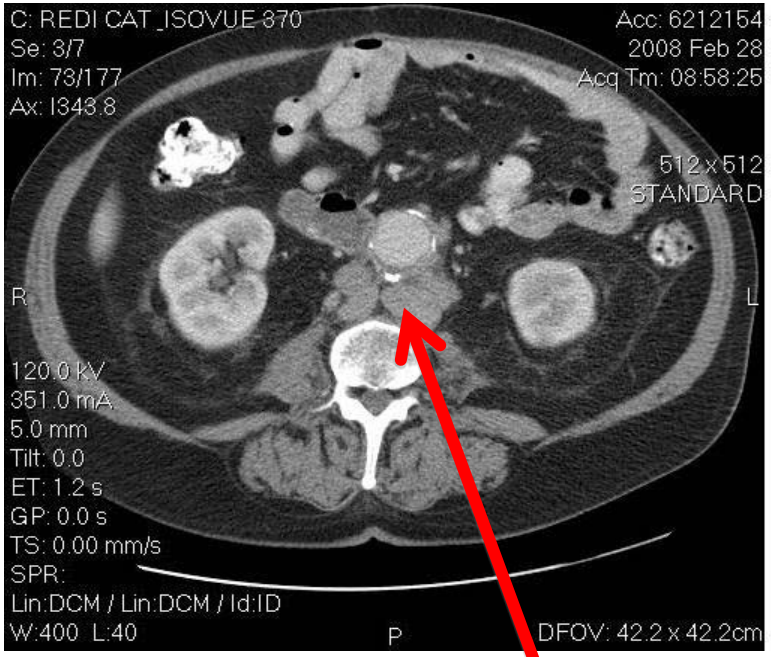
Attard G. *J Clin Oncol.* 2009;27:3742-3748.

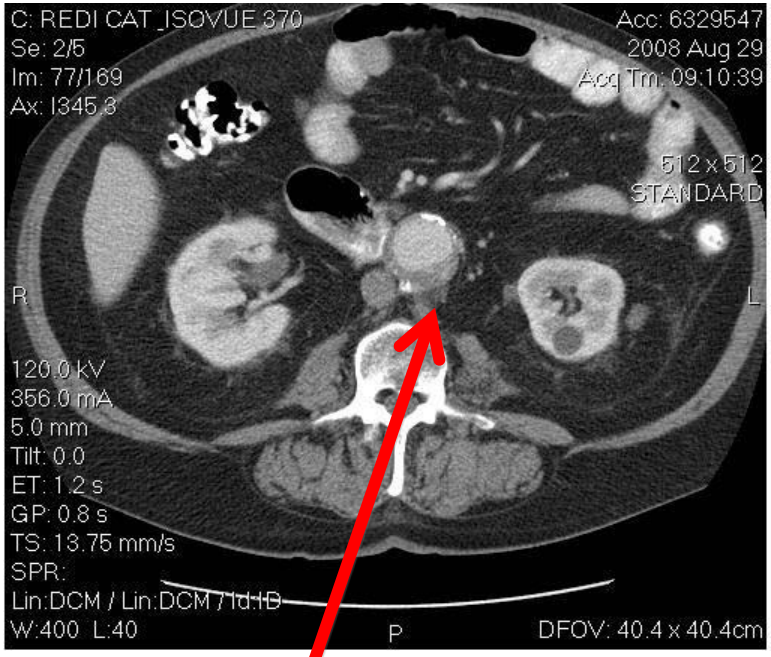
Study 002 Phase 2: Significant activity in chemo-naïve patients



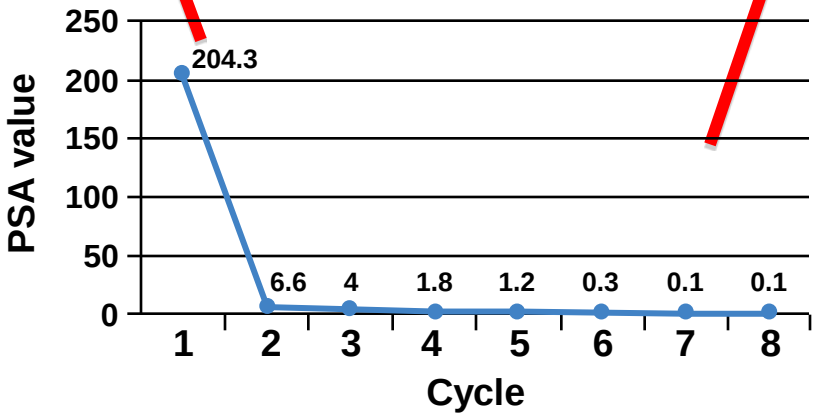
Ryan CJ et al. *J Clin Oncol.* 2010;28(suppl). Abstract 4671.

Study 002 Phase 2: Representative case of objective response with PSA decline





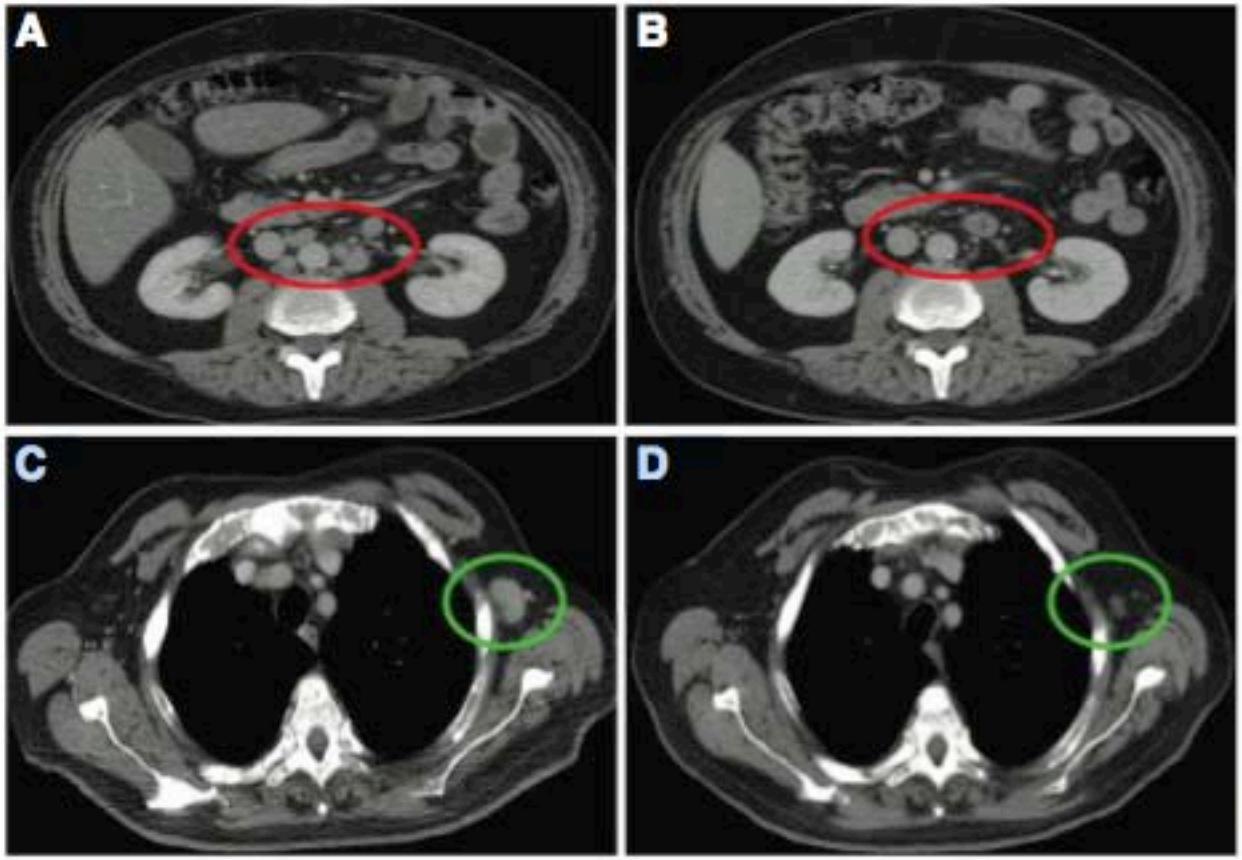
At Baseline

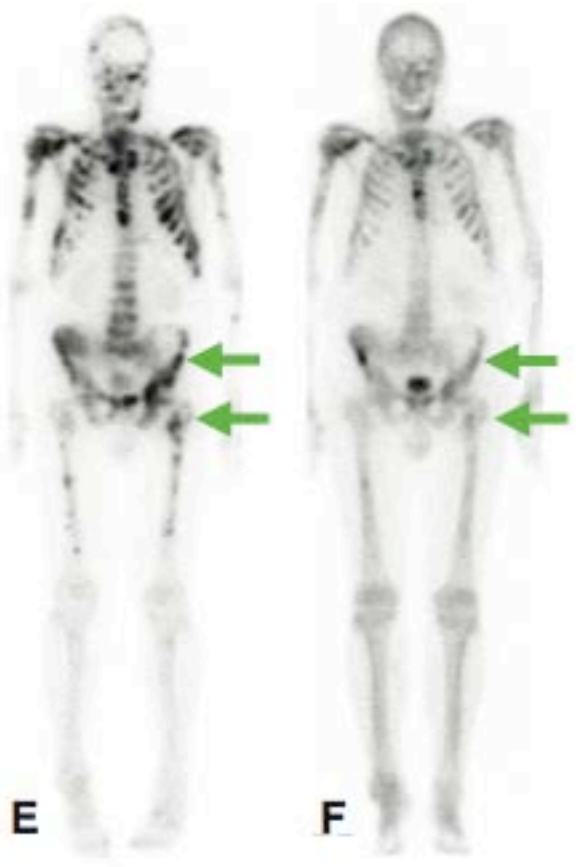


At Post Cycle 6

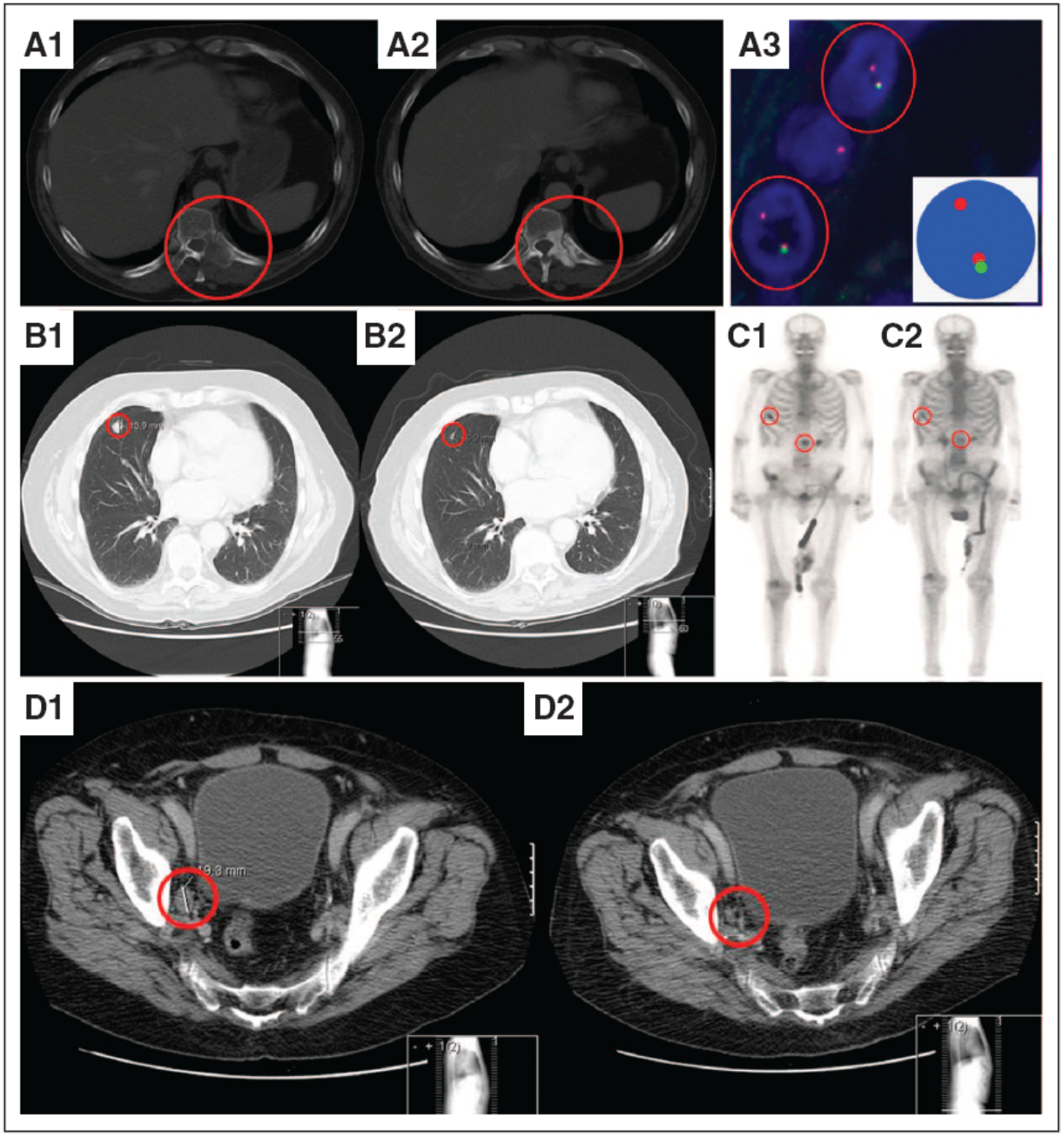
Unpublished data.

Study 003 Phase 2: Measurable disease responses



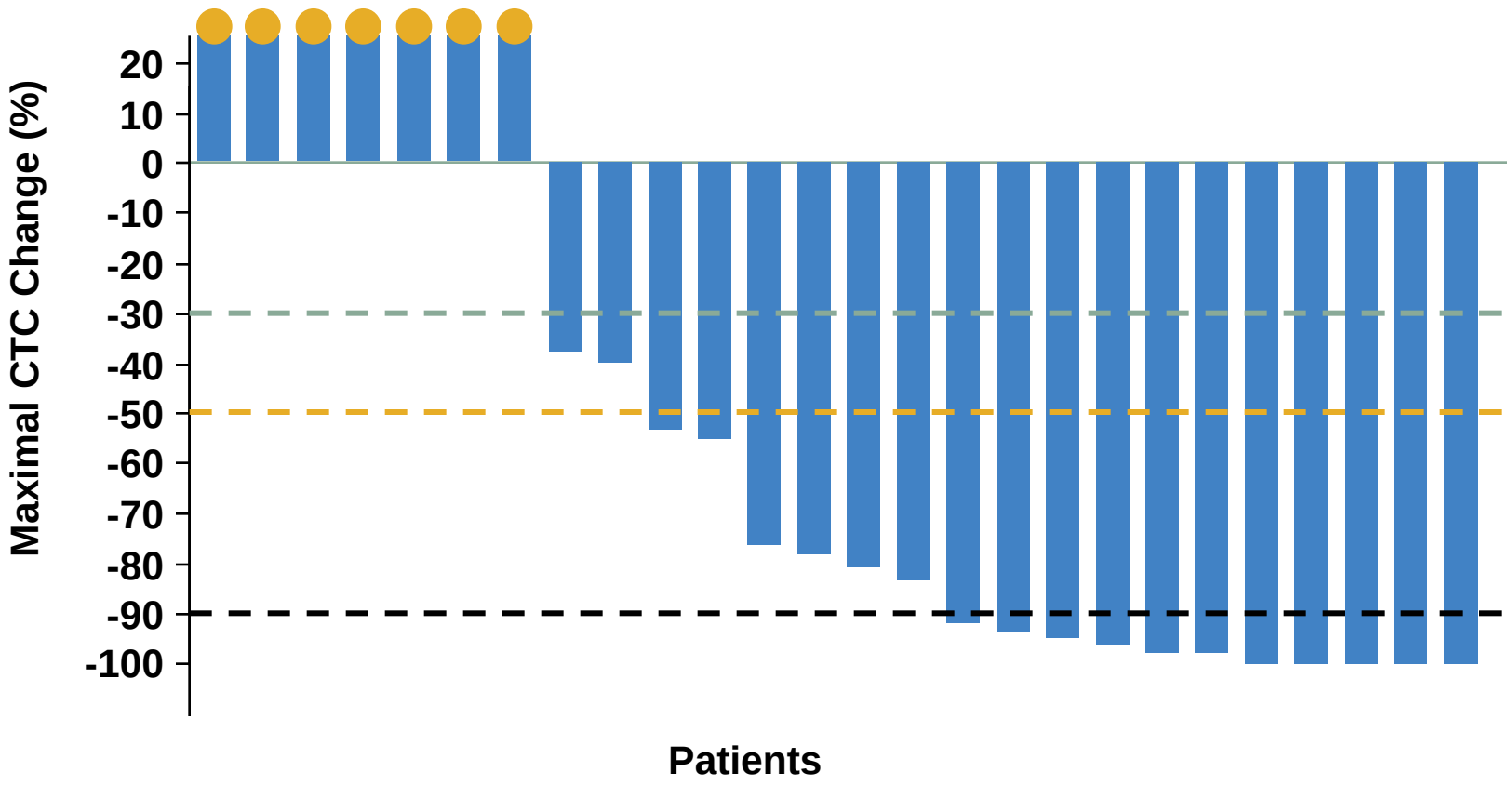


Reid AHM et al. *J Clin Oncol.* 2010;28:1489-1495.



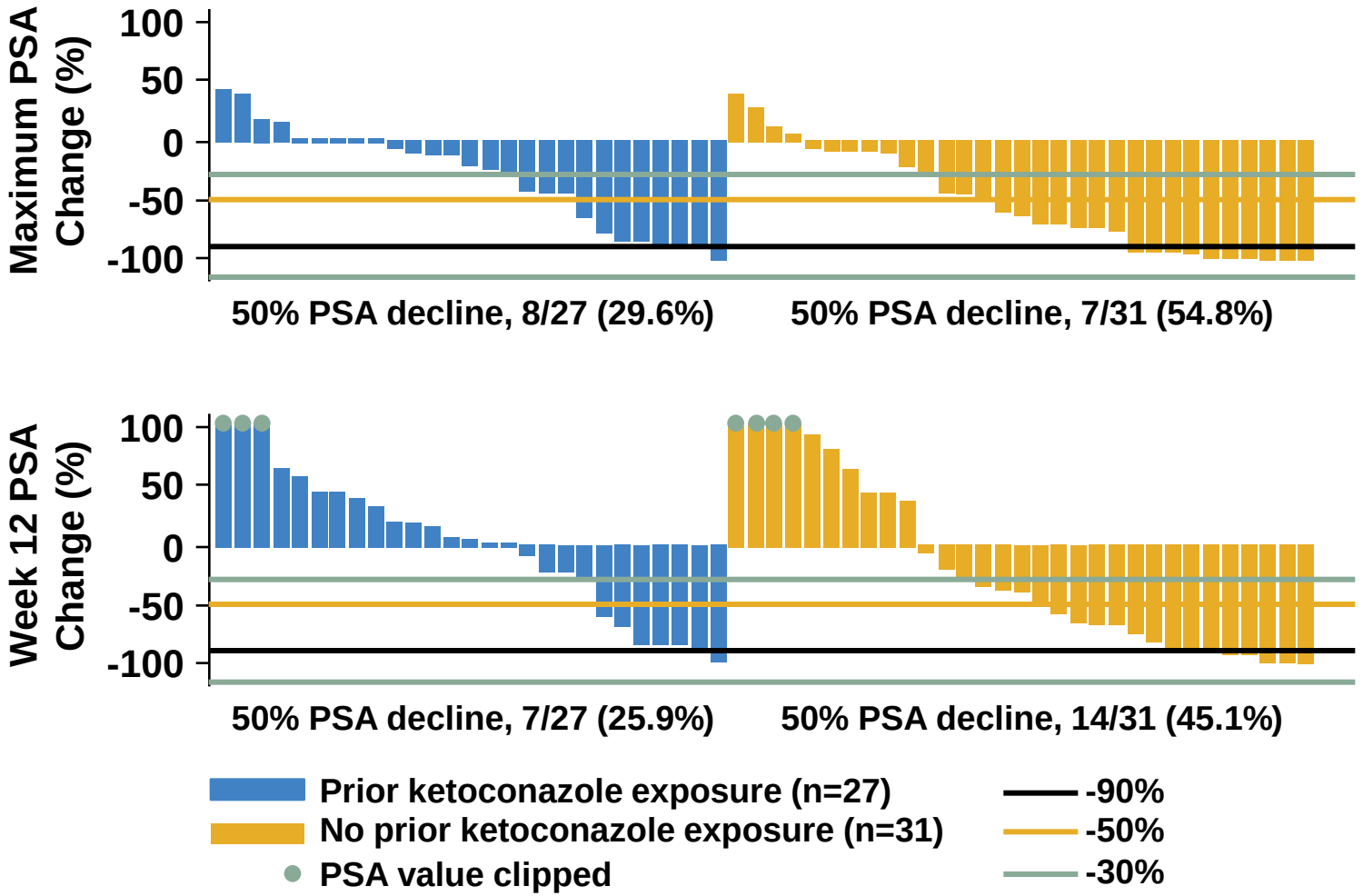
Attard G et al. JCO 26:4563-71, 2008

Study 003 Phase 2: Circulating Tumor Cell (CTC) Count



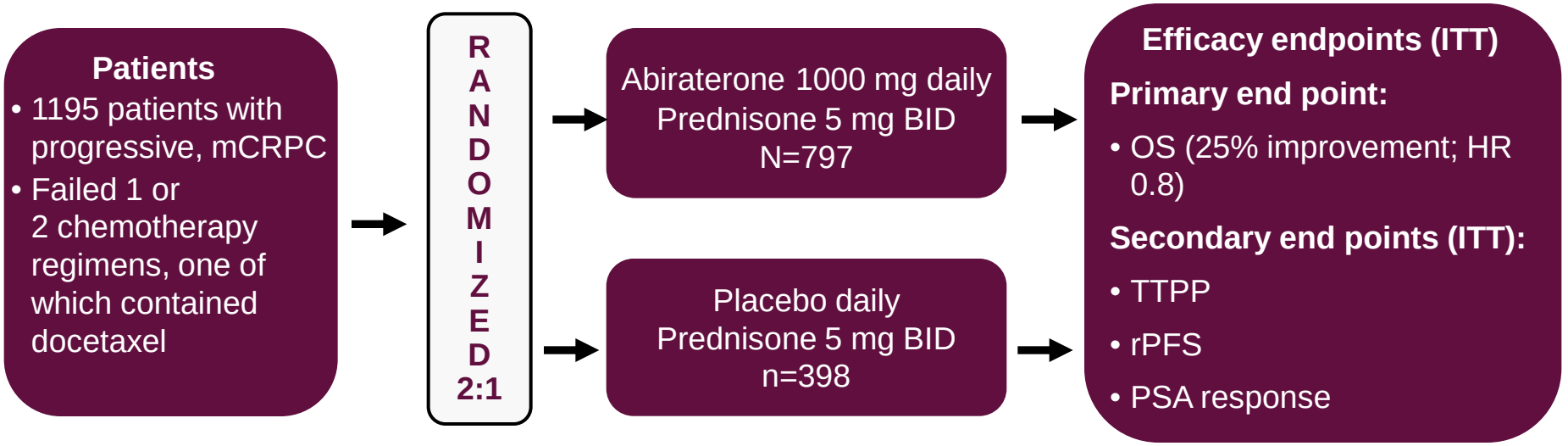
Reid AHM et al. *J Clin Oncol.* 2010;28:1489-1495.

Study 004 Phase 2: Significant Activity in CRPC Patients with Prior Docetaxel



Danila DC et al. *J Clin Oncol.* 2010;28:1496-1501.

COU-AA-301 Study Design



- **Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)**
- **Stratification according to:**
  - **ECOG performance status (0-1 vs. 2)**
  - **Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])**
  - **Prior chemotherapy (1 vs. 2)**
  - **Type of progression (PSA only vs. radiographic progression with or without PSA progression)**
- **Data presented from interim analysis**

Clinicaltrials.gov identifier: NCT00638690.

COU-AA-301 Baseline Demographics

	AA (n = 797)	Placebo (n = 398)	Total (n = 1195)
Median age, years (range)	69.0 (42-95)	69.0 (39-90)	69.0 (39-95)
Race			
White	93.3%	92.7%	93.1%
Black	3.5%	3.8%	3.6%
Asian	1.4%	2.3%	1.7%
ECOG-PS 2	10.7%	11.1%	10.8%
Significant pain present	44.3%	44.0%	44.2%
2 Prior chemotherapies	28.2%	28.4%	28.3%
Radiographic Progression	70.1%	68.6%	69.6%

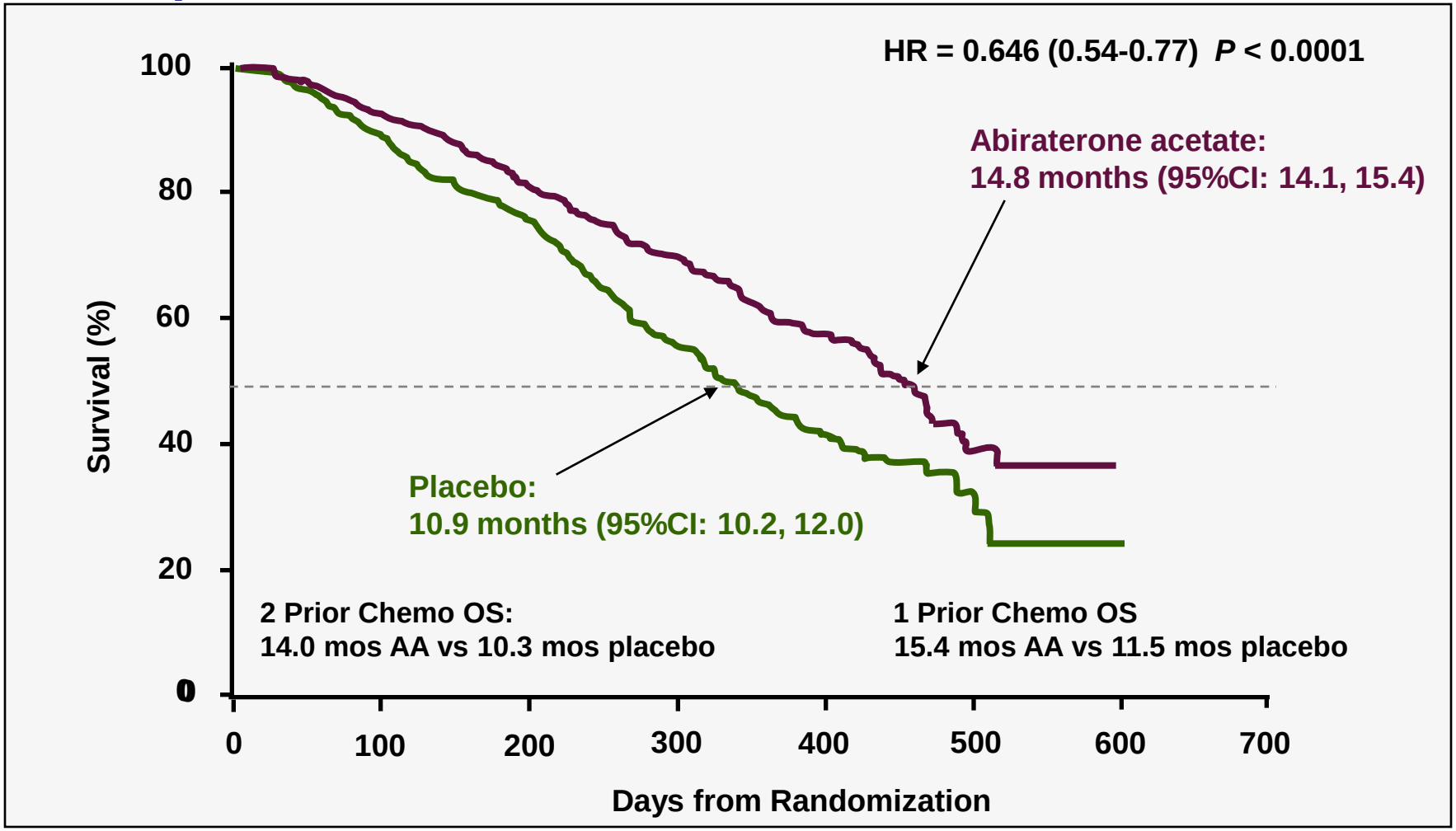
COU-AA-301 Baseline Disease Characteristics (1)

	AA (n = 797)	Placebo (n = 398)
Extent of disease		
Bone	**89.2%**	**90.4%**
Node	**45.4%**	**41.5%**
Visceral Metastasis	**29.0%**	**24.1%**
Liver	**11.3%**	**7.6%**
Lung	**13.0%**	**11.4%**
Other Visceral	**5.8%**	**5.3%**

COU-AA-301: All Secondary End Points Achieved Statistical Significance

	AA (n = 797)	Placebo (n = 398)	HR 95% CI	*P* Value
TTPP (months)	**10.2**	**6.6**	**0.58 (0.46, 0.73)**	**< 0.0001**
rPFS (months)	**5.6**	**3.6**	**0.67 (0.59, 0.78)**	**< 0.0001**
PSA response rate				
Total	**38.0%**	**10.1%**		**< 0.0001**
Confirmed	**29.1%**	**5.5%**		**< 0.0001**

COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC



AA	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

COU-AA-301: AEs of Special Interest

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	**30.5%**	**2.3%**	**22.3%**	**1.0%**
Hypokalemia	**17.1%**	**3.8%**	**8.4%**	**0.8%**
LFT abnormalities	**10.4%**	**3.5%**	**8.1%**	**3.0%**
Hypertension	**9.7%**	**1.3%**	**7.9%**	**0.3%**
Cardiac disorders	**13.3%**	**4.1%**	**10.4%**	**2.3%**

LFT, liver function test

OS Benefit in Recent CRPC Trials

Trial/ Agent Approved	Disease state	Comparator	Hazard Ratio	*P* value
IMPACT (Provenge vaccine) 2010	Chemo-näive CRPC	Placebo	0.775	0.032
TAX327 (Docetaxel) 2004	Chemo-näive CRPC	Mitoxantrone Prednisone	0.76	0.009
TROPIC (Cabazitaxel) 2010	Post-Docetaxel CRPC	Mitoxantrone Prednisone	0.70	<0.0001
COU-AA-301 (Abiraterone acetate) 2010	Post-Docetaxel CRPC	Placebo Prednisone	0.646	<0.0001

COU-AA-301 Conclusions (1)

AA prolongs OS in patients with mCRPC who have progressed after docetaxel-based chemotherapy

- AA plus prednisone significantly improves TTPP, rPFS, and PSA response rate
  - 35% risk reduction of death (HR = 0.65)
  - Median OS improvement with AA of 14.8 vs 10.9 months with placebo
  - 36% improvement in median OS
  - For patients with 1 prior chemo regimen
    - Median OS improvement with AA of 15.4 vs 11.5 months with placebo (HR = 0.63)
  - Median time to PSA progression and median time to rPFS significantly improved

COU-AA-301 Conclusions (2)

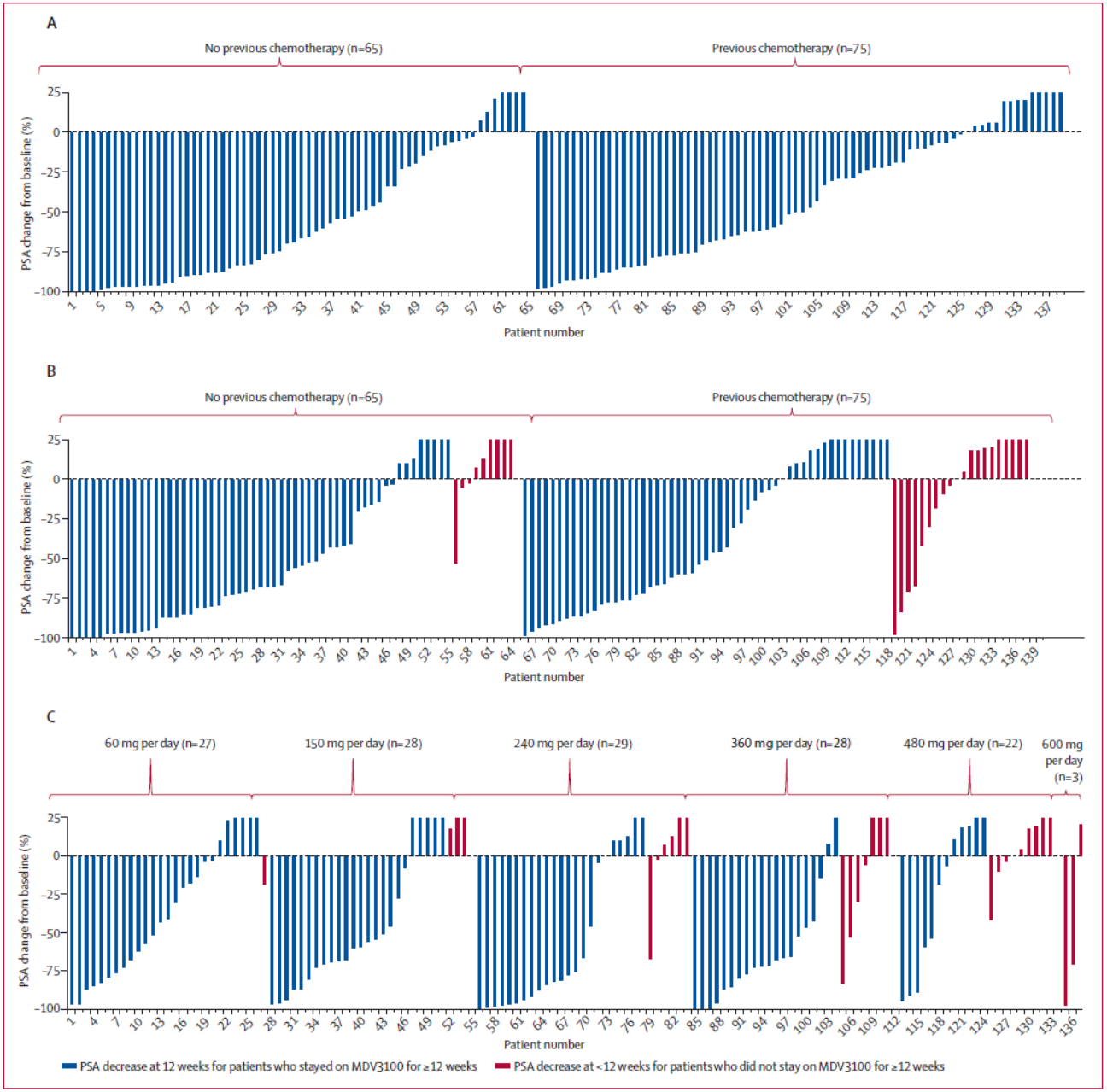
- Abiraterone is well tolerated without the toxicity of chemotherapy
  - AEs more common with AA included:
    - Fluid retention
    - Hypokalemia
    - LFT abnormalities
    - Hypertension
- Inhibition of persistent androgen synthesis and AR mediated signaling with abiraterone acetate improves survival and represents a new treatment option for CRPC

MDV3100

Maximum decrease from baseline

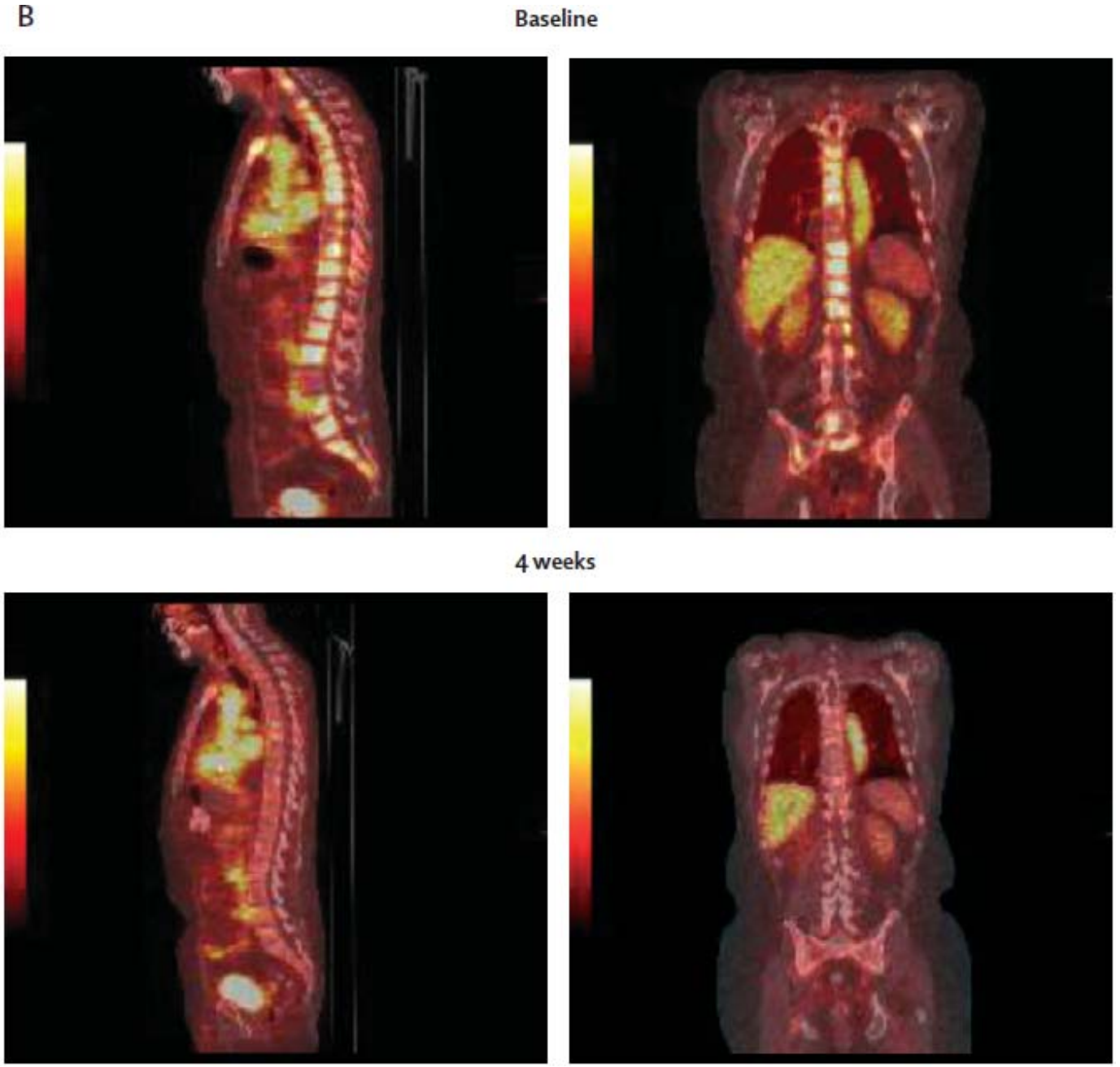
Decrease from baseline at 12 weeks

12 week decreases by dose



Scher HI et al. The Lancet 375:1437-46, 2010

MDV3100



^{18}F-FDHT PET

Scher HI et al. The Lancet 375:1437-46, 2010

Conclusions

- CRPC is often still dependent on AR
- Novel approaches:
  - Abiraterone: reduction in androgen production
    - Survival benefit after docetaxel
  - MDV3100: potent antiandrogen
    - Results pending
- Issues:
  - Response assessment:
    - RECIST, PSA, bone scan all unreliable
  - Sequencing of treatments
  - Combination treatments
  - Other health effects of androgen deprivation
    - Bone health, metabolic syndrome, psychological