Abiraterone acetate: Targeting CYP17 to treat advanced prostate cancer

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Paris March 2011

Hypothesis

Hypothesis 2004:

- ‘Hormone Refractory’ prostate cancer was NOT hormone refractory but frequently remained driven by a ligand-activated androgen receptor (AR).

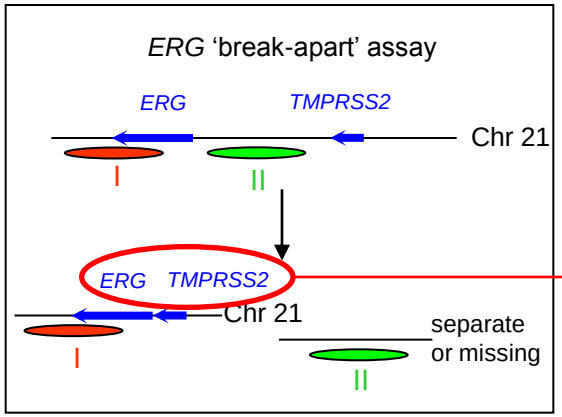
Attard, Belldegrun and de Bono; BJU, 2004
de Bono & Ashworth, Nature 2010

Evidence that AR is a hard habit to break

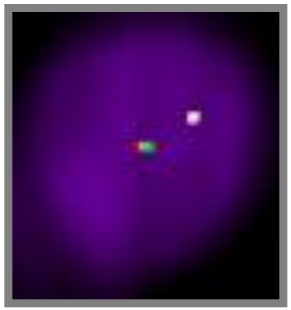
- Hormonal treatments continue to have antitumor activity
- High intratumoral androgens despite castration
  - Preclinical and clinical evidence of intracrine synthesis
- Castration resistance associated with:
  - AR amplification (increased gene dose)
  - AR mutations that increase AR (transcriptional) activity
  - ↑ AR(<2x) expression (ligand driven) in isogenic resistant lines
- Identification of oncogenic translocations/fusions driven by androgens + oestrogen response elements (ETS genes; TMPRSS2/ERG in 50-70% of PC)

Attard, Cooper and de Bono; Cancer Cell, 2009

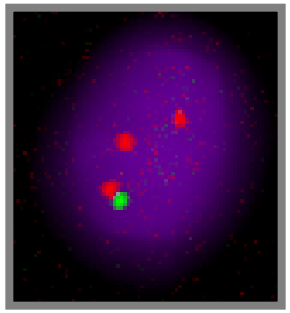
ETS gene rearrangements in Prostate Cancer



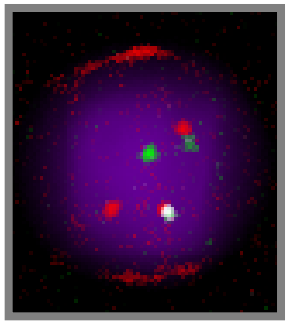
Transcription of ERG becomes regulated by steroid receptors (ARE and ERE)



Class N



Class Edel



Class Esplit

Attard et al, Oncogene 2008; Attard et al Cancer Research 2009

Drug development strategies to target continued AR signaling

- Several strategies to target hormone driven AR
  - Target hormones driving AR signaling
    - Develop inhibitors of intracrine androgenic steroid synthesis
  - Better AR antagonists
    - Can we make a ‘pure’ antagonist (partial agonist effects)?*
  - Target AR chaperones by HSP90i; HDAC6i
  - Tubulin binding drugs!

A new ‘old’ drug for prostate cancer

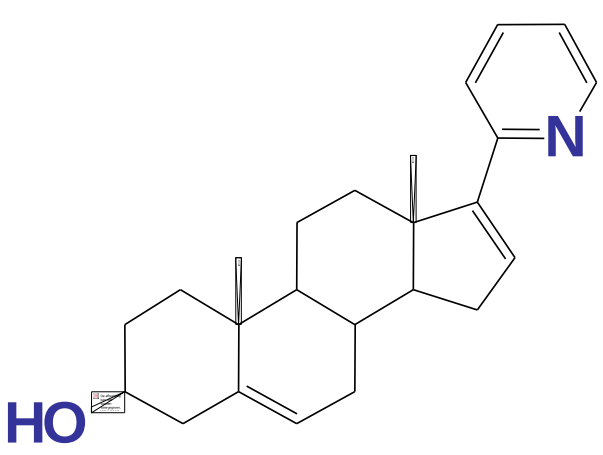
- Drug discovered and made at ICR in 1990s
- First Phase I & II trials performed at RMH
- Results confirmed in multiple US trials
  - Memorial Sloan Kettering, MD Anderson, UCSF
- Abiraterone evaluated in Phase III trials
  - Bought by J&J for $1 billion; regulatory submissions

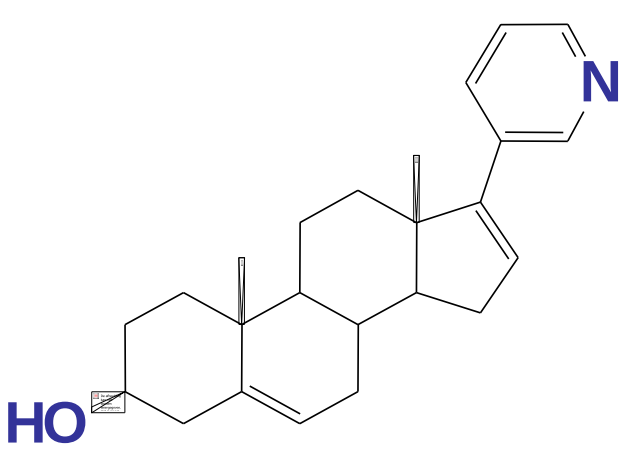
THE ROYAL MARSDEN

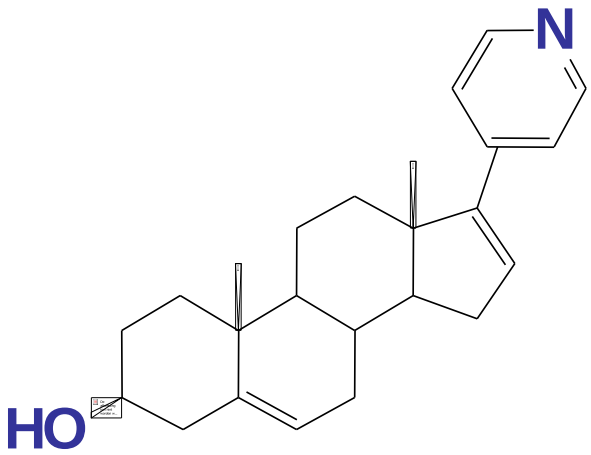
ICR The Institute of Cancer Research | 1909

P450c17 inhibitors: Chemical development

Abiraterone







2-pyridyl

IC_{50} (nm)
lyase 76
hydroxylase 270

3-pyridyl

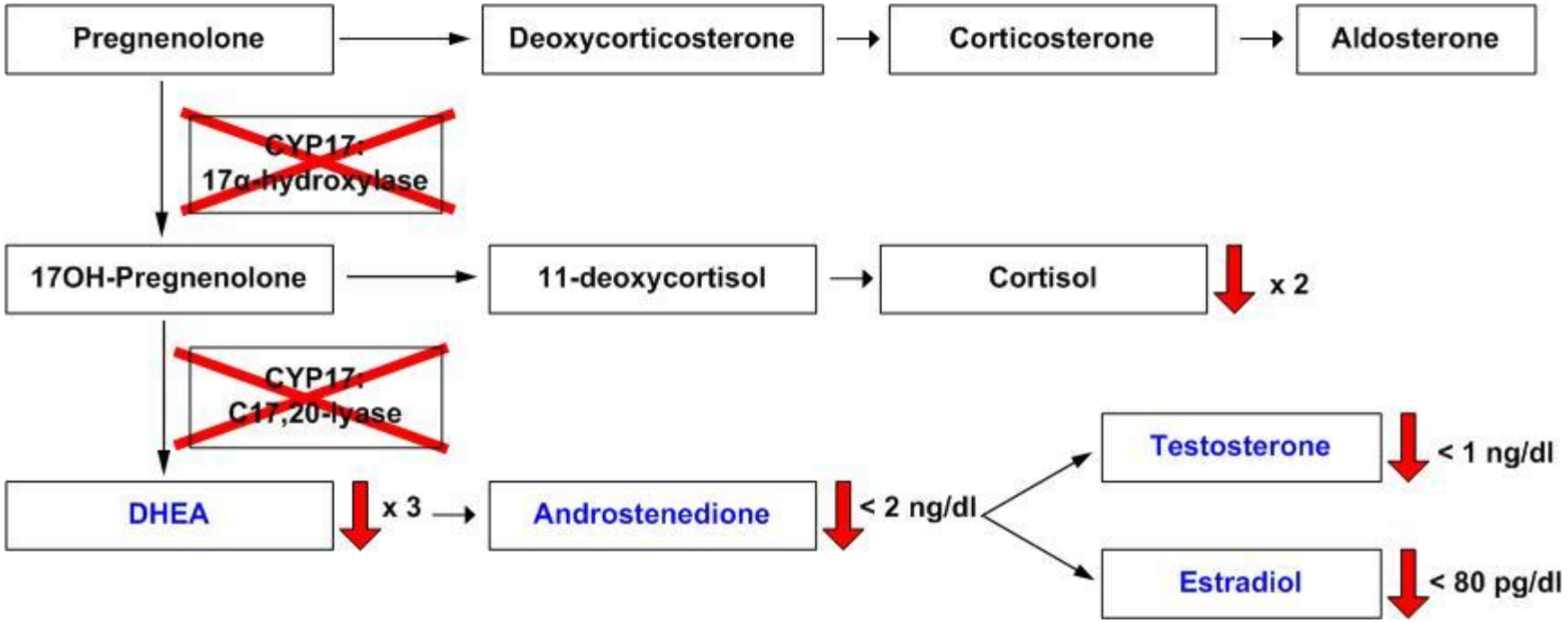
IC_{50} (nm)
lyase 2.9
hydroxylase 4

4-pyridyl

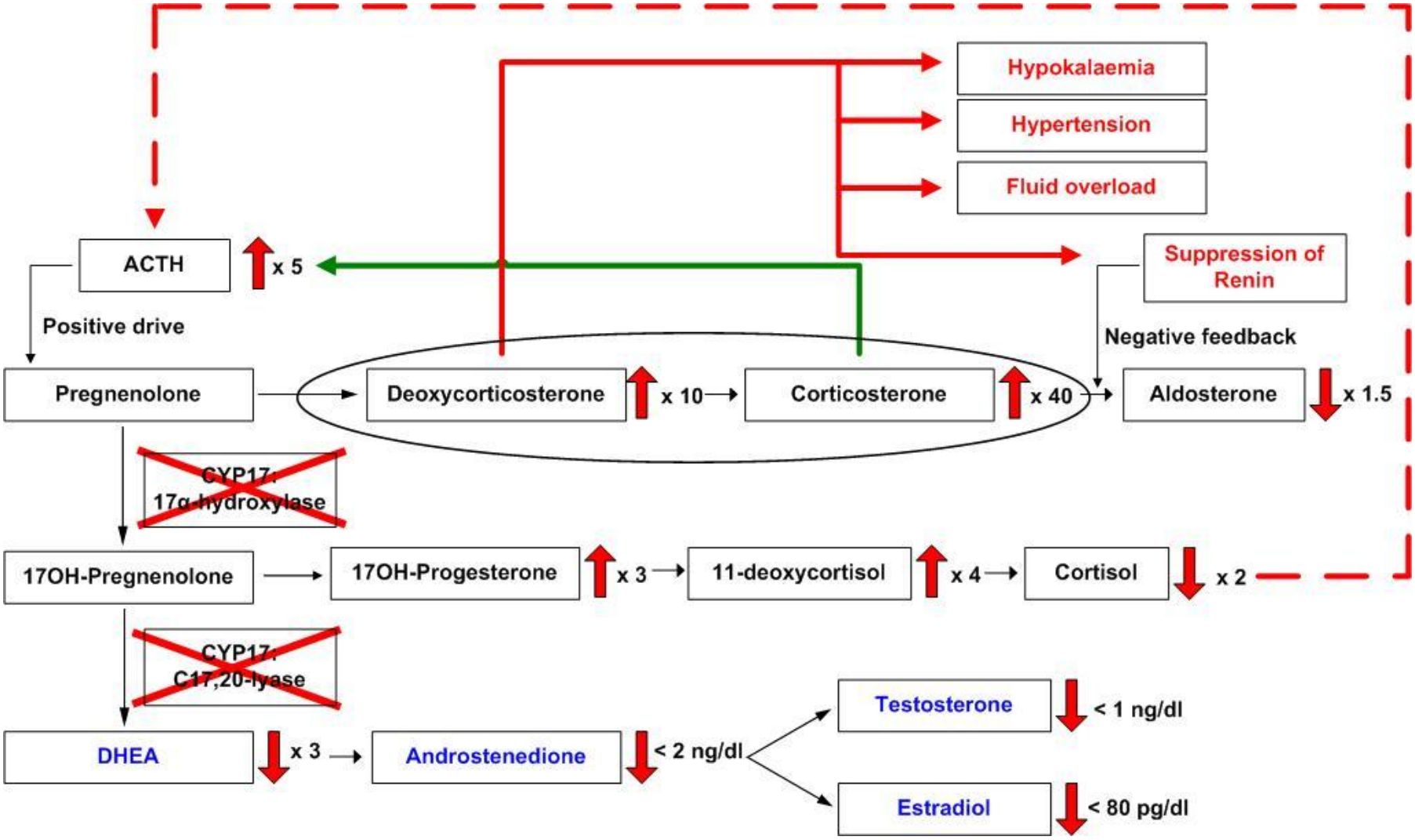
IC_{50} (nm)
lyase 1000
hydroxylase 4000

Developed at The Institute of Cancer Research: Jarman M, Potter G, Barrie E

Mechanism of action of abiraterone



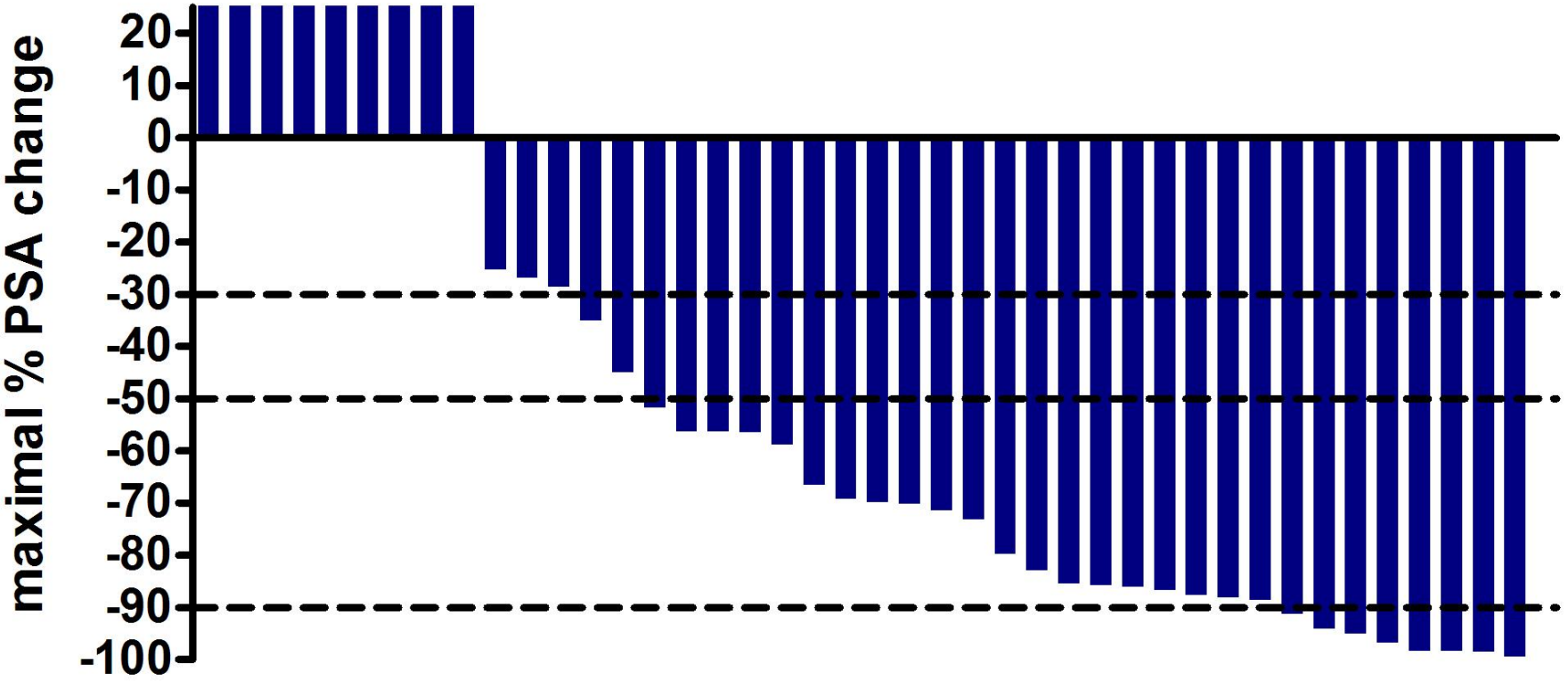
Mechanism of action of abiraterone



Phase I/II Study

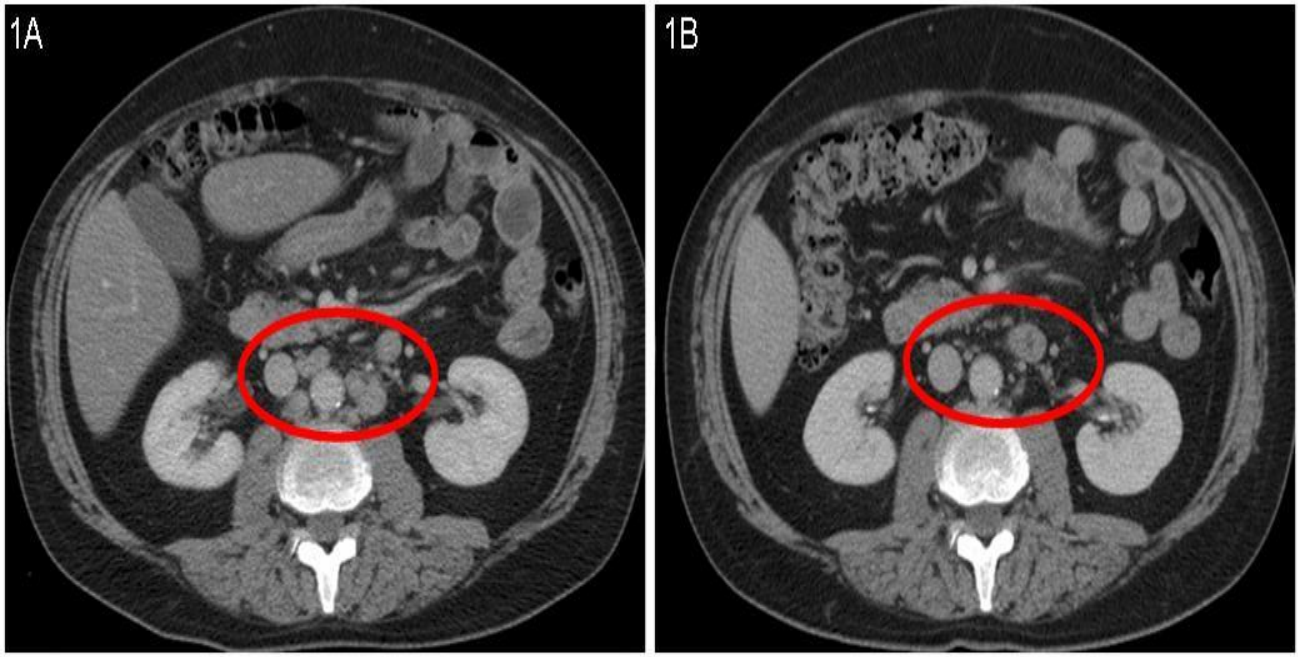
- Continuous daily dosing
  - 250mg/day to 2000mg/day fasted
- Abiraterone administered without steroids
  - Mineralocorticoid antagonist eplerenone utilized
- No dose limiting toxicity
- Satisfactory dose-proportional pharmacokinetics
- Pharmacodynamic endocrine data
  - Falls in hormone levels below CYP17; increases in hormone levels above CYP17; falls in PSA; CTC

PSA declines with abiraterone acetate: Patients who had failed all hormonal Rx

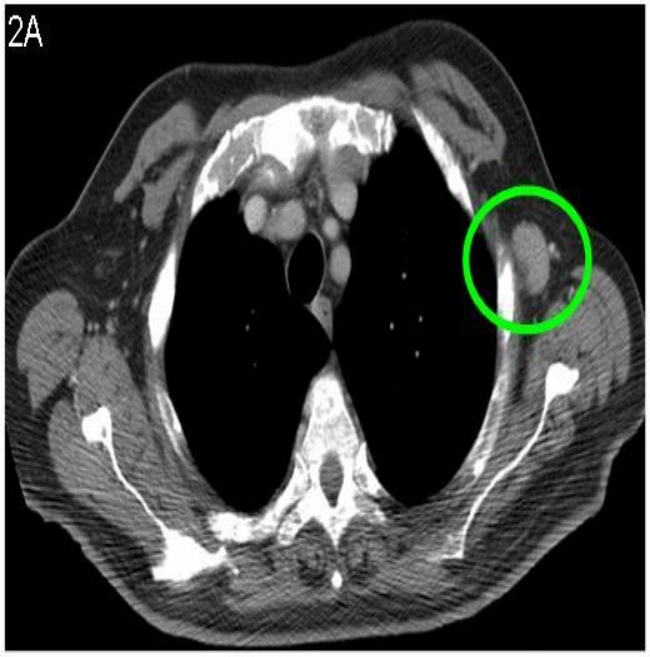


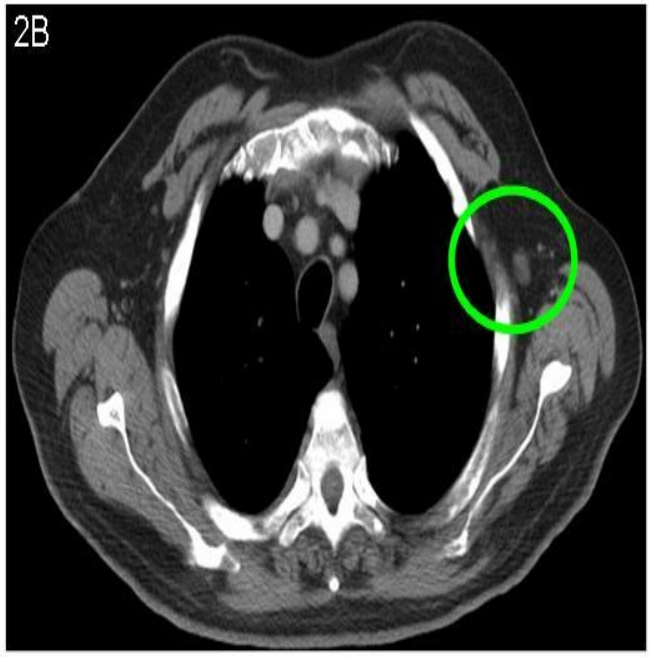
PSA is a pharmacodynamic endpoint of AR signaling blockade

Attard et al, Journal of Clinical Oncology 2008 and 2009


1A

1B


2A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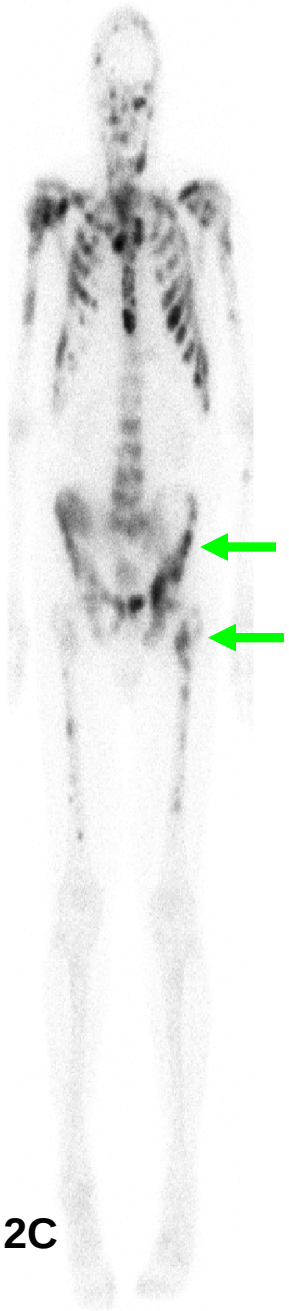
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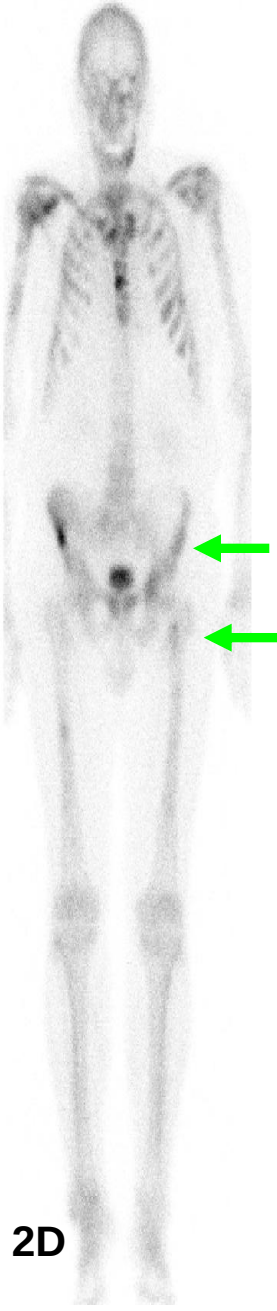
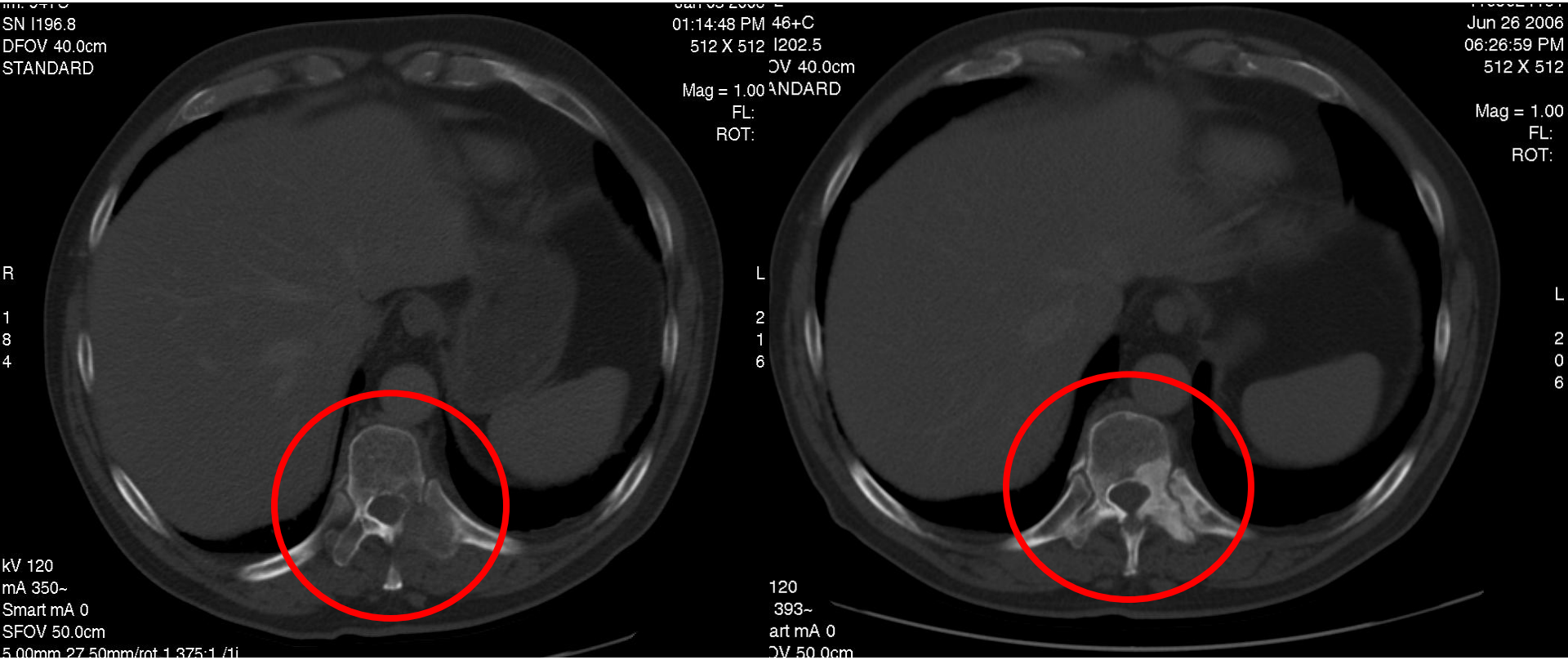
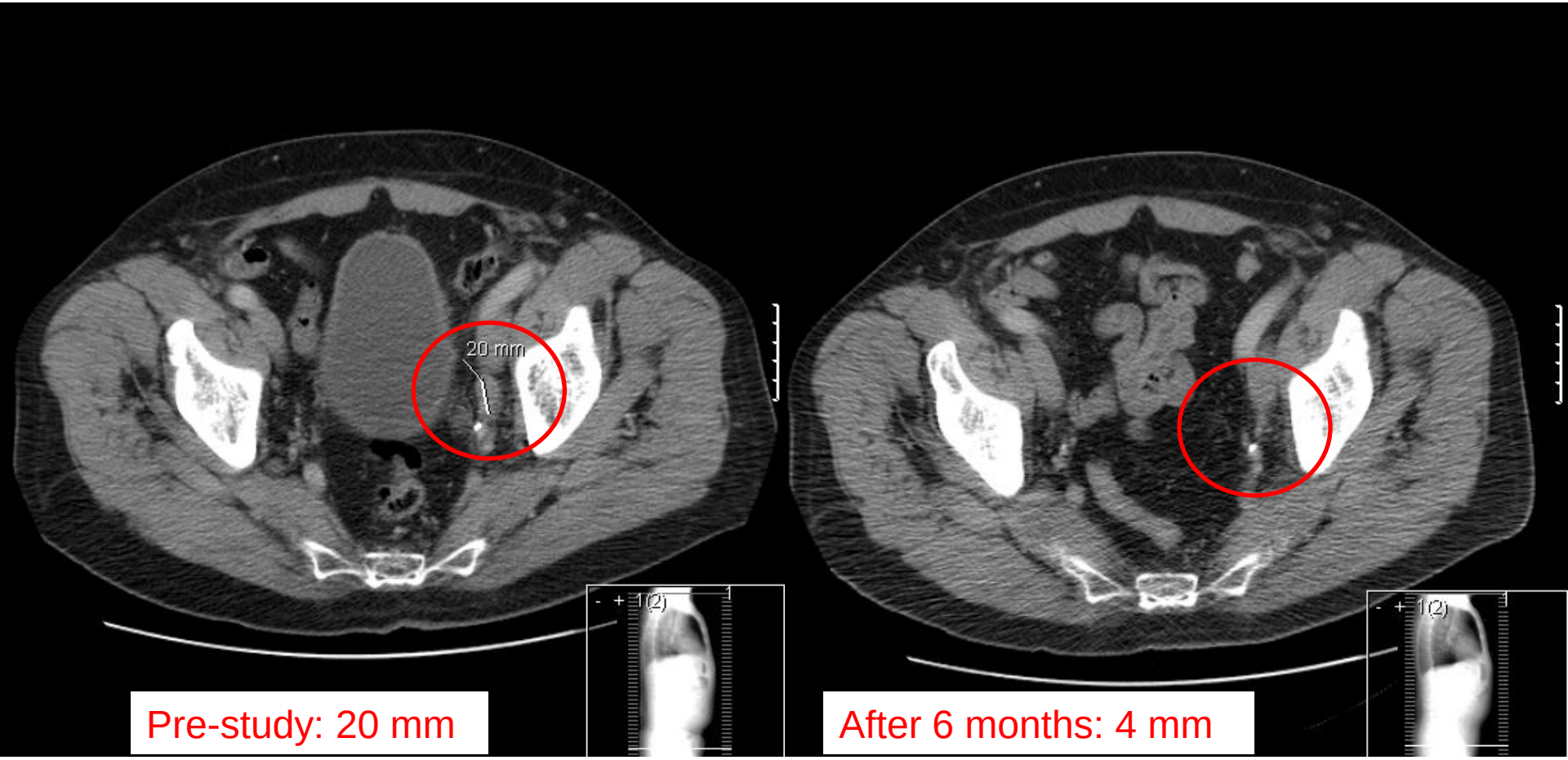

2D

Resolving bone metastases in patient on abiraterone



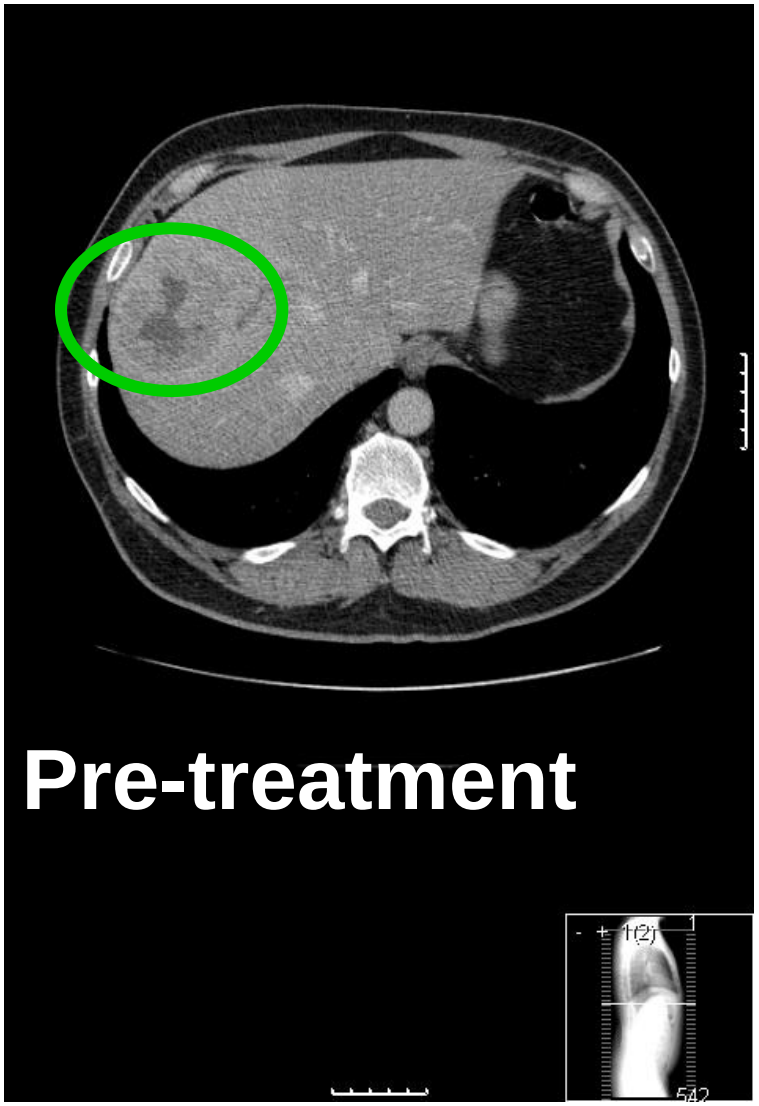
- Prior progression on several treatments
- PSA fall from **76** → **5.5** within 3 months
- Circulating tumour cell count fall from 12 to 1
- Resolution of pain

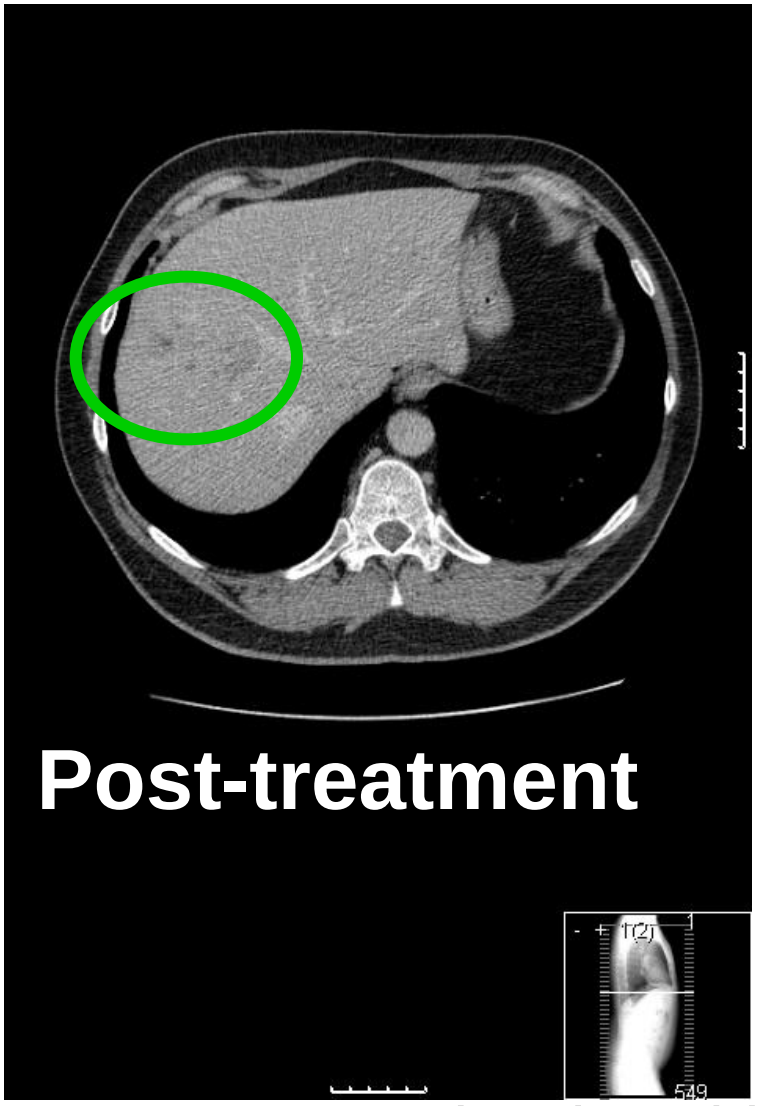
Regressing pelvic nodes



- Prior progression on several hormone treatments
- PSA decline from **34.3** → **0.21** (99%) within 3 months
- Shrinkage of lymph glands shown above on CT scan

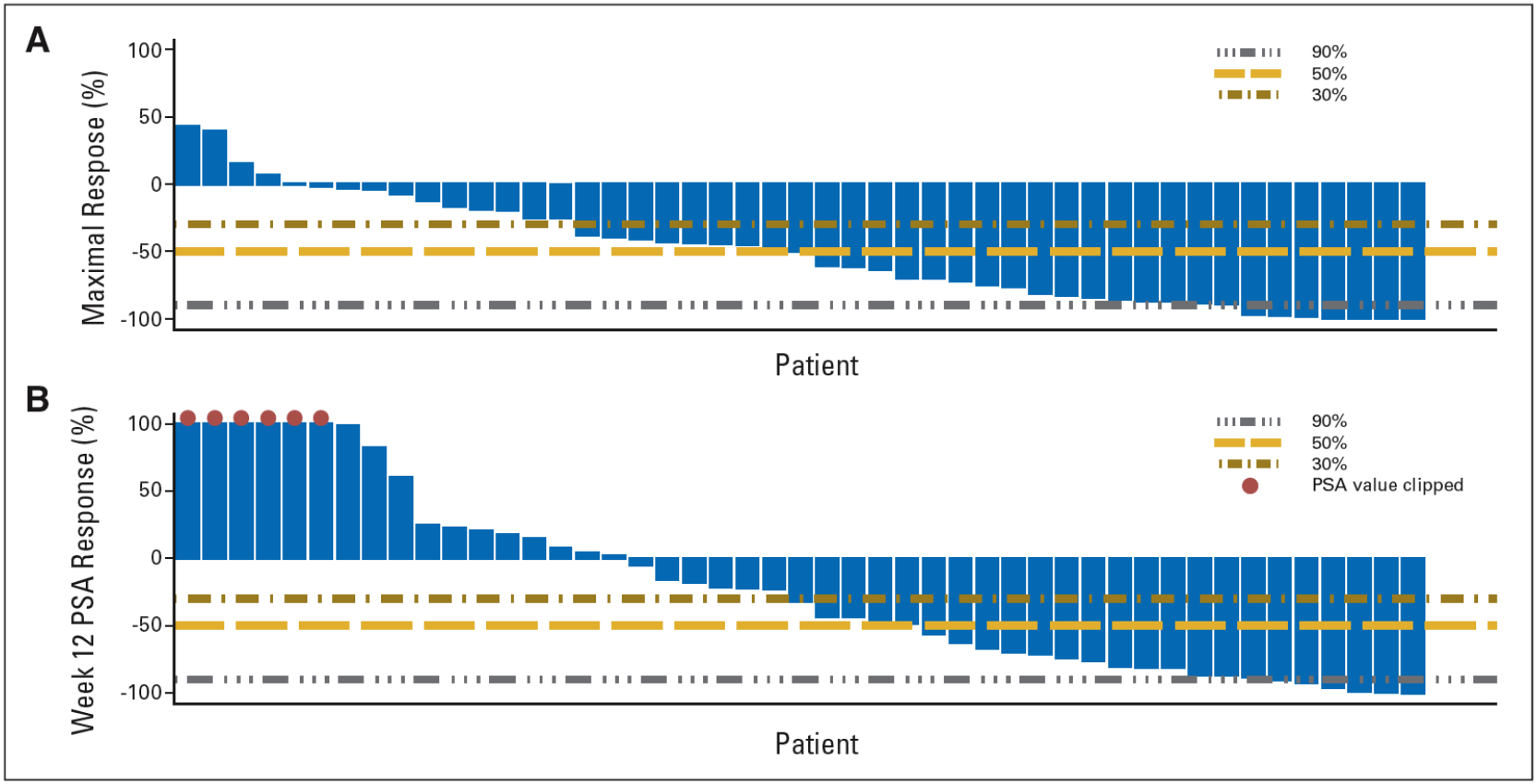
Regressing liver disease





Previous 10 m PR on depsipeptide
Duration of response: 12+ months

Post-chemotherapy PSA data (abiraterone administered with prednisolone 10mg/day)



Reid et al, JCO, 2010

CTC counts: Abiraterone trials

- **Chemotherapy naïve study:**
  - 20/54 (37%) ≥5 CTC at baseline
  - 11/20 **(55%) decline from >5 to <5 CTC**
  - 13/20 **(65%) decline by 30%**
- **Post-docetaxel study:**
  - 26/34 (76%) ≥5 CTC at baseline
  - 13/26 **(50%) decline from >5 to <5 CTC**
  - 19/26 **(73%) decline by 30%**

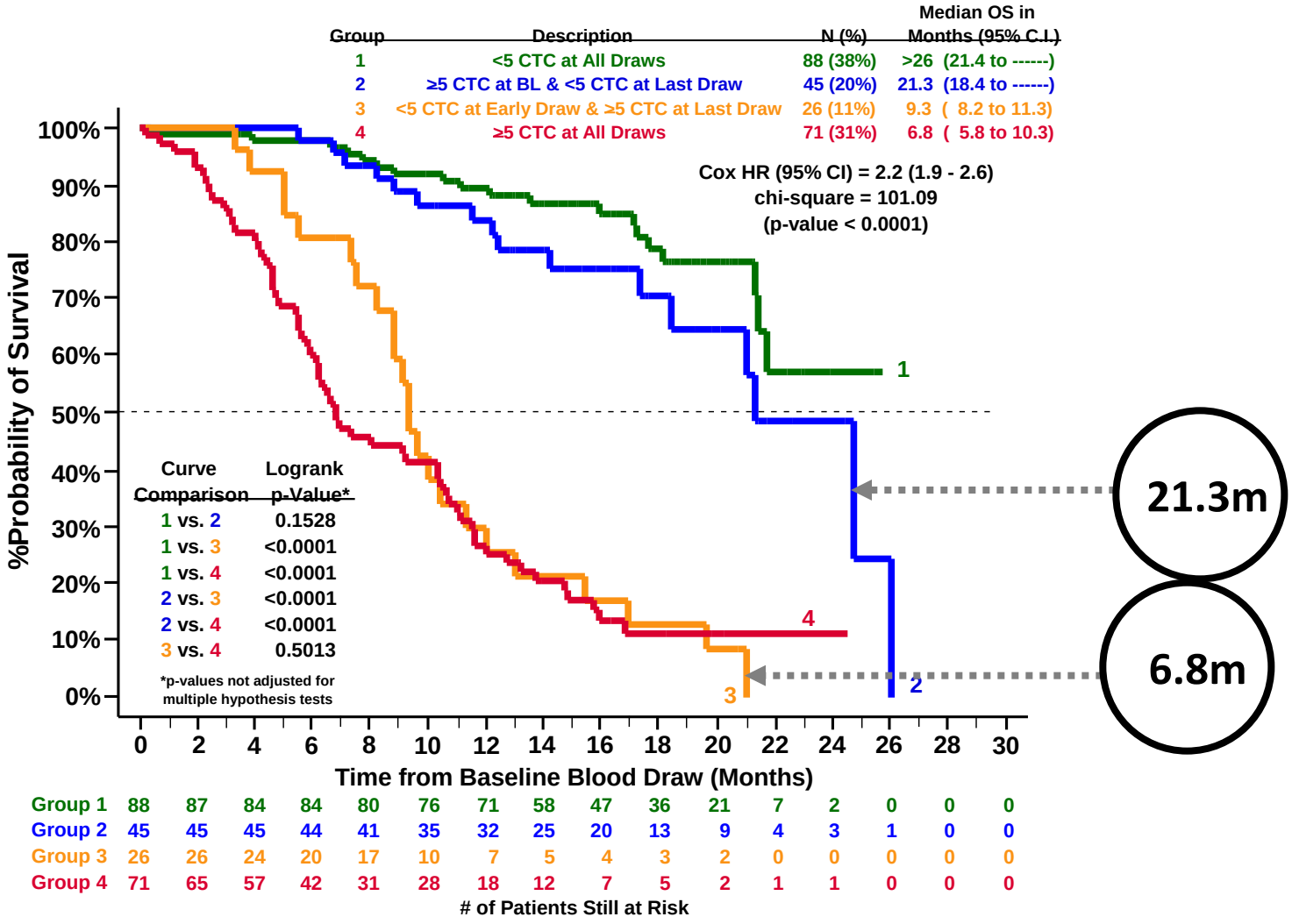
Taken at baseline and monthly throughout the trial

Relevance of CTC counts

- Our previous studies indicate that:
  - Baseline CTC counts are independently prognostic in multivariate analysis
  - Post-treatment falls in CTC from >5 to <5 significantly associate with overall survival
  - Post-treatment falls in CTC counts >30% significantly associate with overall survival

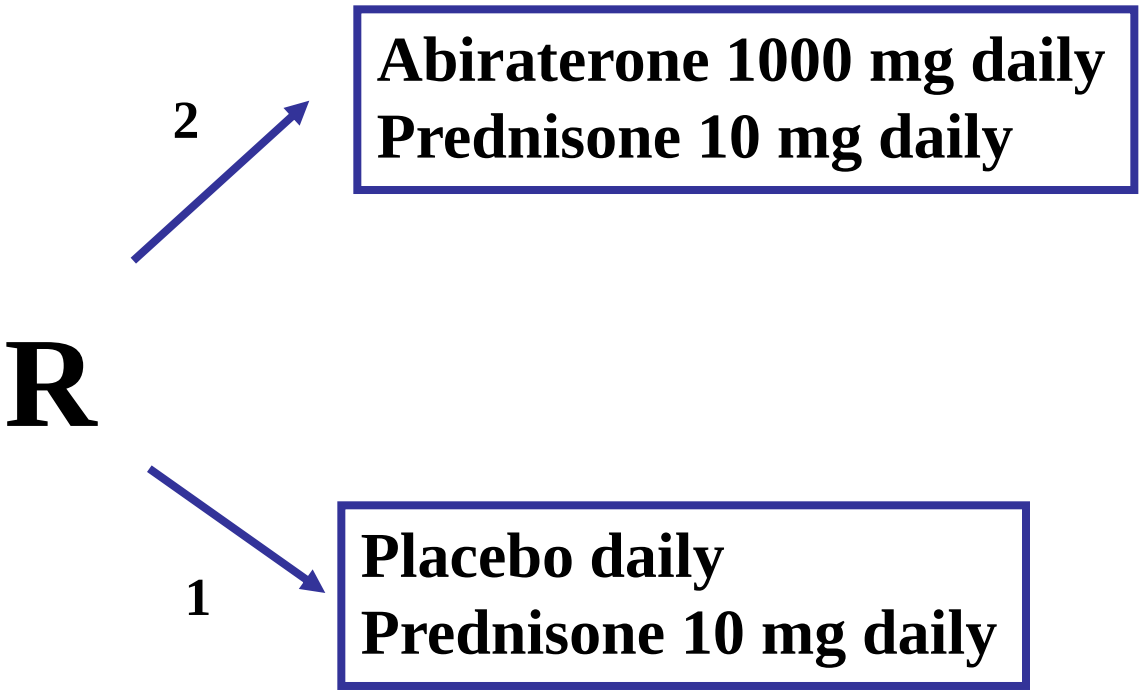
de Bono et al, Clin Cancer Res, 2008;
Olmos et al, Annals of Oncology 2008;
Scher et al, Lancet Oncology 2009.

Fall in CTC count (>5 to <5) associates with improved OS



de Bono et al, CCR, 2008

Abiraterone post-chemotherapy
Phase III trial



Scher, H and de Bono, J.
Cougar Biotechnology

Phase III registration trial for abiraterone

1. **Objective:** **Does the addition of abiraterone to prednisone prolong life?**
   Does post-treatment CTC number indicate treatment was effective?

2. **Eligibility:** **Progression post 1 or 2 cytotoxic drugs.**

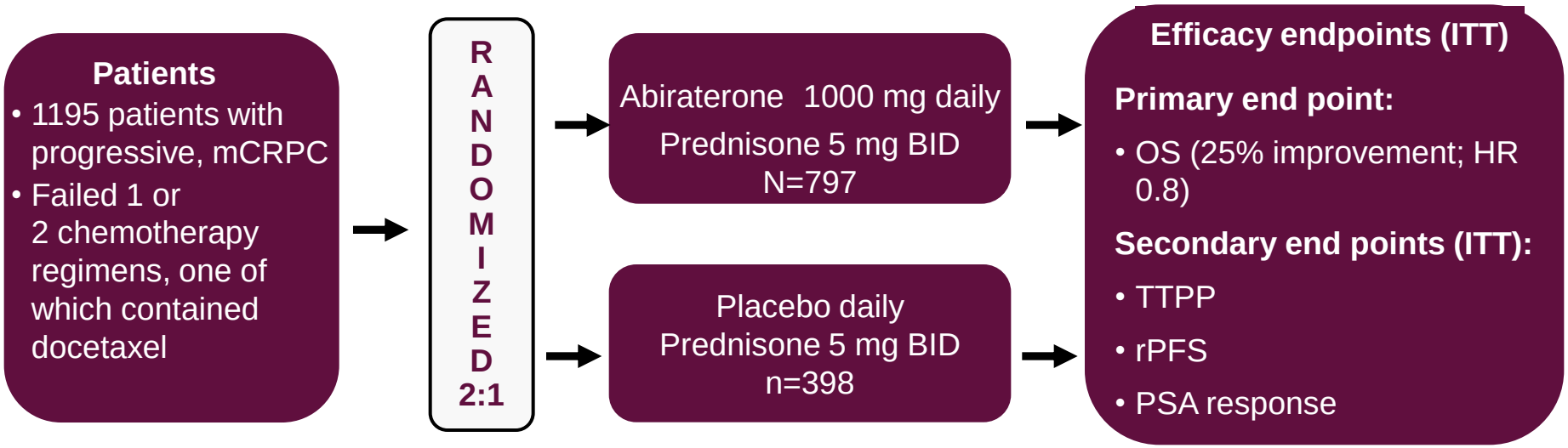
3. **Treatment:** **Abiraterone plus prednisone vs. Placebo plus prednisone.**

4. **Endpoint:** **Overall survival.**

5. **Conclusion:** **Registration.**

Scher, H and de Bono, J. Cougar Biotechnology

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)**

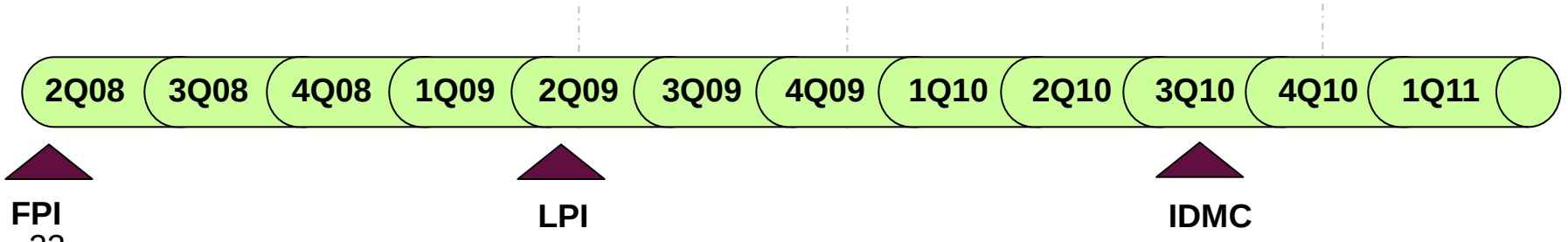
Clinicaltrials.gov identifier: NCT00638690.

COU-AA-301 Statistical Design

Overall Assumption:

- 0.05 two-sided alpha
- 85% Power
- HR=0.80 (Median OS: 12 mo vs. 15 mo)
- One interim analysis and one final analysis planned

	Planned Interim Analysis	Planned Final Analysis
Events	**534**	**797**
Cumulative alpha	**0.012**	**0.05**



COU-AA-301 Planned Interim Analysis

- **August 20, 2010** – independent data monitoring committee (IDMC) recommended unblinding the study
  - 552 events at time of interim analysis
  - Improvement in overall survival crossed predetermined boundary for stopping
  - IDMC recommended placebo arm patients be offered treatment with abiraterone acetate

COU-AA-301 Patient Disposition

	AA (n = 797)	Placebo (n = 398)
Subjects treated	**791**	**394**
Median number of cycles of therapy, range	**8 (1-21)**	**4 (1-21)**
Treatment ongoing	**222 (28.1%)**	**54 (13.7%)**
Treatment discontinued	**569 (71.9%)**	**340 (86.3%)**

Overall median duration of follow up was 12.8 months

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%

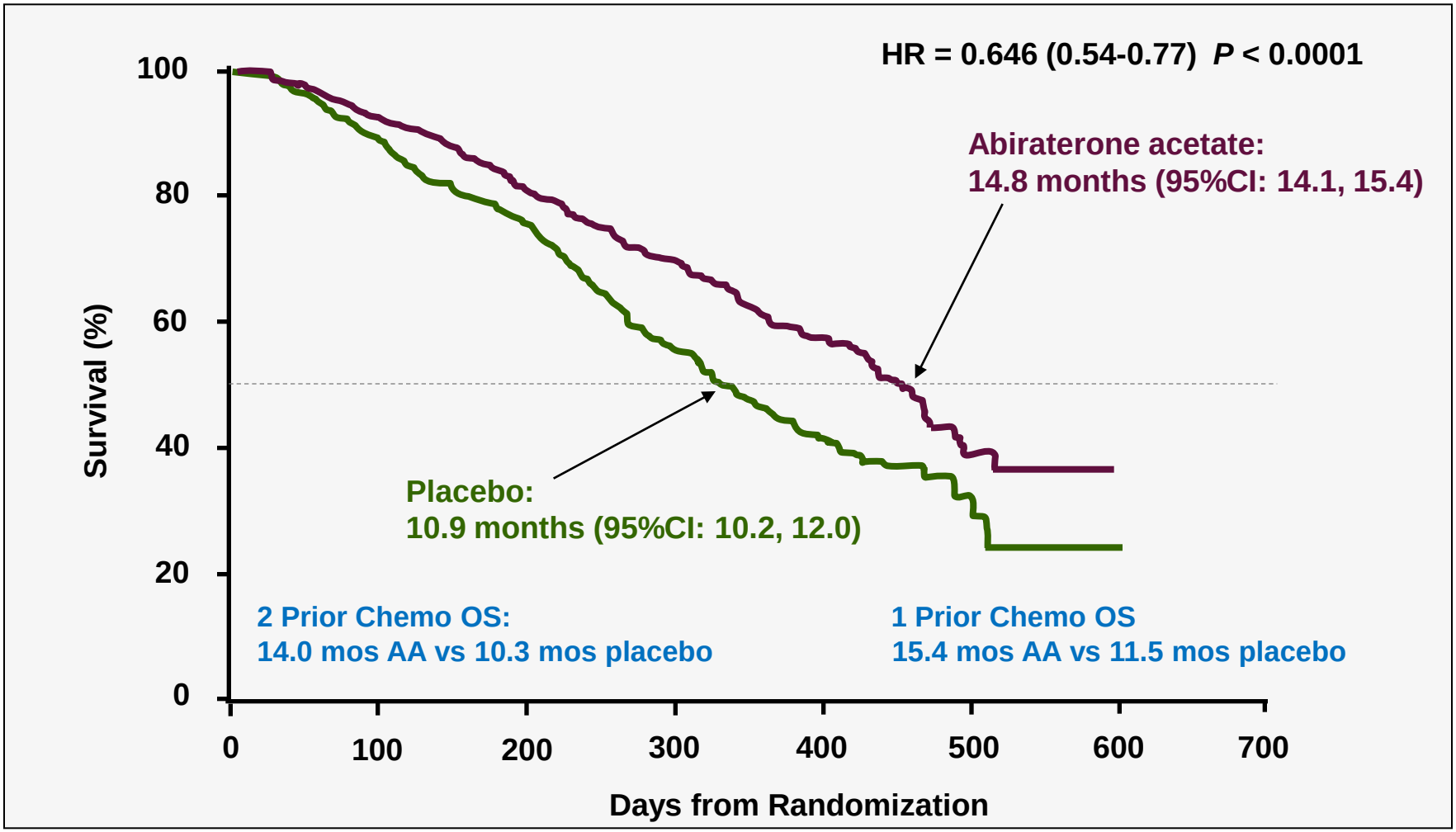
COU-AA-301 Baseline Disease Characteristics (1)

	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 Baseline Disease Characteristics (2)

	AA (n = 797)	Placebo (n = 398)
PSA (median, ng/mL)	128.8	137.7
Hemoglobin (median, g/dL)	11.8	11.8
Alkaline Phosphatase (median, IU/L)	133.5	134.0
LDH (median, IU/L)	223.0	237.5

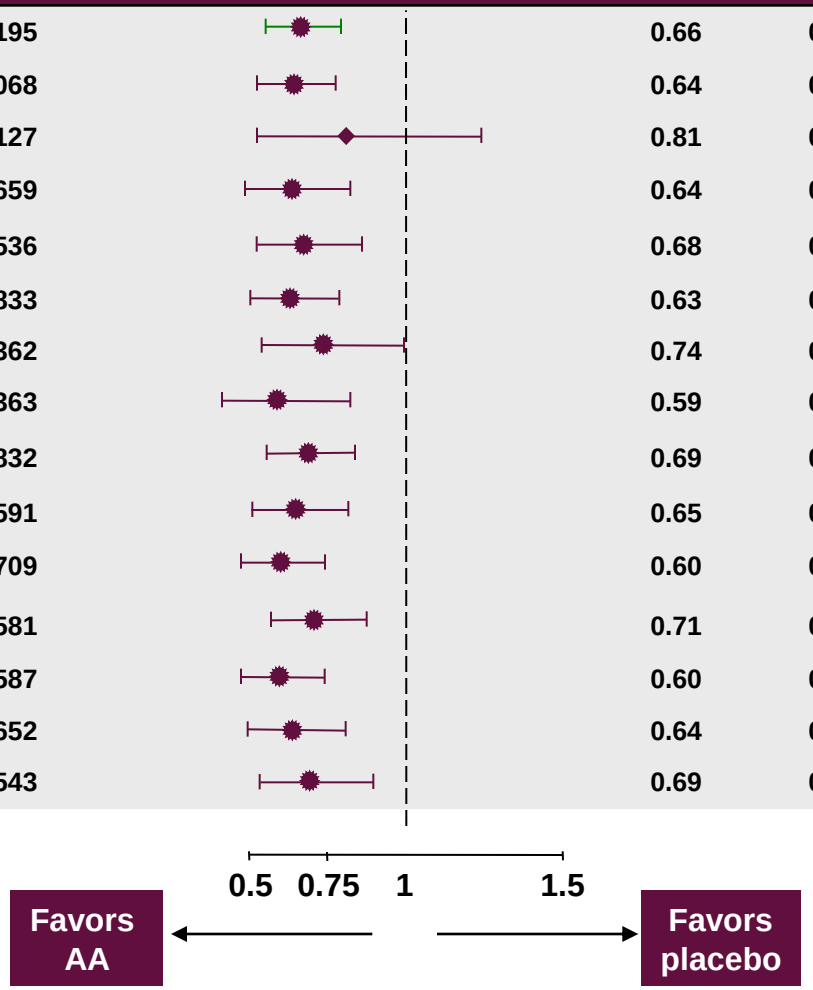
COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC



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

Survival Benefit Consistently Observed Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
All subjects	All	1195	0.66	0.56-0.79
Baseline ECOG	0-1	1068	0.64	0.53-0.78
	2	127	0.81	0.53-1.24
Baseline BPI	< 4	659	0.64	0.50-0.82
	≥ 4	536	0.68	0.53-0.85
No. of prior chemo regimens	1	833	0.63	0.51-0.78
	2	362	0.74	0.55-0.99
Type of progression	PSA only	363	0.59	0.42-0.82
	Radiographic	832	0.69	0.56-0.84
Baseline PSA above median	YES	591	0.65	0.52-0.81
Visceral disease at entry	YES	709	0.60	0.48-0.74
Baseline LDH above median	YES	581	0.71	0.58-0.88
Baseline ALK-P above median	YES	587	0.60	0.48-0.74
Region	North America	652	0.64	0.51-0.80
	Other	543	0.69	0.54-0.90



BPI; Brief Pain Inventory, ALK-P, alkaline phosphatase

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: Summary of AEs

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
All treatment-emergent AEs	98.9%	54.5%	99.0%	58.4%
Serious AEs	37.5%	32.1%	41.4%	35.3%
AEs leading to discontinuation	18.7%	10.5%	22.8%	13.5%
AEs leading to death	11.6%		14.7%	
Deaths within 30 days of last dose	10.5%		13.2%	
Underlying disease	7.5%		9.9%	
Other specified cause	2.9%		3.3%	

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%**
Hypokalaemia	**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

2010 has been a very good year for CRPC: OS Benefit in Recent CRPC Trials

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

Conclusion

- **Advanced prostate cancer** is neither hormone refractory nor androgen independent and remains nuclear steroid receptor driven
  - Role of ERα remains to be defined
- Multiple lines of treatment for advanced prostate cancer
  - Optimal sequence of administration needs defined
- **Hypothesis 2011:** At progression on these new agents, advanced prostate cancer remains driven by nuclear steroid receptors.