Club Phase 1 – Nice – 2013

Erik Mannaert, Janssen R&D

Session:

Lessons Learned from Late Stage Failures and Successes

CLINICAL PHARMACOLOGY AND CLINICAL UTILITY OF ABIRATERONE ACETATE

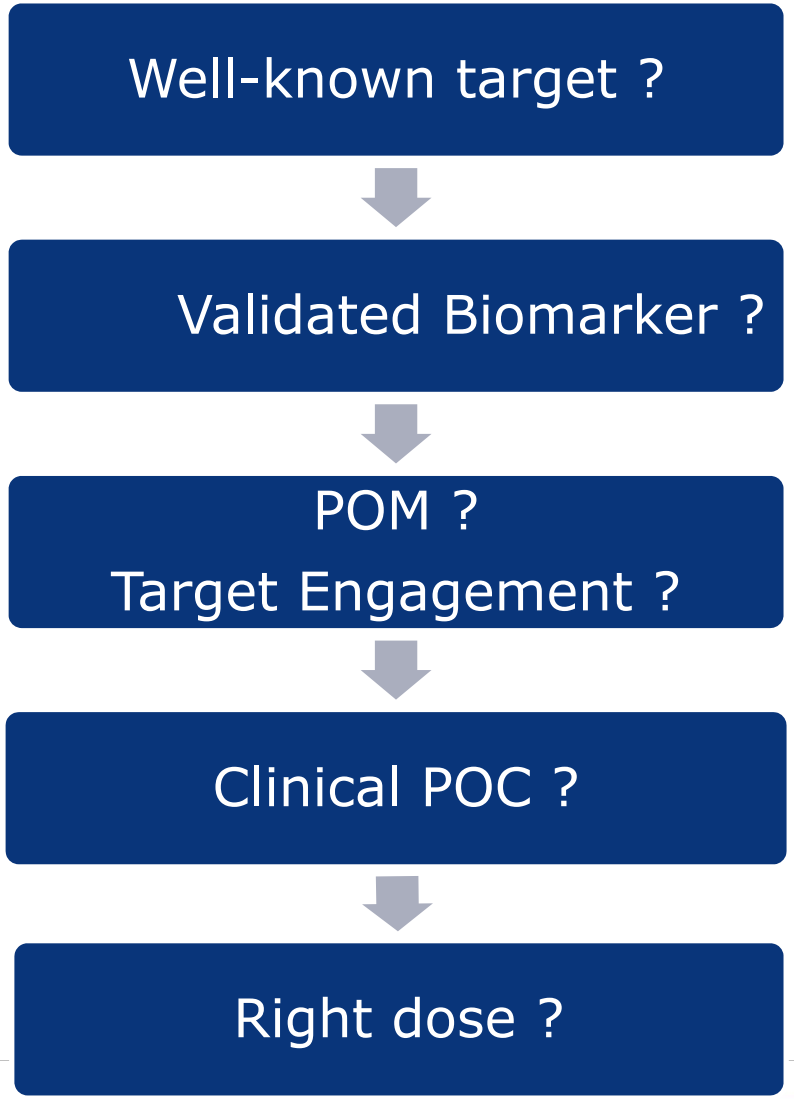
Scope of presentation today:

What do we learn from early clinical development to explain the late-stage success ?

Abiraterone, clearly a "late stage" success

- Development History:
  - Prostate cancer research @ ICR (London): patent filed 1993
  - Rights transferred to BTG plc, later licenced to Cougar Biotechn.
  - Came into Janssen R&D through acquisition of Cougar (2009)
    - Clinical POC had already been demonstrated
    - Phase-3 was ongoing in post-chemo m-CRPC
    - Janssen further developed clinical trials to expand clinical use
- 2011: ZYTIGA™ approved in postchemo (docetaxel) mCRPC
  - OS: 14.8 (AA/prednisone) vs 10.9 m (placebo/prednisone)
- 2012: ZYTIGA™ approved in chemo-naieve mCRPC
  - PFS: 16.5 m (AA/prednisone) vs 8.3 m (placebo/prednisone)

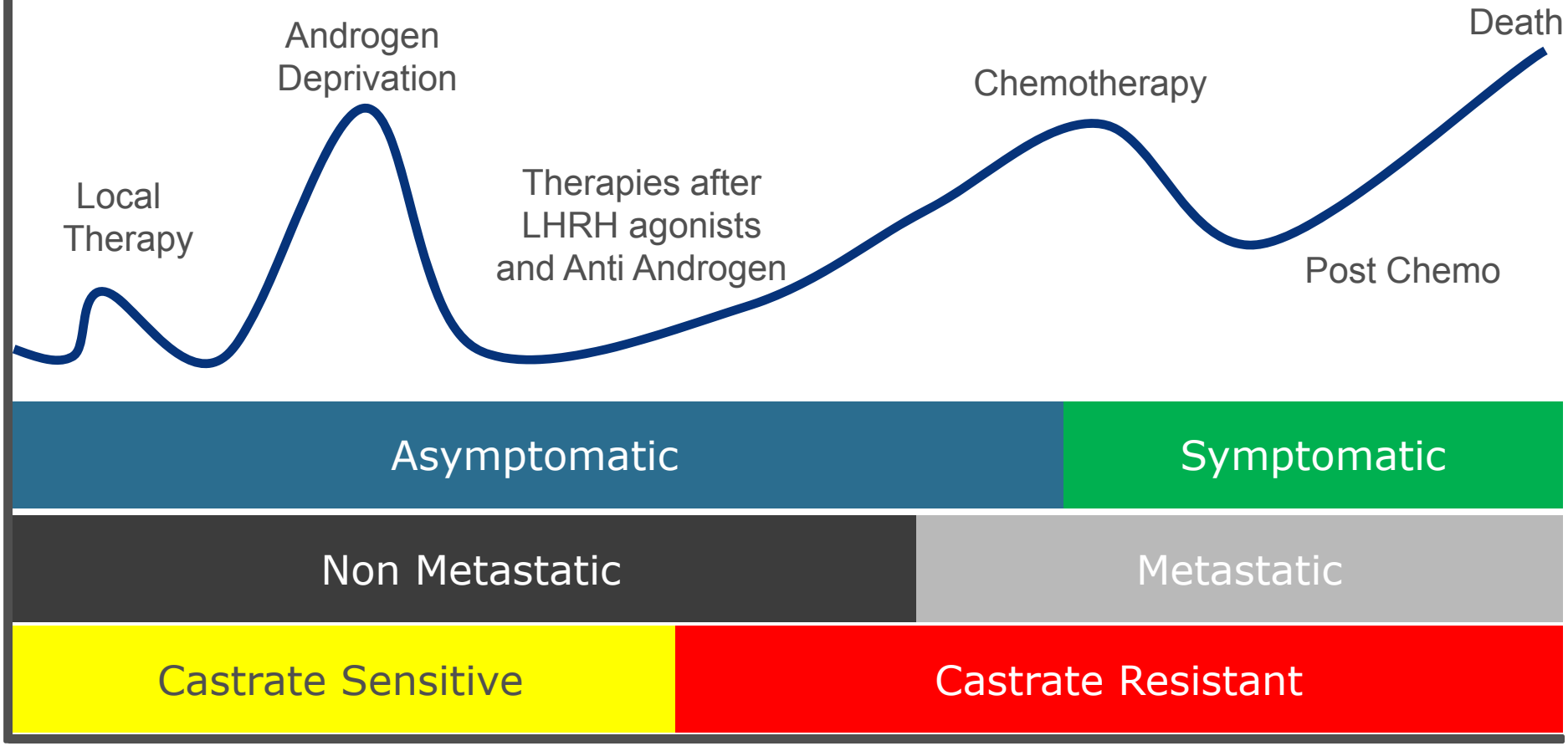
How to explain ?



Prostate cancer

Disease progression and treatments

Prostate Cancer: disease progression

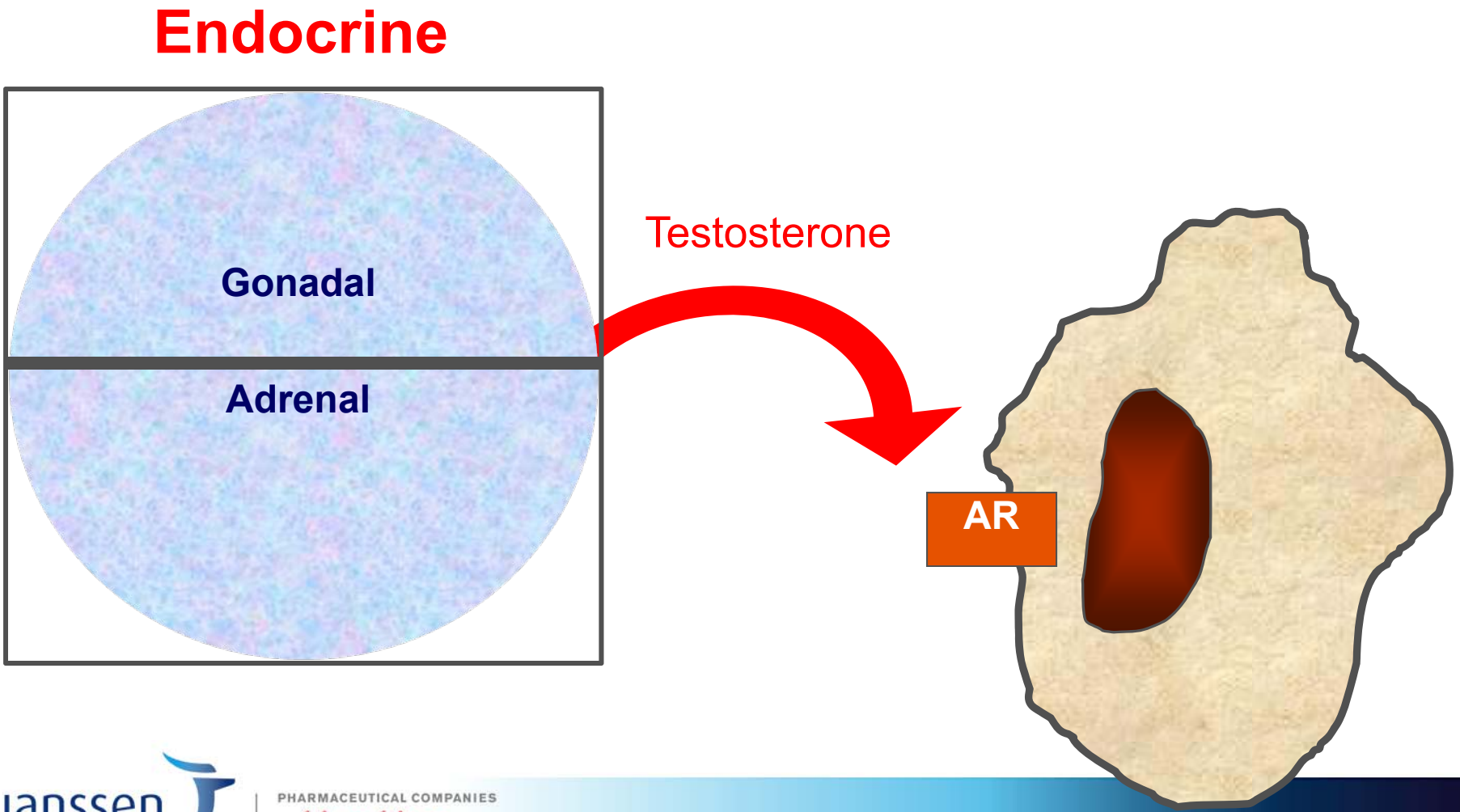


Typical presentation of patient as they move through the different stages. The line represents level burden of disease. Time is not proportional.

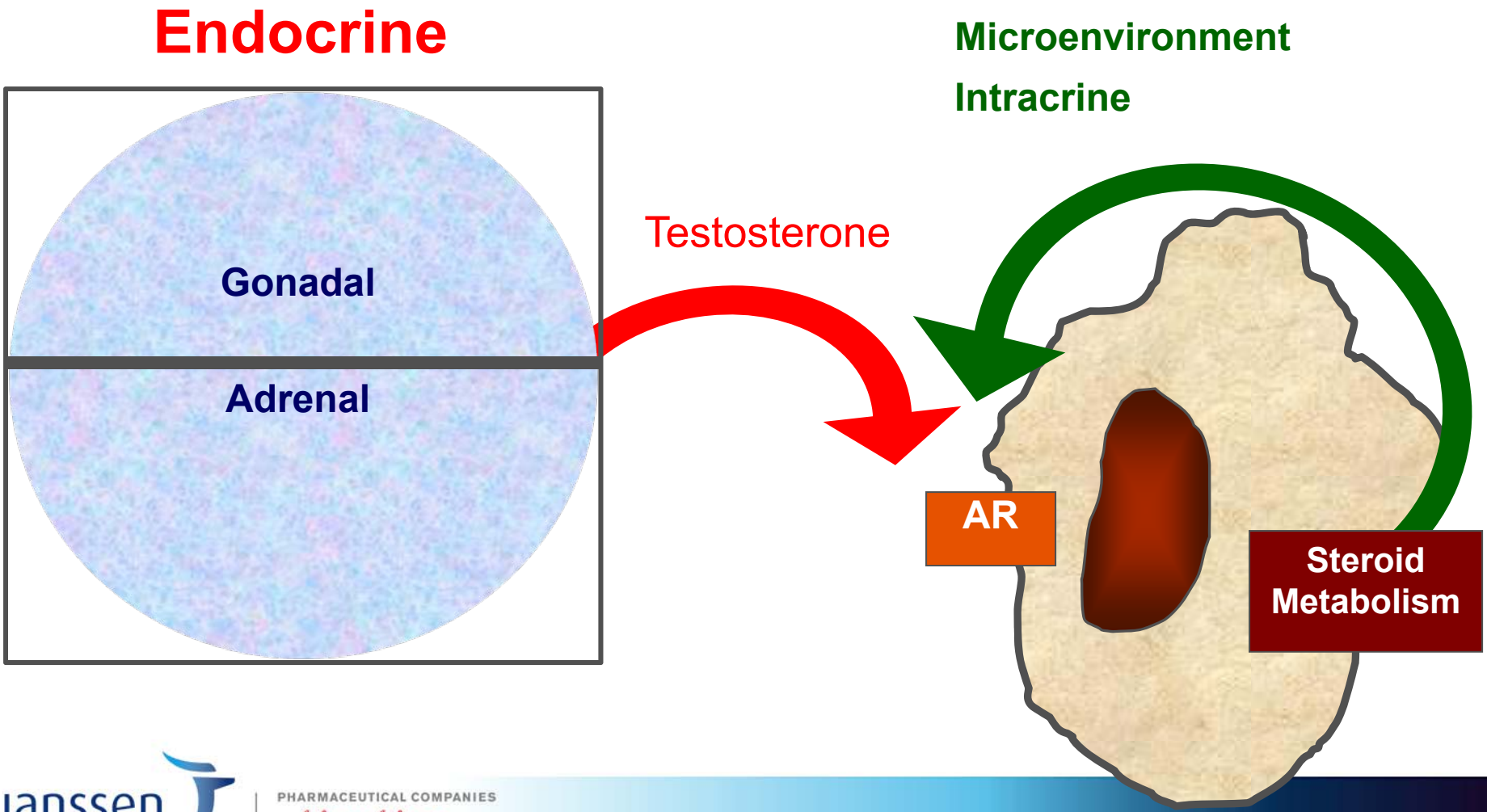
Prostate Cancer

The target

Androgen Mediated Progression of Prostate Cancer



Androgen Mediated Progression of Prostate Cancer



Intracrine Androgen Production

Study	Tissue	Pathway
• Mohler, CCR, 2004	• Recurrent PCa after ADT vs. benign prostate	• Androgens sufficient to activate AR
• Locke, Ca Res, 2008	• Castration-resistant LnCaP xenografts	• De Novo synthesis of androgens
• Montgomery, Ca Res, 2008	• Castrate mets vs. primary tumors	• Elevated androgens, and transcripts encoding steroidogenic enzymes (including CYP17)
• Stanbrough, Ca Res, 2006	• Castration-resistant mets	• Elevated gene expression of enzymes related to androgen metabolism
• Montgomery, AACR 2009	• Xenograft model	• Abiraterone suppresses CRPC in the absence of testicular and adrenal androgens

Abiraterone
The Product & Opportunity

- Current therapies did not fully ablate androgens
  - Medical/surgical castration does not inhibit adrenal or intra-tumor androgen synthesis
- Responses observed with ketoconazole – POC
  - Poor tolerability and potential for drug-drug interactions

Biomarker: PSA and beyond

PSA

- Secreted protein as product of prostate gland
  - Secreted in semen
  - Normal tissue: low levels in blood
  - Increased PSA indicative of abnormalities in prostate gland architecture/vascularisation
- Non-invasive, inexpensive, extensive experience
  - Disease detection; monitoring progression/recurrence
- Far from being perfect:
  - Poor specificity
    - False-positives (BPH, infection, trauma) => PPV 25-40%
    - False-negatives: 15% show low PSA despite advanced Gleason scores (a prognostic histopathological marker of PCA)

John R. Prensner et al., Sci Transl Med 4, 127rv3 (2012)

Beyond PSA

- PCA3 (prostate cancer antigen 3)
  - Non-invasive (urine) and highly specific:
    - Elevated in 90% of PCA, but not in normal and BPH tissues
  - Approved in 2012 by FDA as a diagnostic
- TMPRSS2-ERG gene fusion
  - Specific gene fusion for PCA, present in 50% of cases
  - Detected in biopsy, but also investigated in urine
- CTC's (circulating tumor cells)
  - Biomarker for cancer detection
  - Increased abundance is predictor of worse overall survival (OS)

John R. Prensner et al., Sci Transl Med 4, 127rv3 (2012)

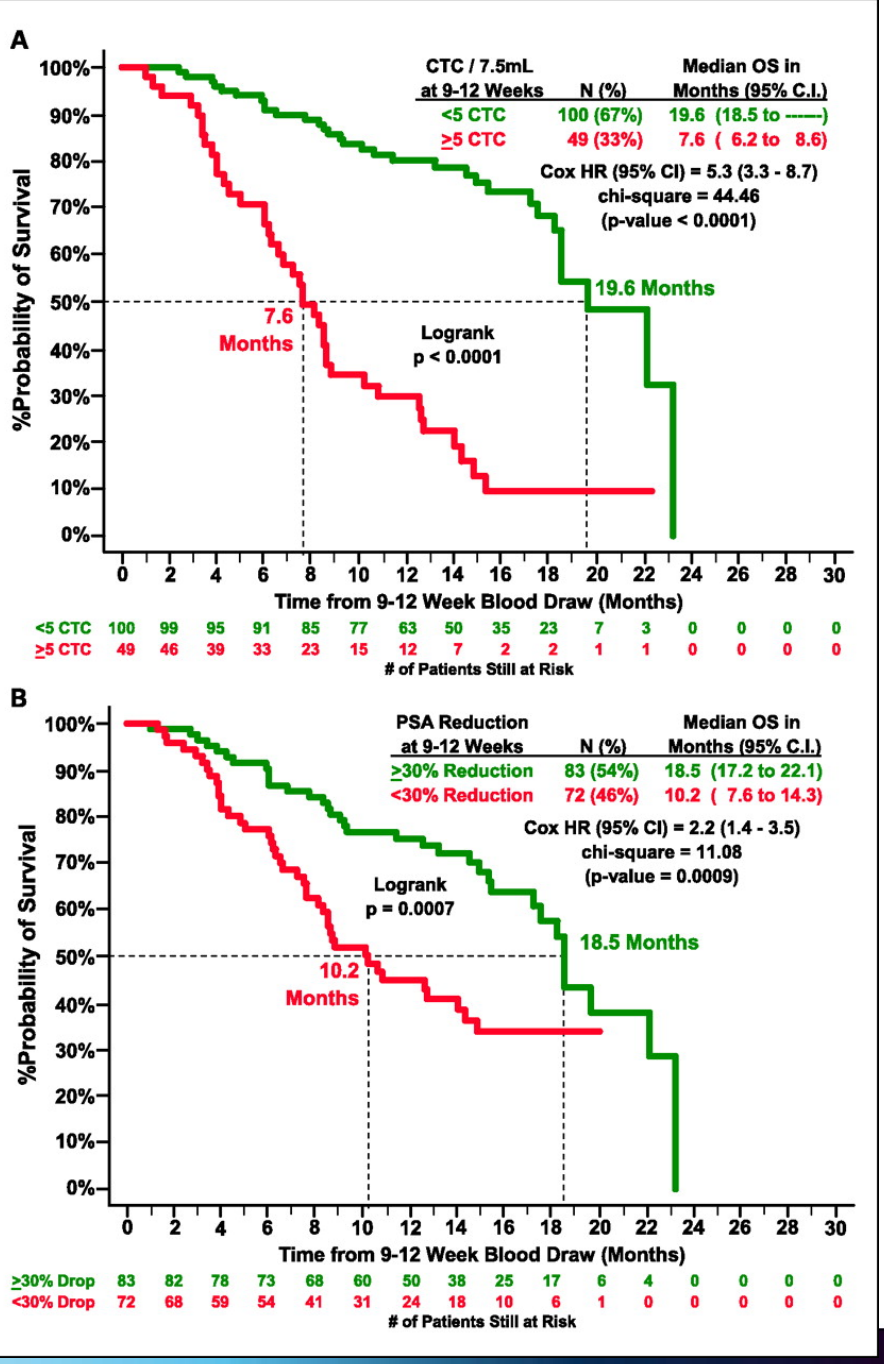
***PSA vs CTC as prognostic marker for OS**:*
Study population: mCRPC patients with progressing disease and starting a new line of chemotherapy

CTC - Probability of overall survival:
Favorable (<5) and Unfavorable (≥5) CTC after 9 to 12 wk of therapy.

PSA - Probability overall survival:
Favorable, (≥30%) and Unfavorable (<30%), PSA decrements after 9 to 12 wk of therapy

CTC are the most accurate and independent predictor of OS in CRPC. These data led to FDA clearance of this assay for the evaluation of CRPC.

de Bono J S et al. Clin Cancer Res 2008;14:6302-6309



POM – Target engagement

Ketoconazole provided the POM

- Androgen independent, progressive and metastatic PCA patients were randomized to
  - AAWD alone (n = 132)
  - AAWD + Ketoconazole (400 mg orally t.i.d.) and hydrocortisone (30 mg po each morning, 10 mg po each evening; n = 128).
- AAWD (anti-androgen withdrawal) means:
  - Gonadal ADT with an LHRH analog or orchi-ectomy, AND
  - Concomitant therapy with an anti-androgen (flutamide, bicalutamide or nilutamide)

Small et al, JCO March 15, 2004 vol. 22 no. 6 1025-1033
Antiandrogen Withdrawal Alone or in Combination With Ketoconazole in Androgen-Independent Prostate Cancer Patients: A Phase III Trial (CALGB 9583)

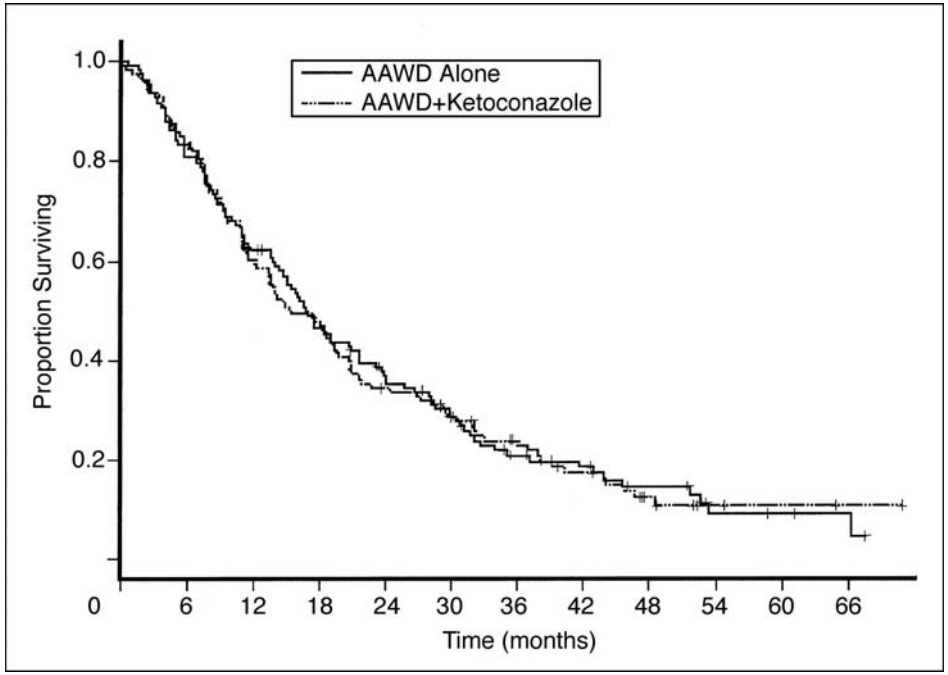
Ketoconazole provided the POM (ctd)

	AAWD Alone (n = 132)	AAWD and Ketoconazole (n = 128)	*P*
PSA decline ≥ 50%			
No. of patients	15/132	34/128	.002
%	11	27	
Objective response rate			
No. of patients	1/41	10/50	.020
%	2%	20%	
Survival time, months			
Median	16.7	15.3	.936
Time to PSA progression in PSA responders, months			
Median	5.9	8.6	.063
No. of patients	15	34	

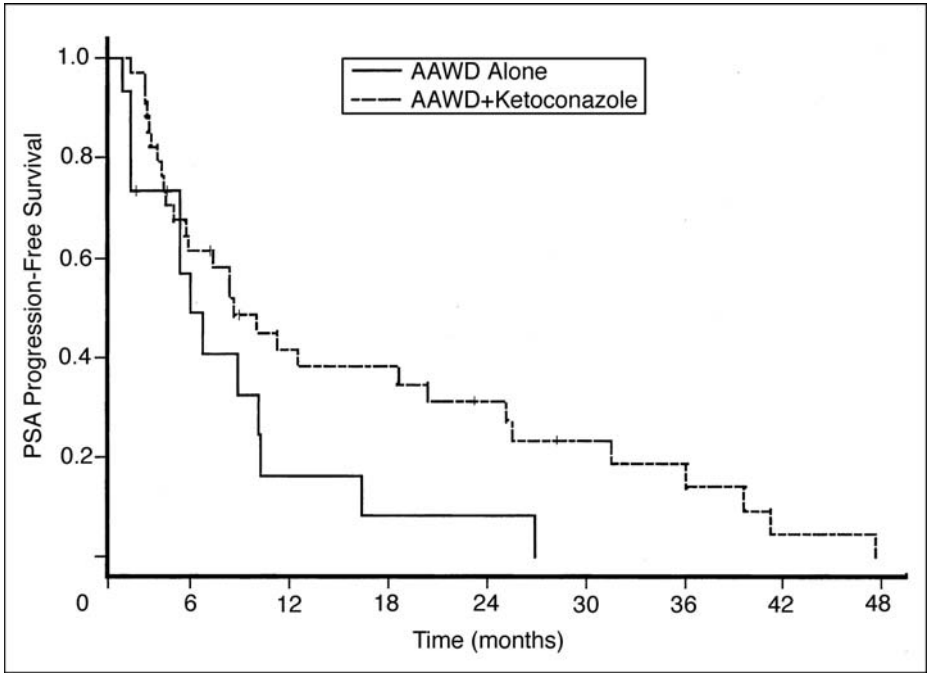
Small E J et al. JCO 2004;22:1025-1033

Ketoconazole provided the POM (ctd)

Overall survival by treatment arm.



Overall prostate-specific antigen (PSA) progression-free survival by treatment arm in patients with 50% decline in PSA. AAWD, antiandrogen withdrawal.

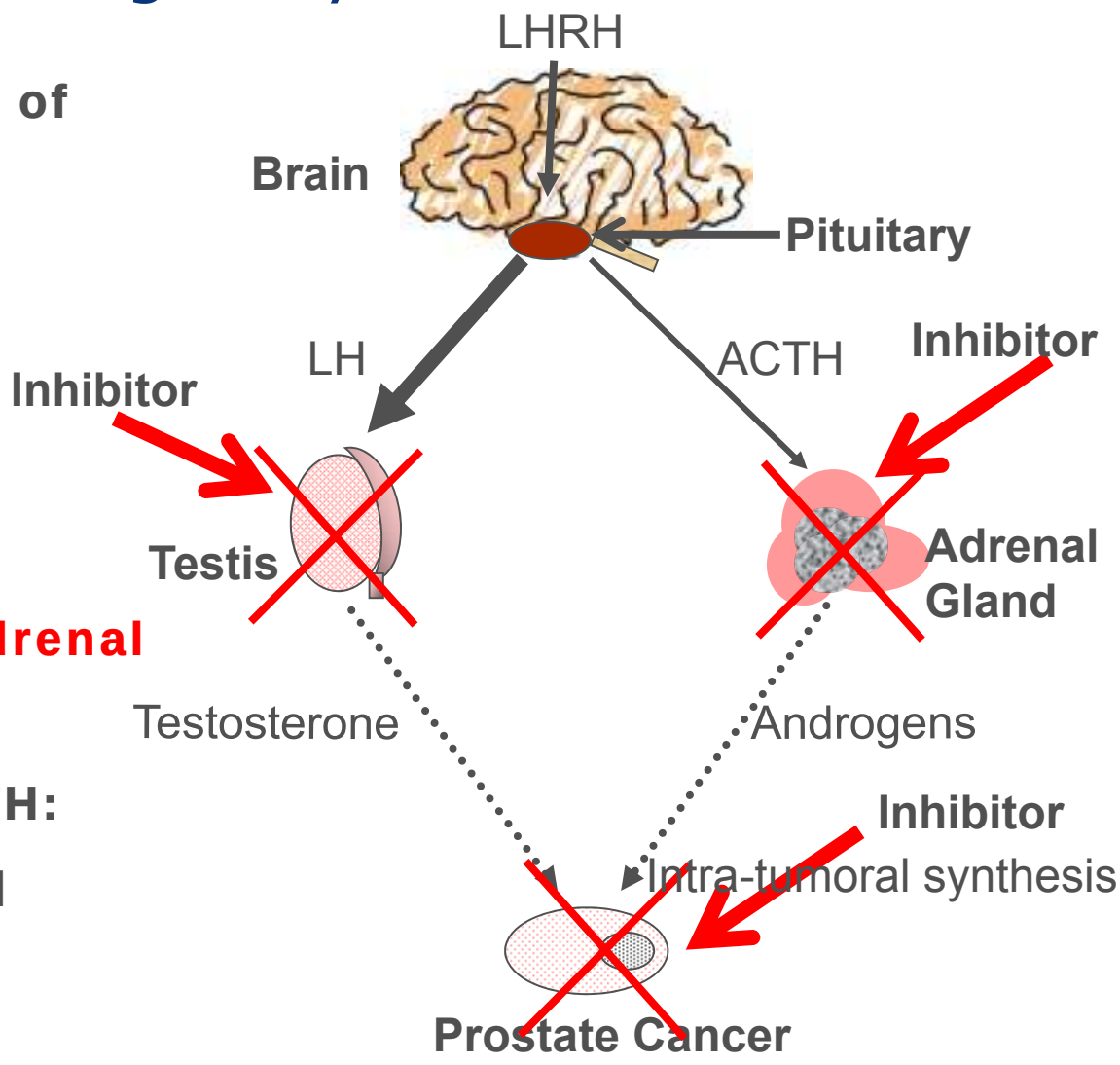


Small E J et al. JCO 2004;22:1025-1033

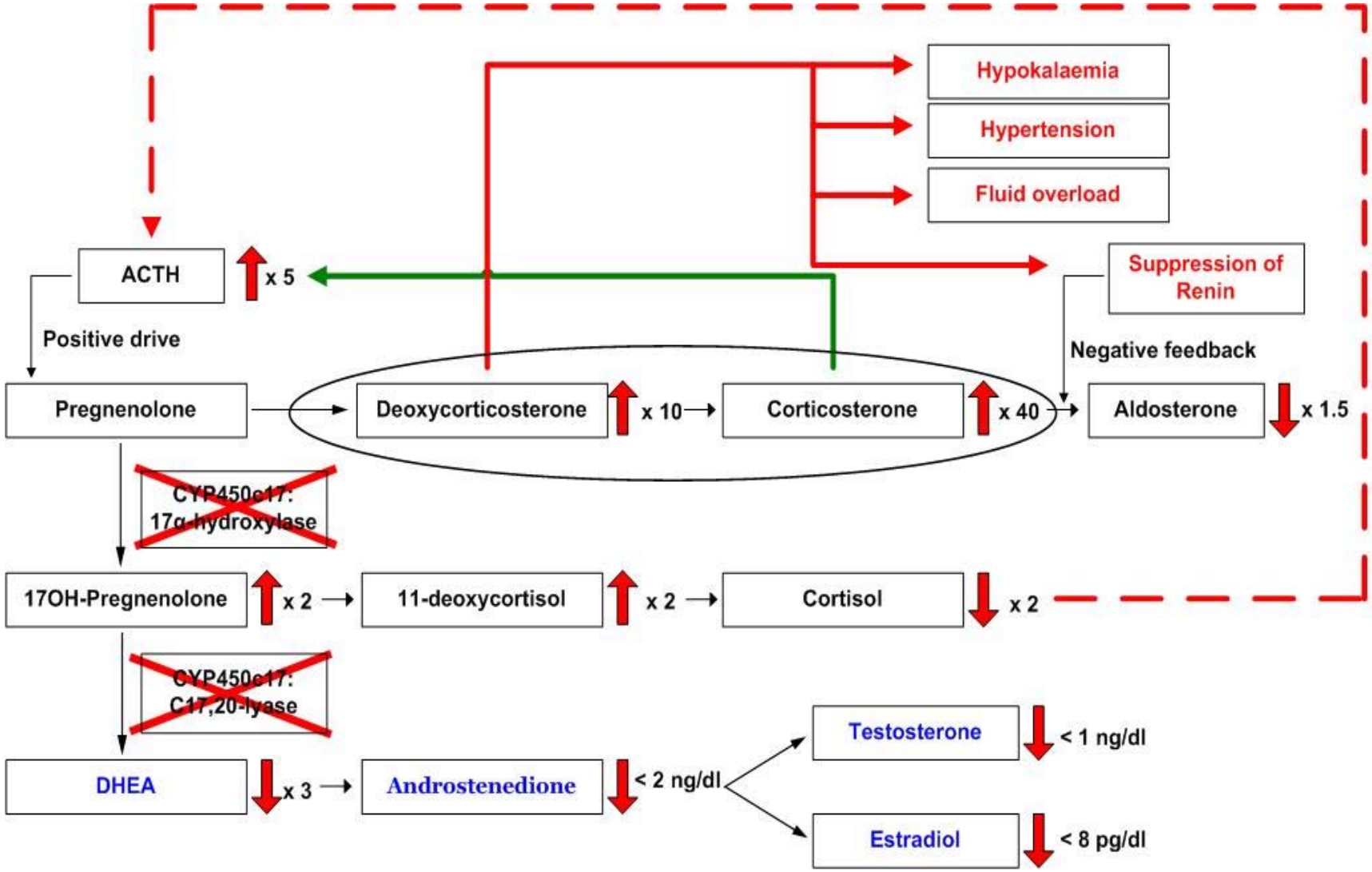
Conclusion: Ketoconazole has modest activity in AiPCa patients, while AAWD alone has minimal activity.

Abiraterone Acetate: Novel "Targeted" Pan-Inhibitor of Androgen Synthesis

- **Oral irreversible inhibitor of CYP17 (P450c17)**
  - 17α–hydroxylase
  - C17,20-lyase
- **Androgen biosynthesis inhibitor:**
  - **inhibits testosterone production in testis, adrenal glands and prostate**
- **Feedback increase in ACTH:**
  - leads to mineralocorticoid excess that is blocked by prednisone



CYP17 blockade inhibits androgen synthesis

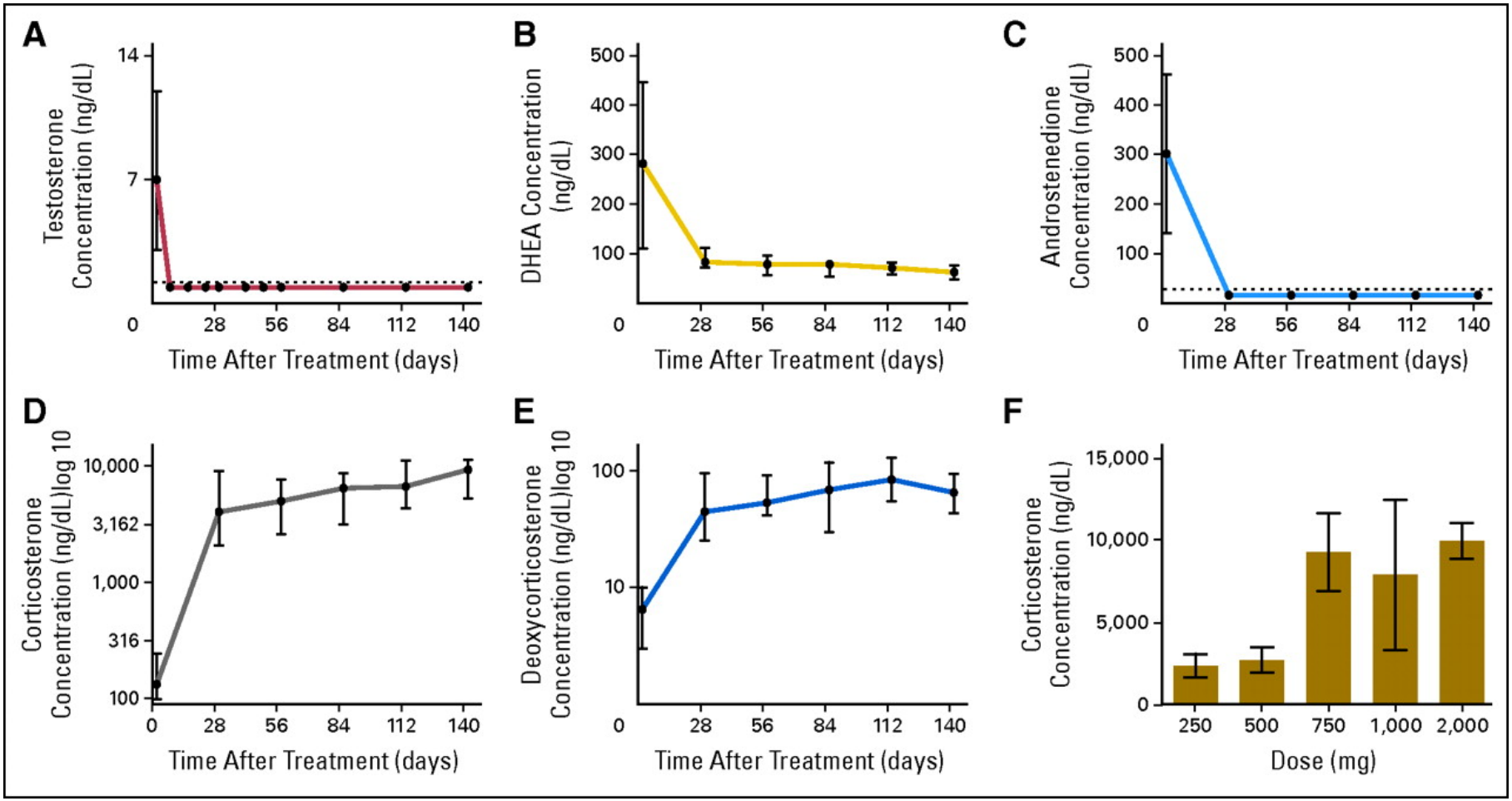


Clinical POC and Dose selection

Abiraterone Phase 1/2: Key Clinical Results

	Patient #	Chemo	≥ 50% PSA decline	Obj. Response (RECIST)	
				Partial	Stable
Attard/ De Bono Cou-AA-001 JCO 2008, 2009 ASCO 2009	Ph I: 21 (no pred)	Pre	12/21 (57%)	5/8 (62%)	N/A
	Ph II: 42 (no pred)	Pre	28/42 (67%)	9/24 (37.5%)	16/24 (66%)
Ryan Cou-AA-002 ASCO/JCO 2009	Ph I: 30 (No pred)	Pre	16/30 (53%)	N/A	N/A
	Ph II: 33 (+pred)		29/33 (88%)	N/A	N/A
Reid Cou-AA-003 ASCO/JCO 2009	47 (+/- pred)	Post	24/57 (51%)	6/35 (17%)	23/35 (66%)
Danila Cou-AA-004 ASCO/JCO 2009	58 (+pred)	Post	25/58 (43%)	3/18 (17%)	11/18 (61%)

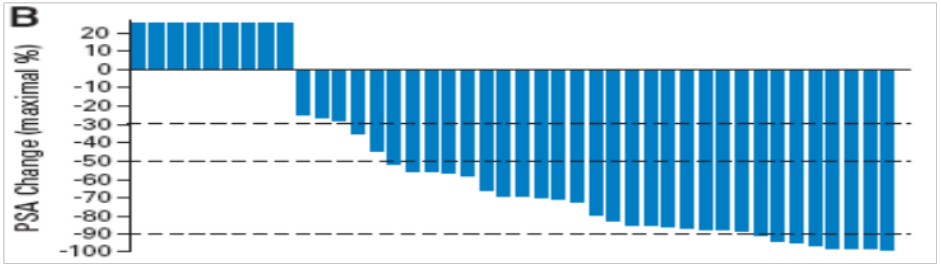
COU-AA-001: Clinical dose of 1000 mg once daily determined based on plateau in upstream gluco-corticoid levels



Attard G et al. JCO 2008;26:4563-4571

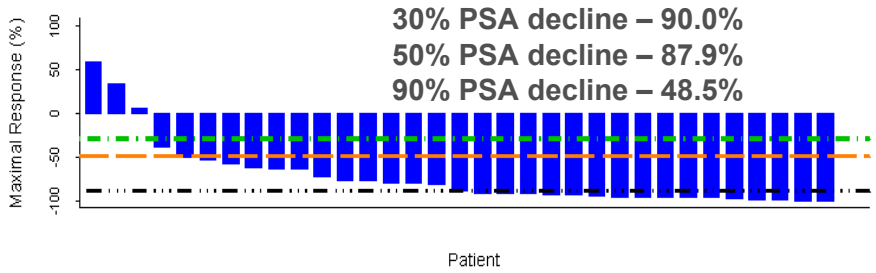
Abiraterone Phase II: PSA response

Attard JCO 2009

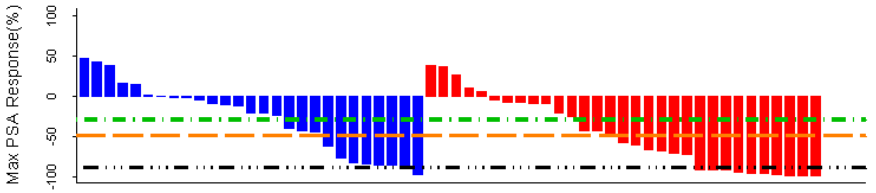


Pre-chemo

Ryan ASCO 2009

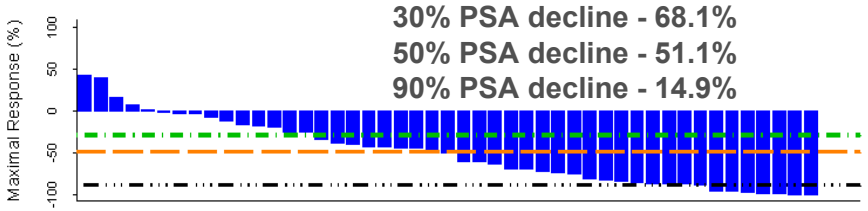


Danila ASCO 2009



Post-chemo

Reid ASCO 2009



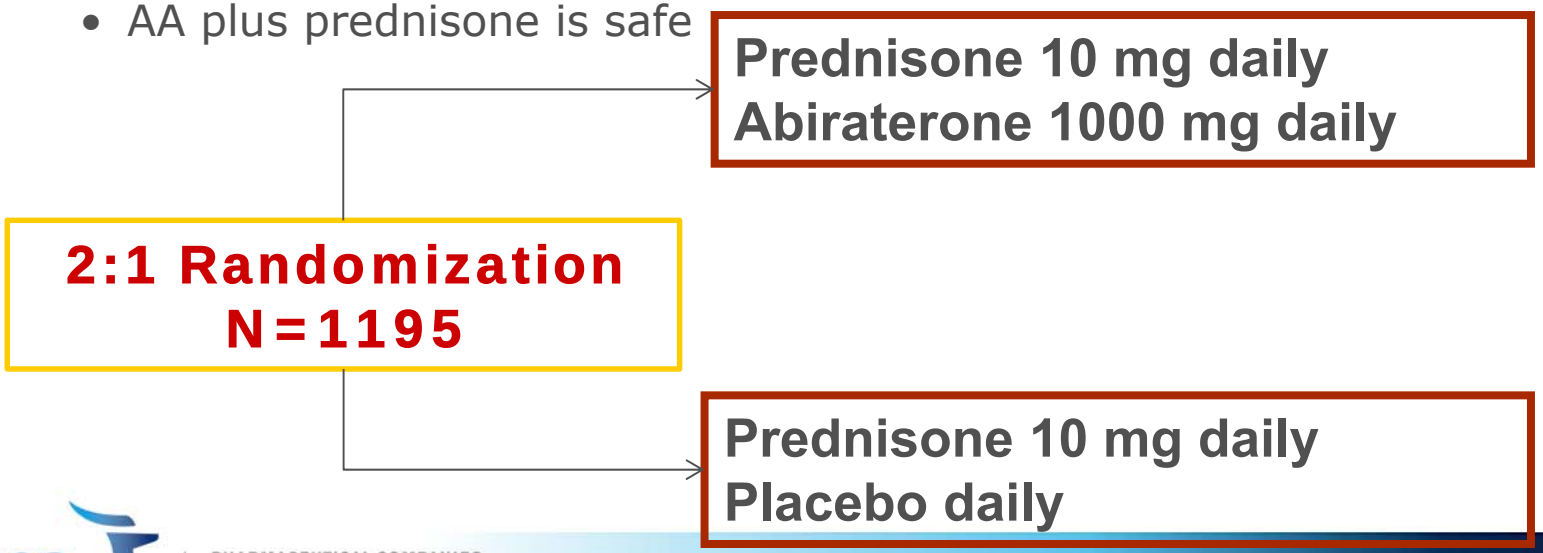
CTC conversions with treatment from ≥ 5 to < 5 were noted in 10 (34%) of 29 patients in a phase-II study with AA in post-chemo mCRPC

Danila et al, JCO March 20, 2010.

CTC/7.5 mL of Blood *Cell counts available for 42 patients*	Time on Protocol (weeks)		
	≤ 12	12-24	> 24
Baseline < 5 CTC (n = 13)			
Post-treatment CTC ≥ 5 (n = 4)	1	1	2
Post-treatment CTC < 5 (n = 9)	1	4	4
Baseline ≥ 5 CTC (n = 29)			
Post-treatment CTC ≥ 5 (n = 19)	9	7	3
Post-treatment CTC < 5 (n = 10)	1	3	6

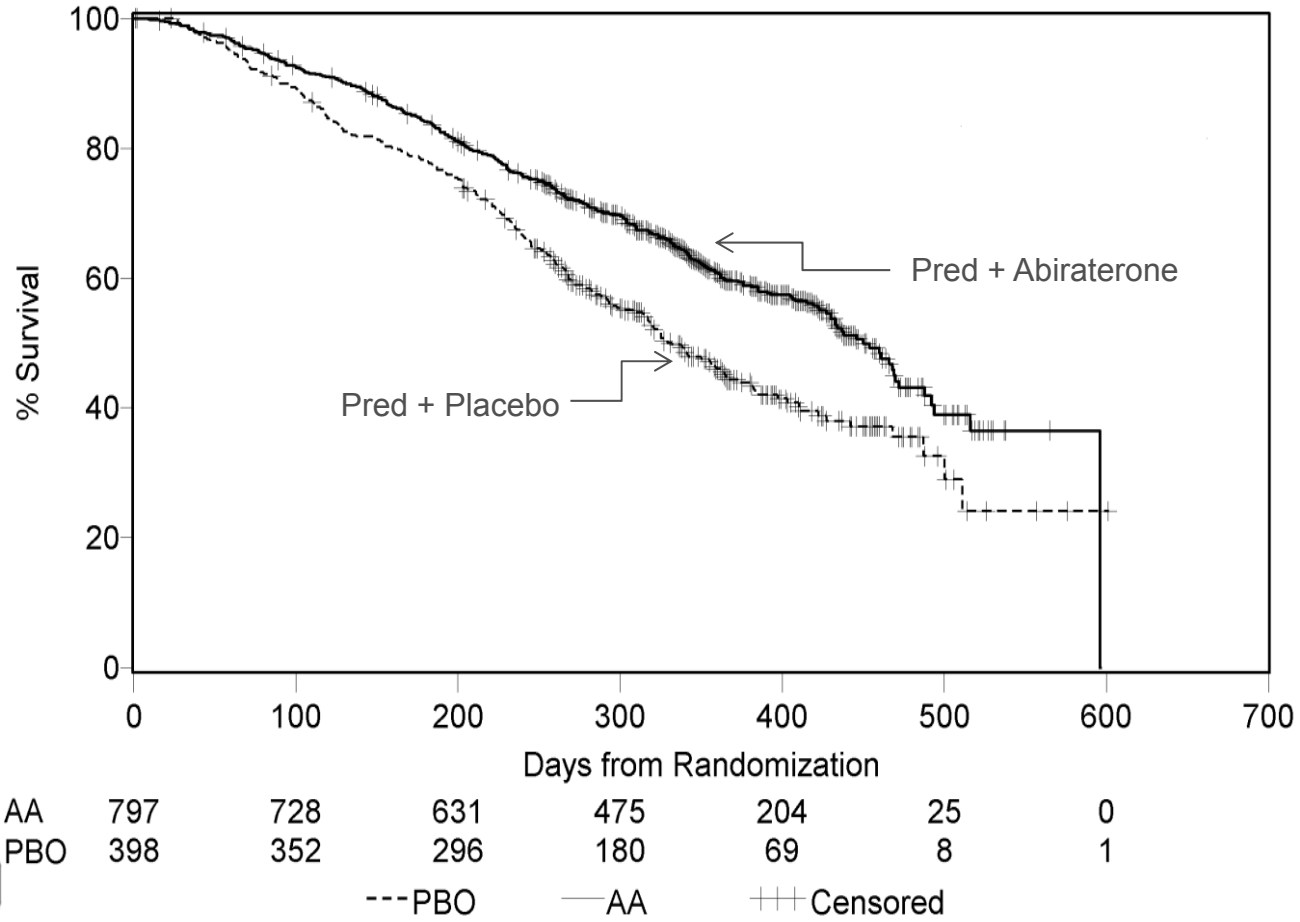
Phase-3 pivotal study: COU-AA-301

- Goal
  - To determine whether or not abiraterone acetate, a potent and selective CYP17 inhibitor, is a safe and effective treatment for patients with CRPC post-chemotherapy
- Specific Objectives
  - To determine whether or not
    - AA plus prednisone is more effective than placebo plus prednisone
    - AA plus prednisone is safe



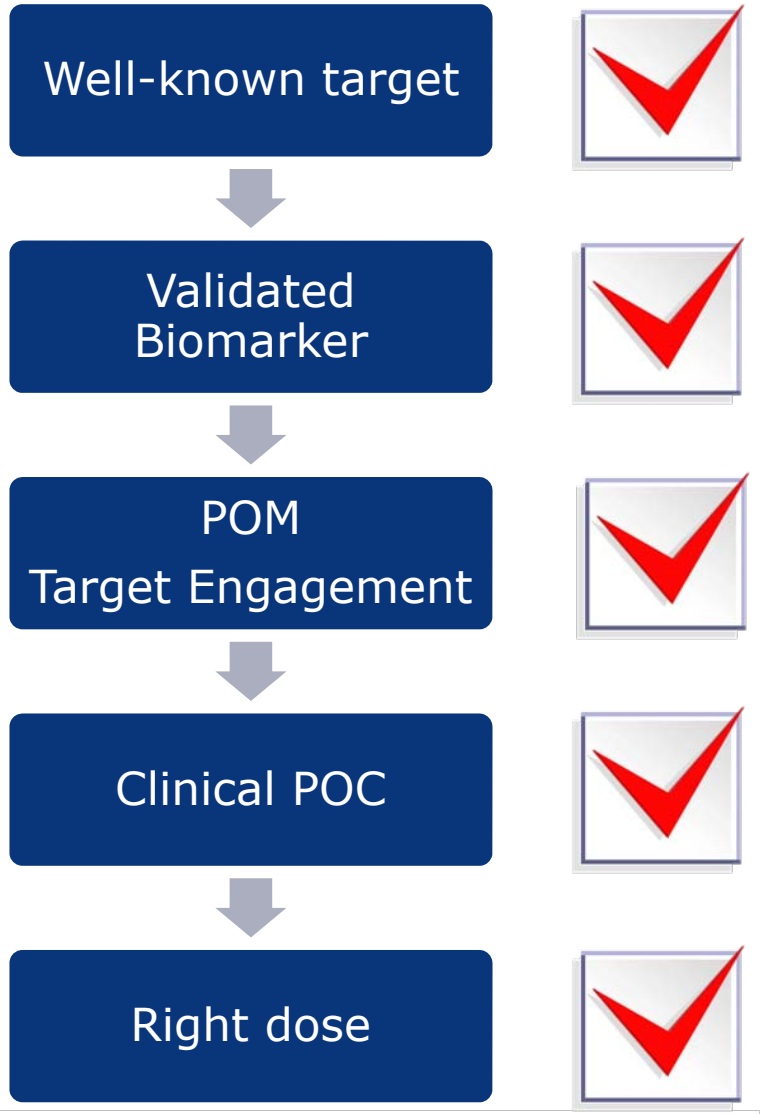
COU-AA-301 Overall Survival

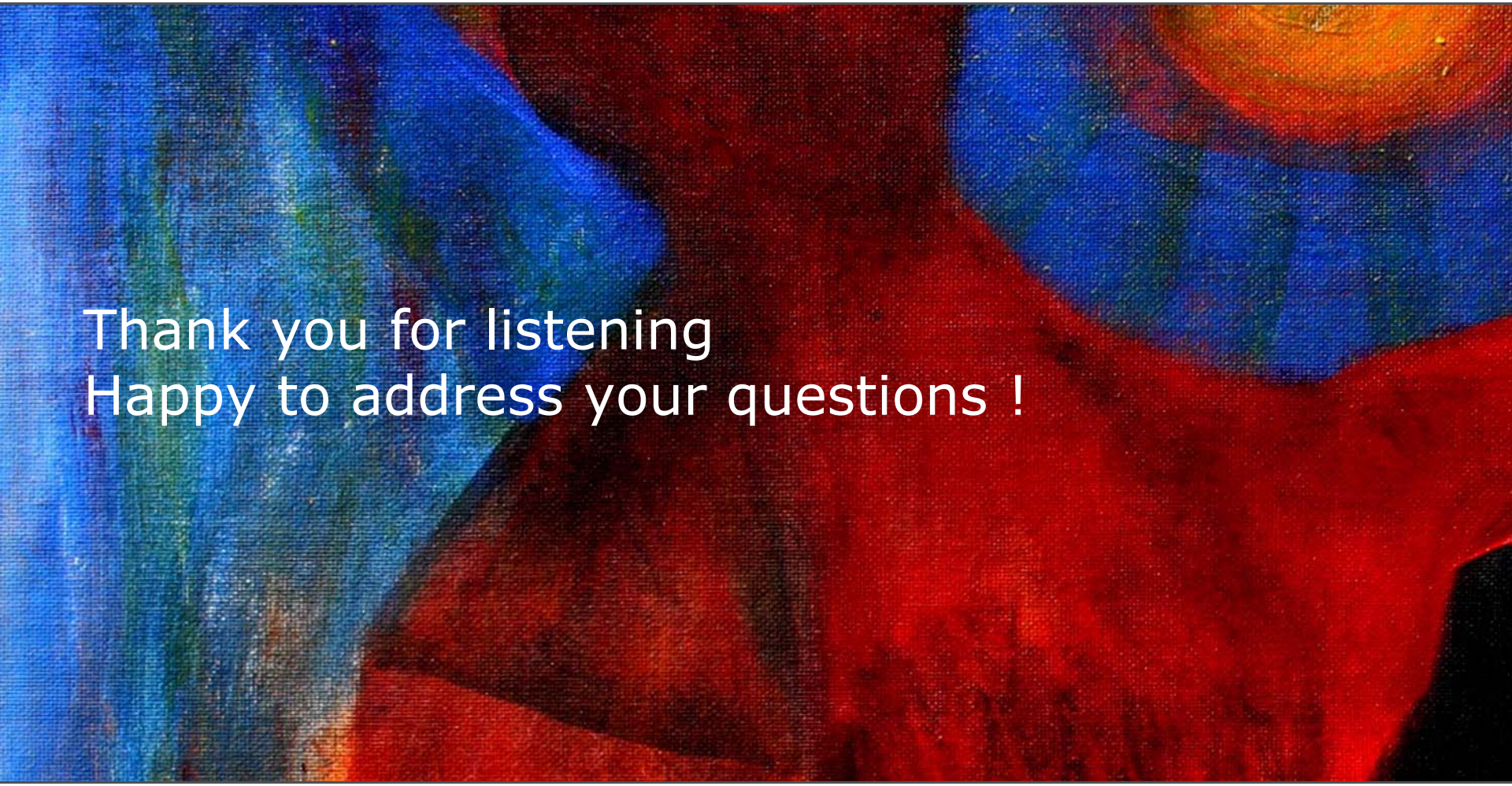
	Pred + Placebo	Pred + AA
OS (median)	332 days (10.9 mos)	450 days (14.8 mos)
HR (95% CI)	0.646 (0.54, 0.77)	
P value	<0.0001	



Conclusion

- ***Late-stage success for Abiraterone was built on a strong pharmacology foundation***
- ***Another key to success was the strong individual talent with an eye for new opportunities at ICR and the groups that persisted in developing it at Cougar Biotechnology***





janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson