

Improving the treatment of CRPC: Drugs, sequencing and stratification

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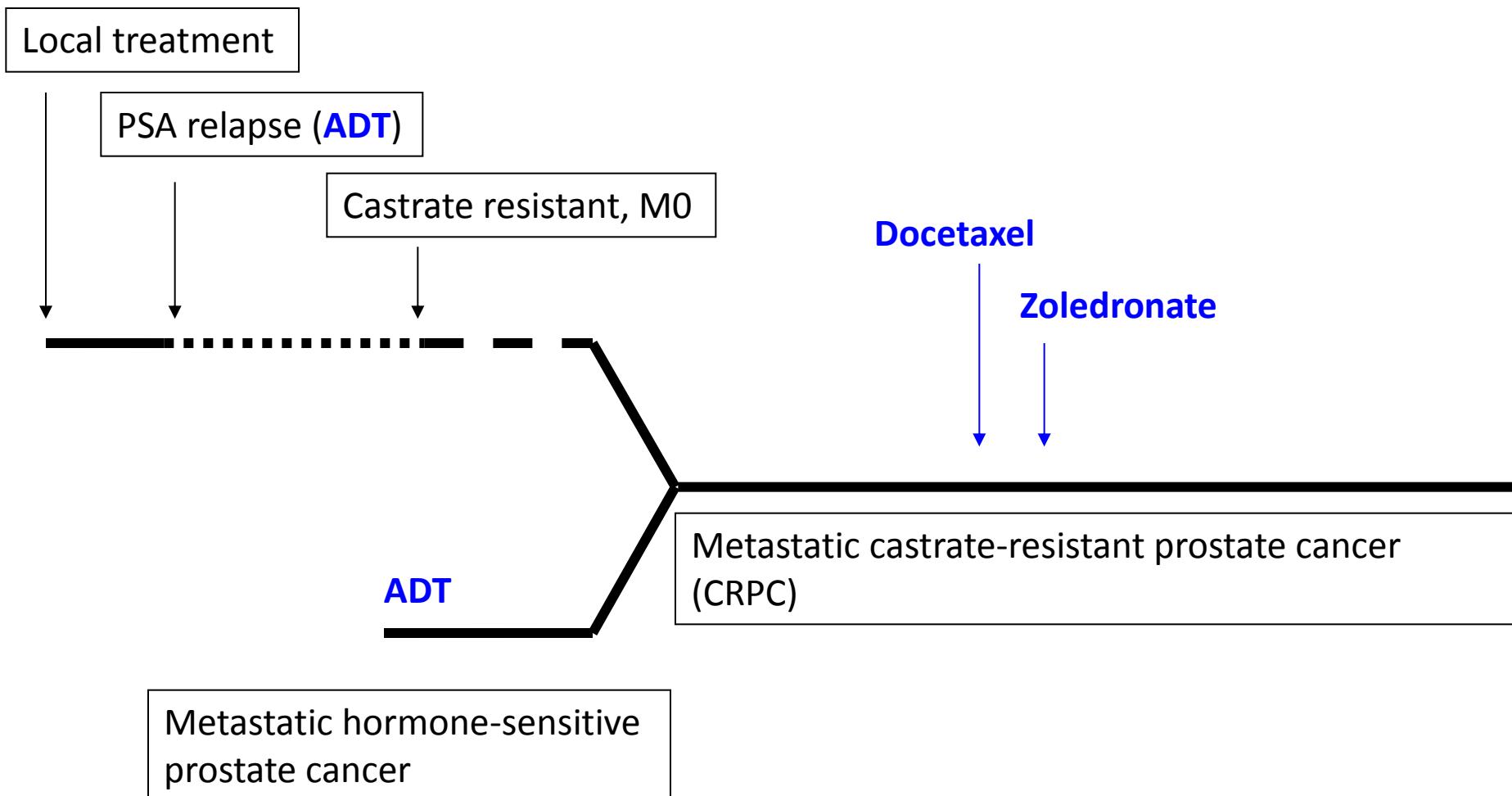
Villejuif, France



Disclosures

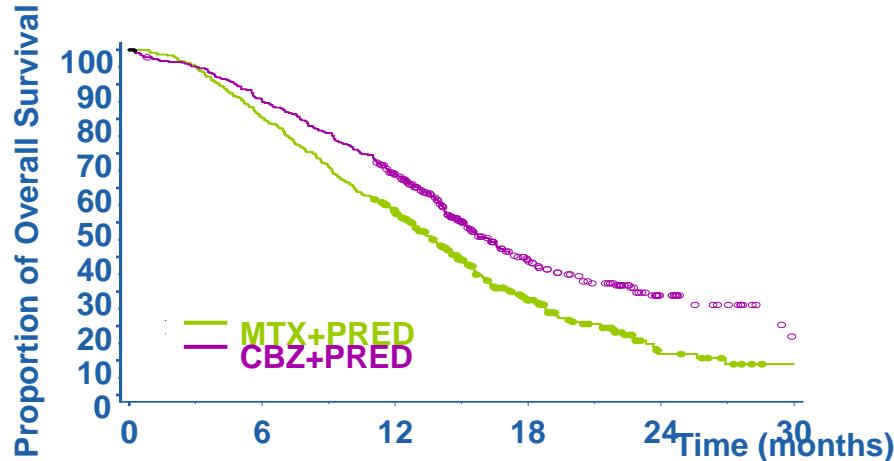
Participation in advisory boards/honoraria for:
Amgen, Astellas, Bayer, Janssen, Novartis, Orion,
Sanofi, Takeda

Advanced Prostate Cancer: Natural History (until 2010)

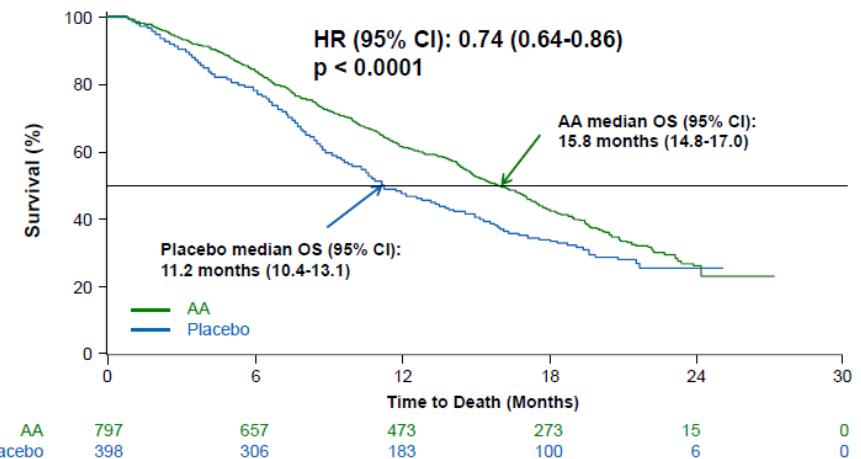


4 new active drugs in 4 years for post-docetaxel CRPC !

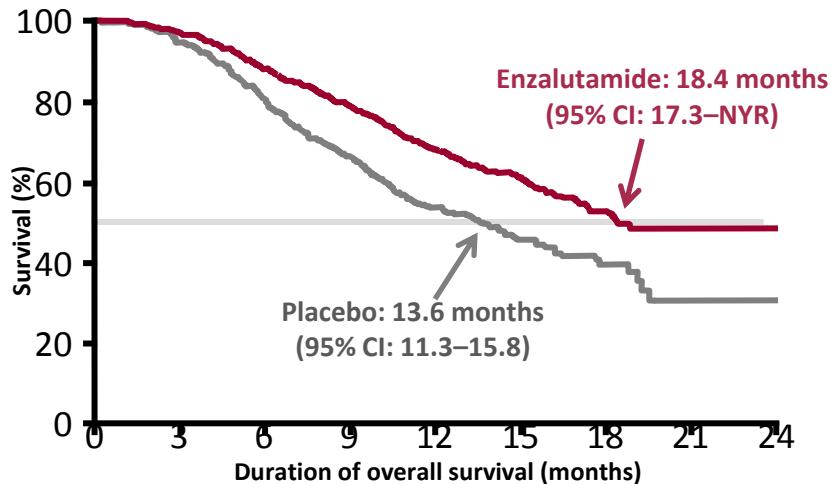
Cabazitaxel, De Bono J, Lancet 2010



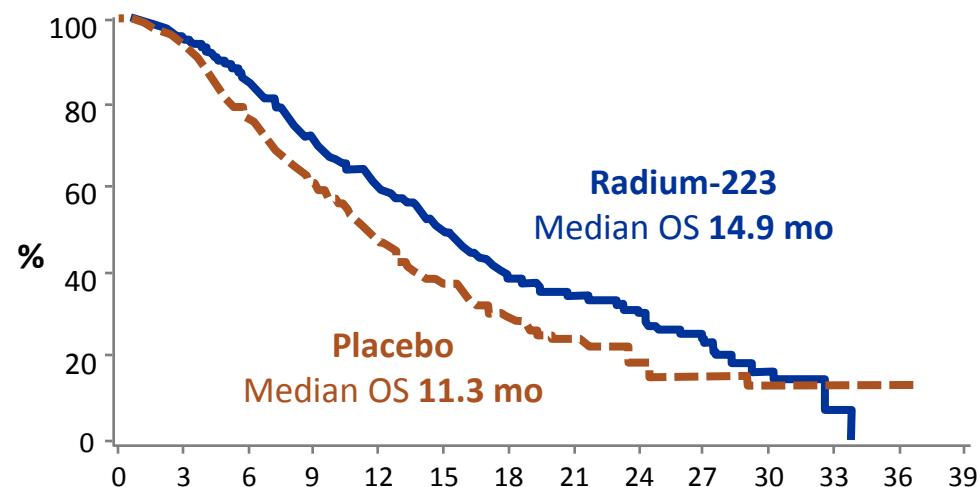
Abiraterone, Fizazi K, Lancet Oncol 2012



Enzalutamide, Scher HI, NEJM 2012

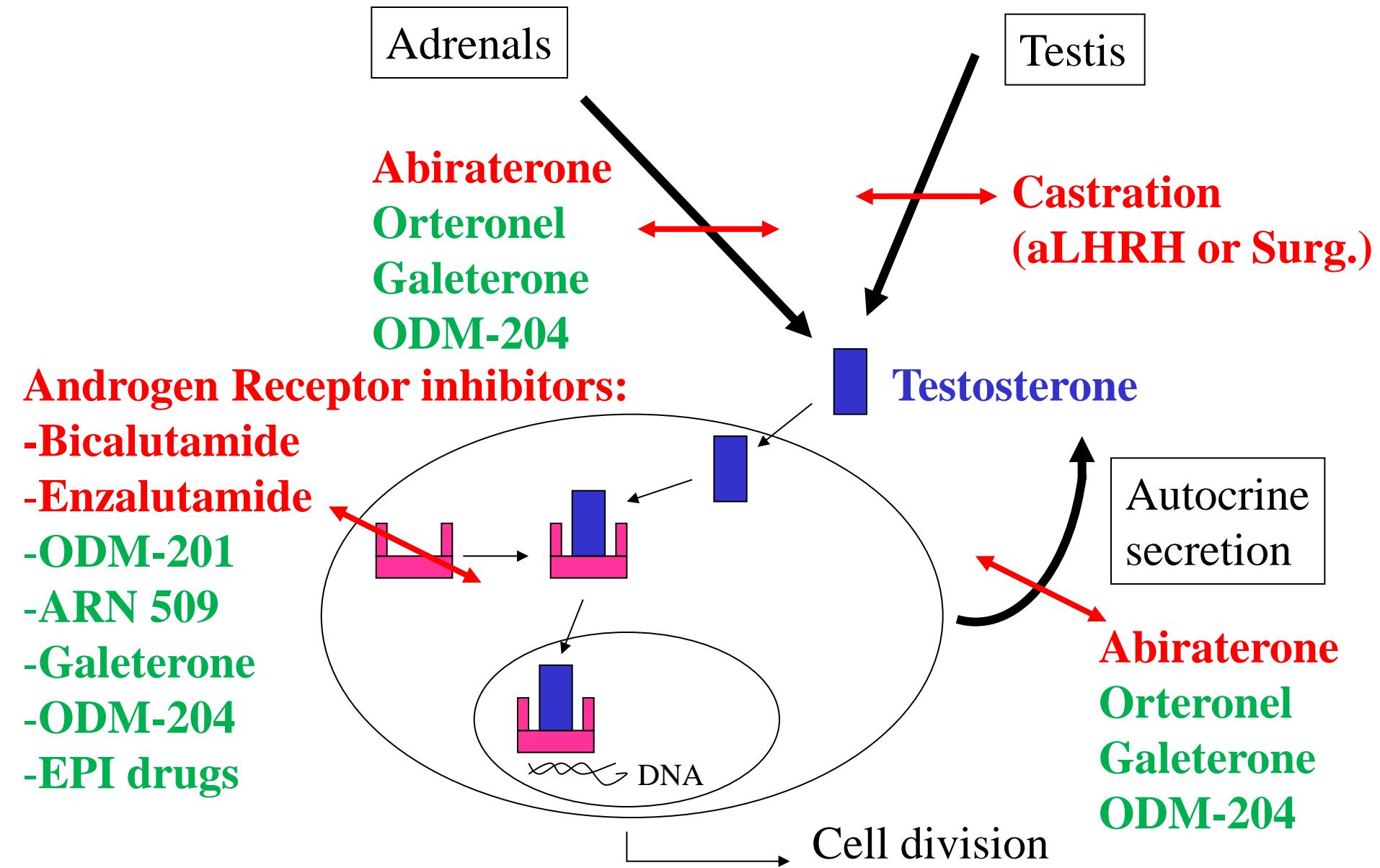


Radium-223, Parker J, NEJM 2013

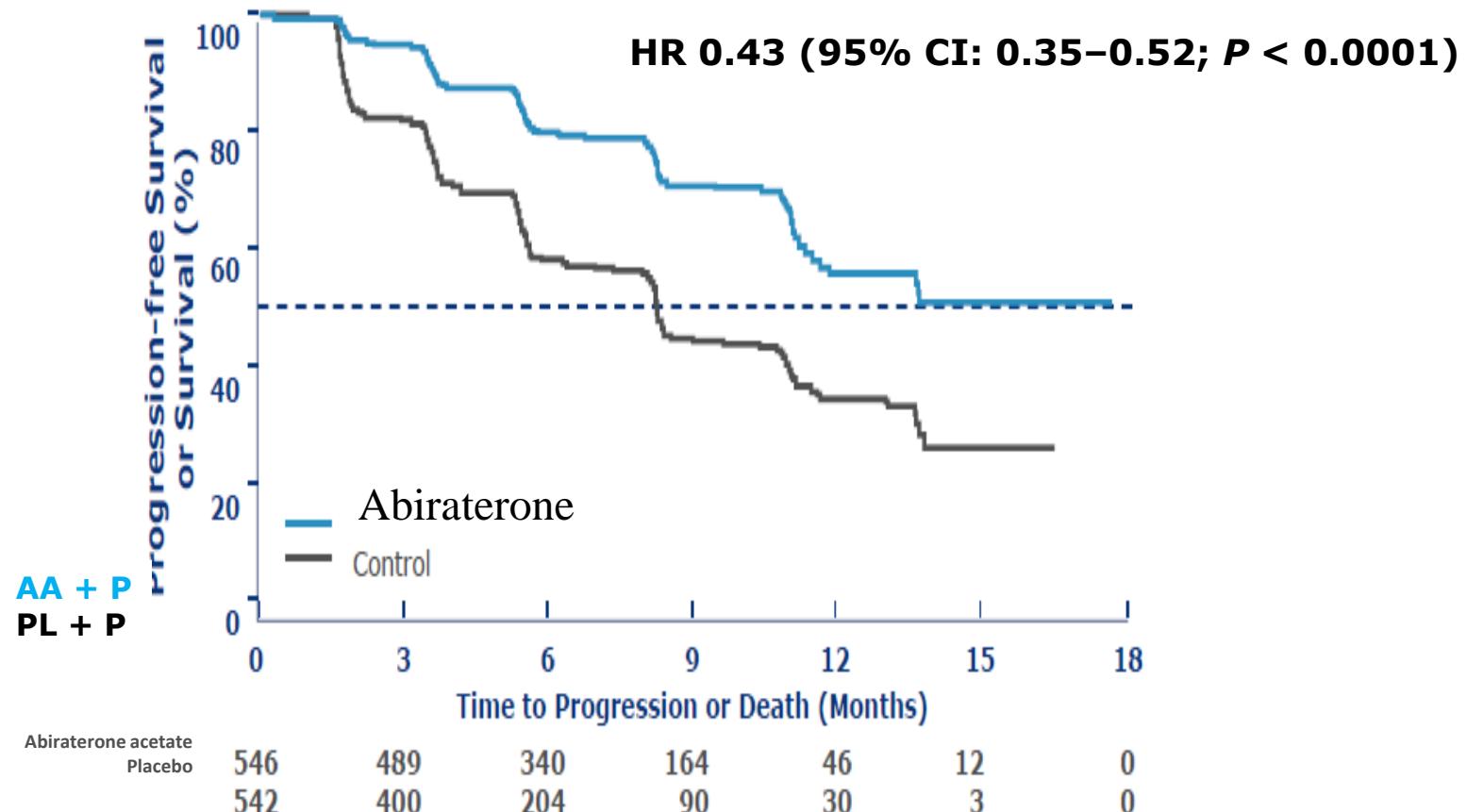


Treatment of “early” (asymptomatic) metastatic castrate-resistant prostate cancer

Targeting the AR pathway

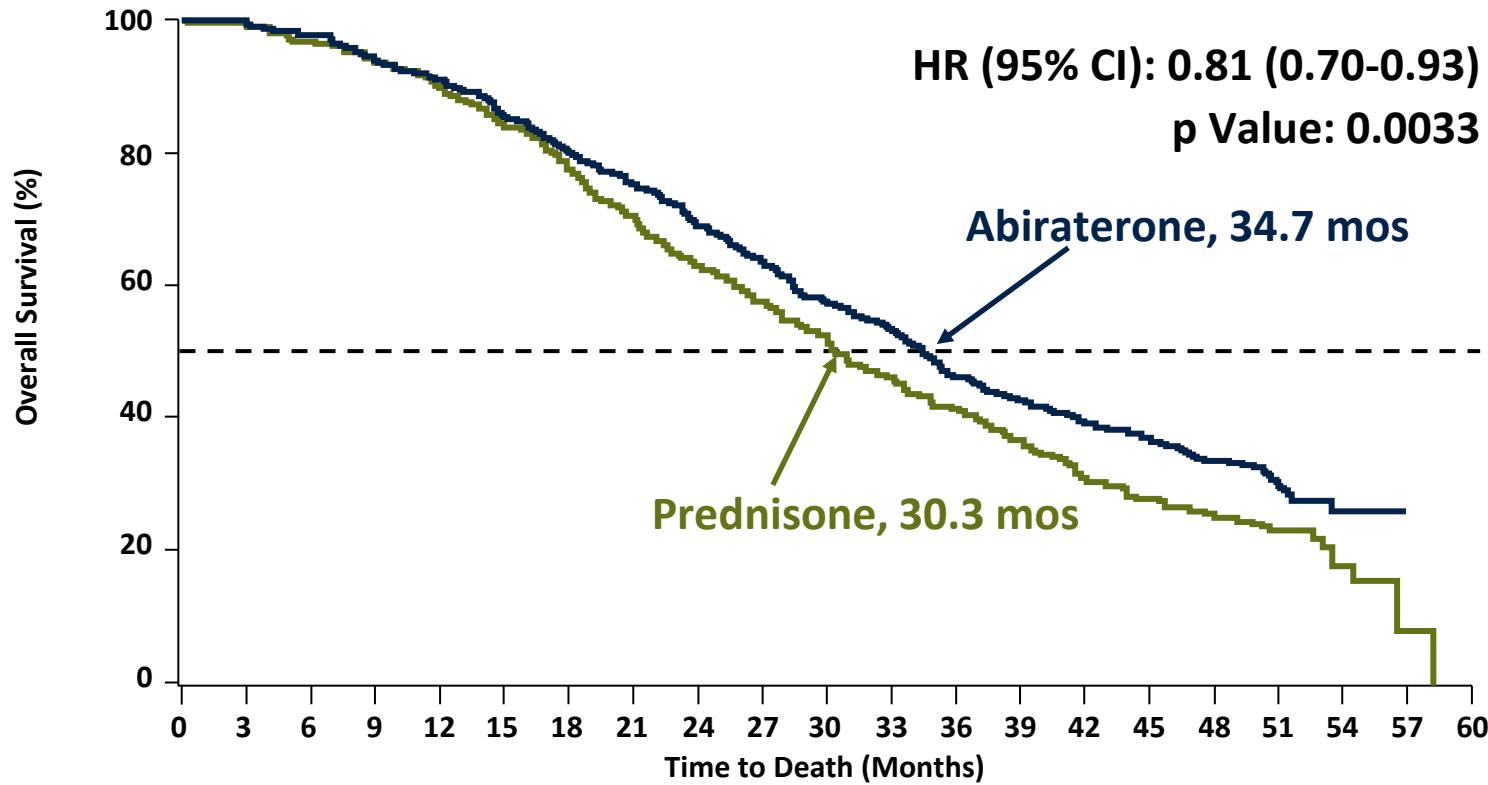


COU-302: Abiraterone in docetaxel-naïve CRPC patients: rPFS

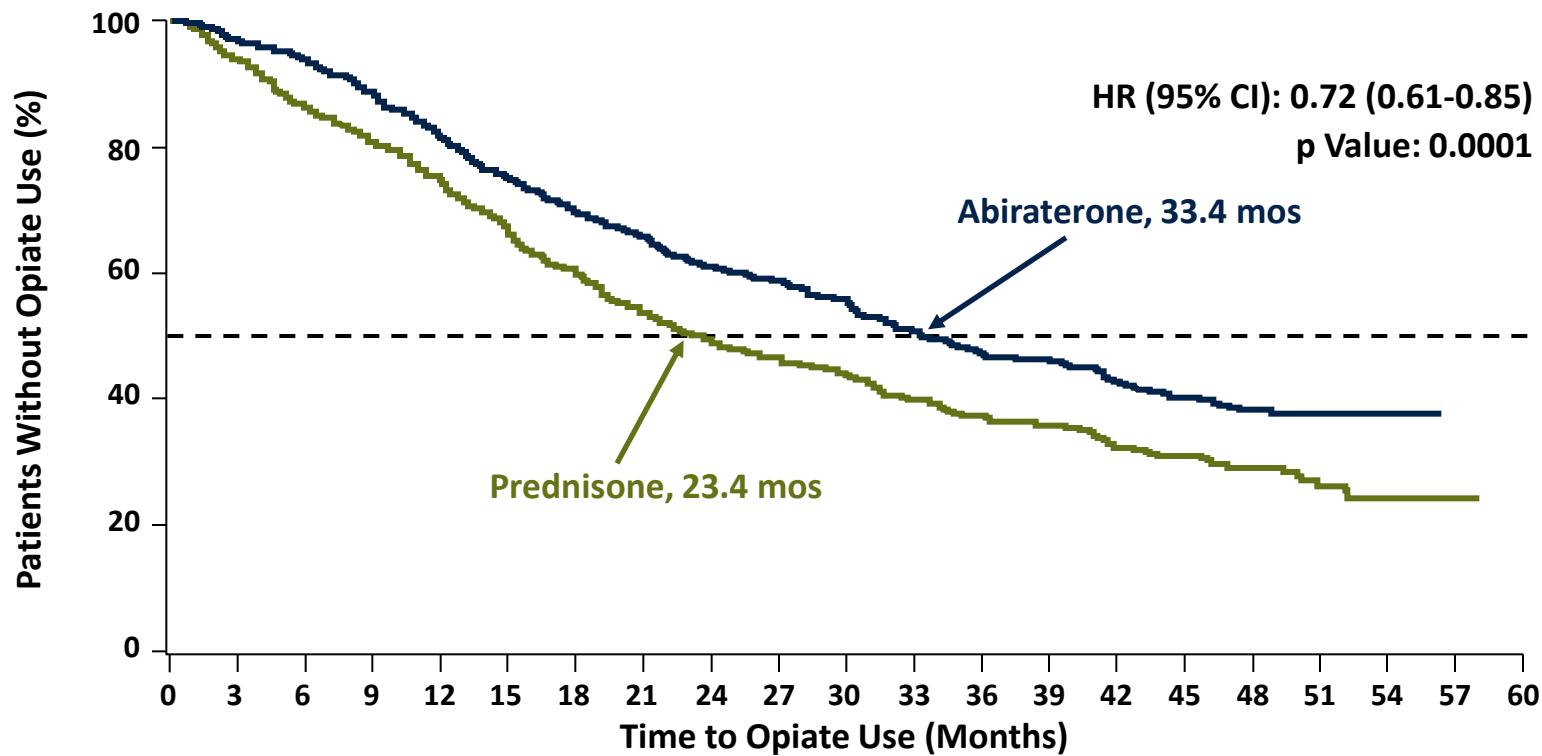


Ryan C, et al. N Engl J Med 2013

COU-302: Abiraterone in docetaxel-naïve CRPC patients: Overall survival



Significant Improvement in Time to Opiate Use for Cancer-Related Pain in the Final Analysis



Abiraterone	546	519	495	454	407	364	328	297	263	244	219	192	169	162	143	128	74	35	9	0	0
Prednisone	542	500	442	406	365	317	273	237	208	186	168	141	121	108	97	85	56	25	6	1	0

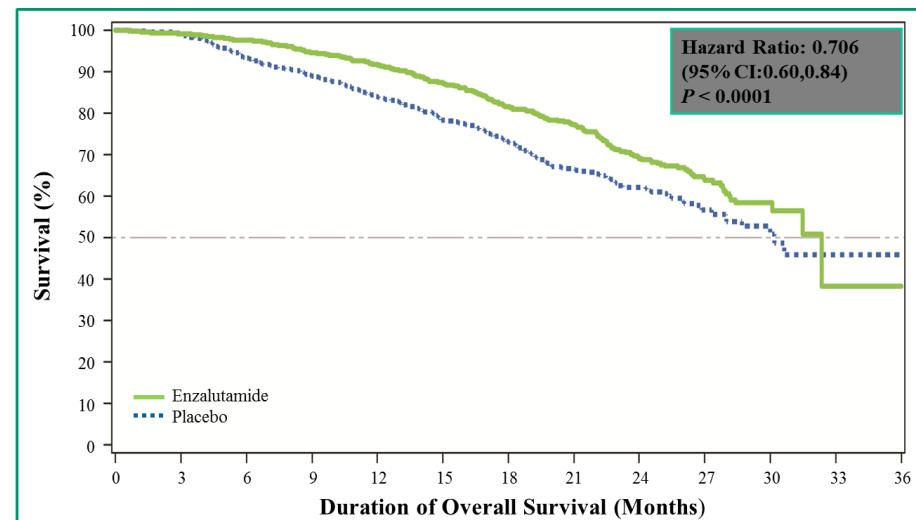
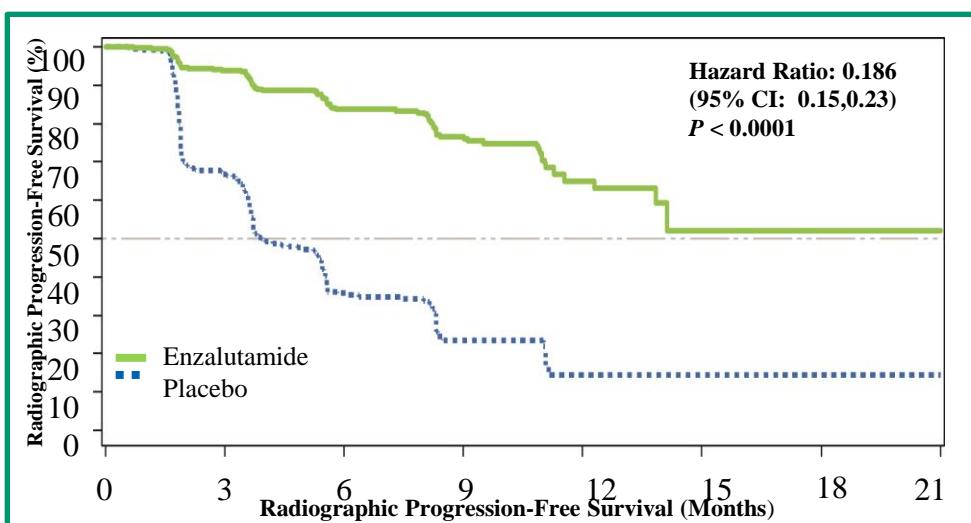
- At the time of IA3, the median time to opiate use had not been reached for abiraterone
- All secondary end points showed significant improvement with abiraterone

Cou-302: Safety Profile

	Abiraterone (n = 542) %		Prednisone (n = 540) %	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid retention/edema	31	1	24	2
Hypokalemia	19	3	13	2
Hypertension	24	5	14	3
Cardiac disorders	23	8	18	4
Atrial fibrillation	6	2	5	1
ALT increased	13	6	5	1
AST increased	12	3	5	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Prevail: Enzalutamide in docetaxel-naïve mCRPC patients



Prevail: safety of Enzalutamide pre-docetaxel

	All Grades (%)		Grade ≥3 events (%)	
	Enzalutamide (n=871)	Placebo (n=844)	Enzalutamide (n=871)	Placebo (n=844)
Fatigue	35.6	25.8	1.8	1.9
Back pain	27.0	22.2	2.5	3.0
Constipation	22.2	17.2	0.5	0.4
Arthralgia	20.3	16.0	1.4	1.1
Cardiac AEs	10.1	7.8	2.8	2.1
Hypertension	13.4	4.1	6.8	2.3
ALT increased	0.9	0.6	0.2	0.1
Seizure	0.0 [†]	0.1	0.0 [†]	0.0

Treatment decision making in CRPC: several obvious situations

- History of seizure
- Visceral metastases
- Patient too old/sick
- Contra-indication to steroids (severe diabetes, etc)
- Enzalutamide
- Radium-223
- Taxanes
- Abiraterone

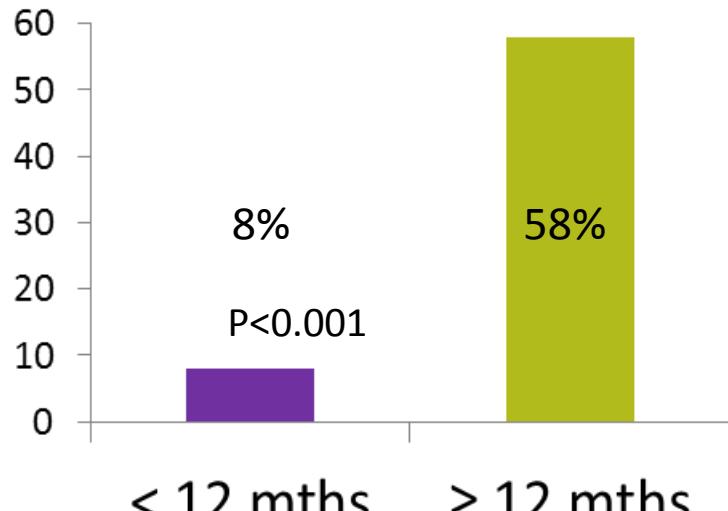
Drug-drug interactions

- **Enzalutamide = powerful CYP3A4 inducer** and a moderate CYP2C9 and CYP2C19 inducer:
 - Avoid Cabazitaxel,
 - Be careful with many drugs (zolpidem, fentanyl, clopidrogel, lovastatin, triazolam, amiodarone, etc)
- **CYP2C8 induces Enzalutamide metabolism** into its active metabolite and its elimination:
 - Avoid CYP2C8 inhibitors (gemfibrozil) and inducers (rifampicine)
- **Abiraterone = CYP 2C8 inducer and CYP 2D6 inhibitor**

**Can we predict who benefits from
Next-generation AR-Targeting
Drugs?**

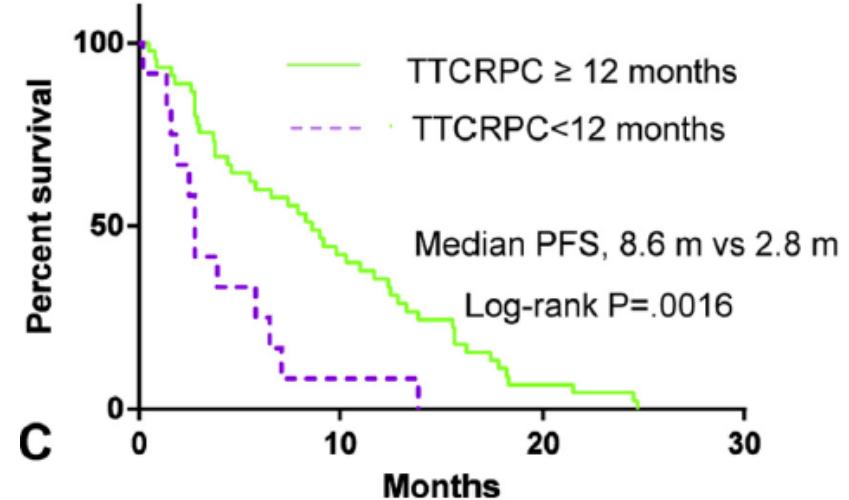
Short response to ADT predicts poor response to Enzalutamide (post-docetaxel)

PSA decrease \geq 50%



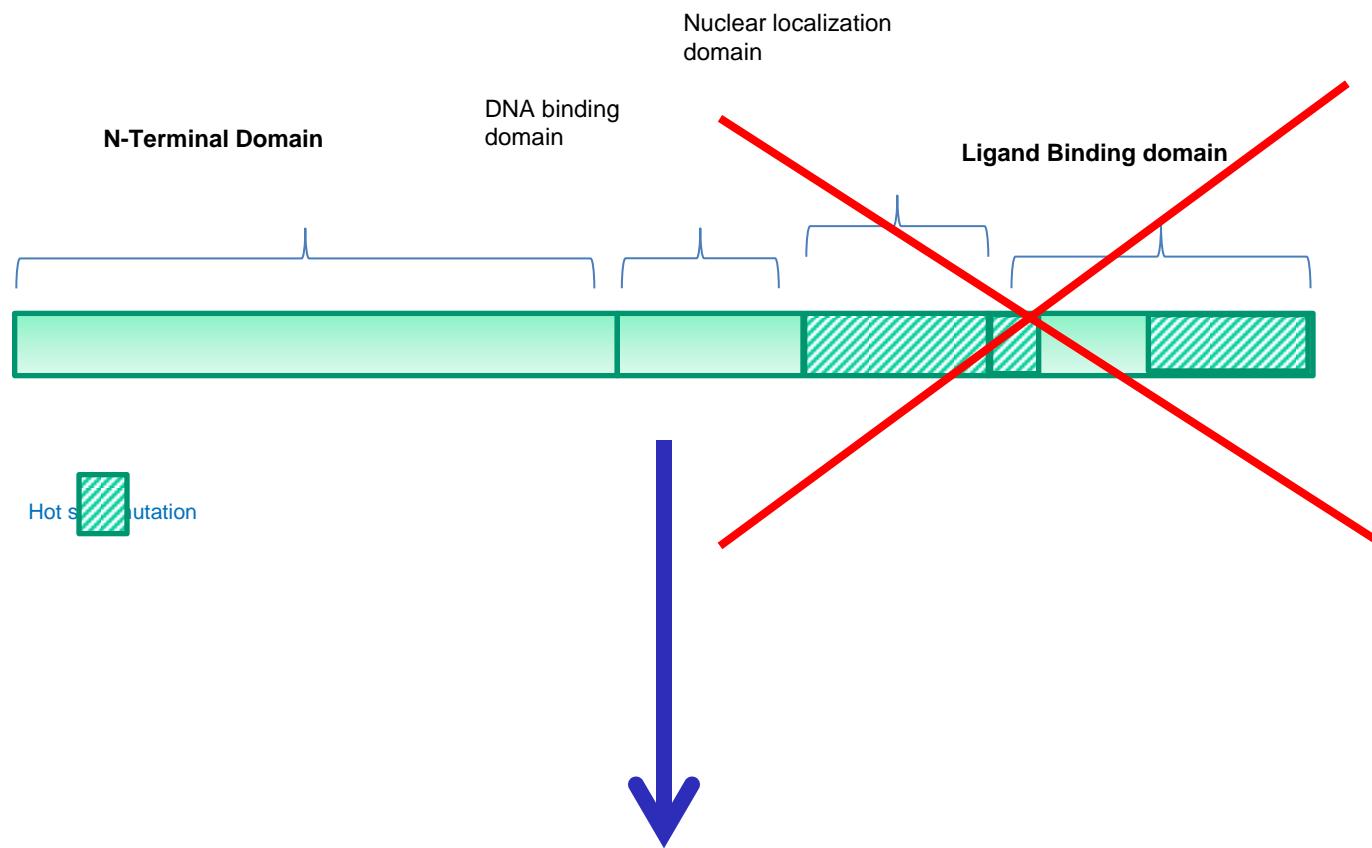
TTCRPC

PFS



Loriot Y et al., Eur J Cancer 2015; 51: 1946-52

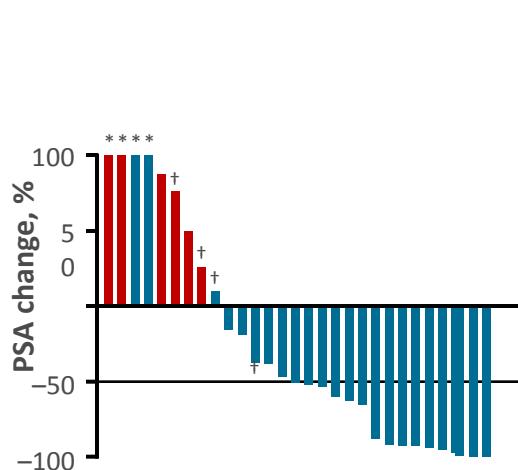
AR splice variants (V7)



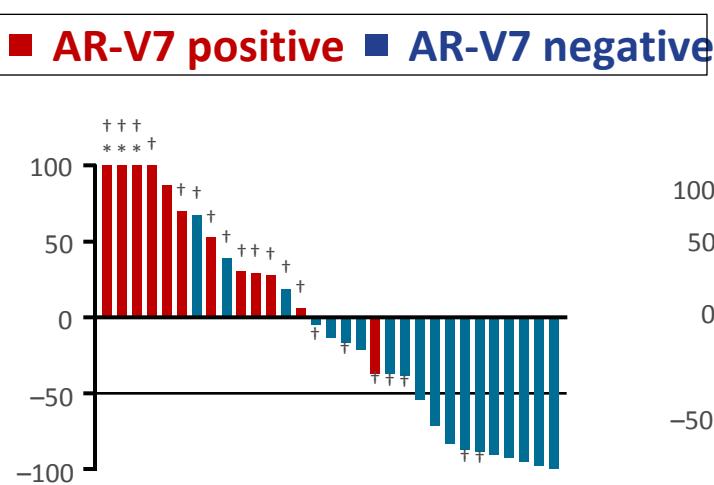
**Splice variant -> AR constitutively active
(no need for androgens)**

CTCs: AR-V7 seems a promising predictor of treatment response

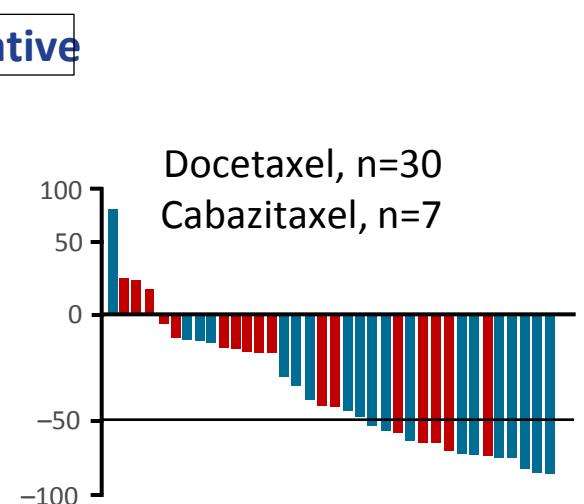
Abiraterone¹



Enzalutamide¹



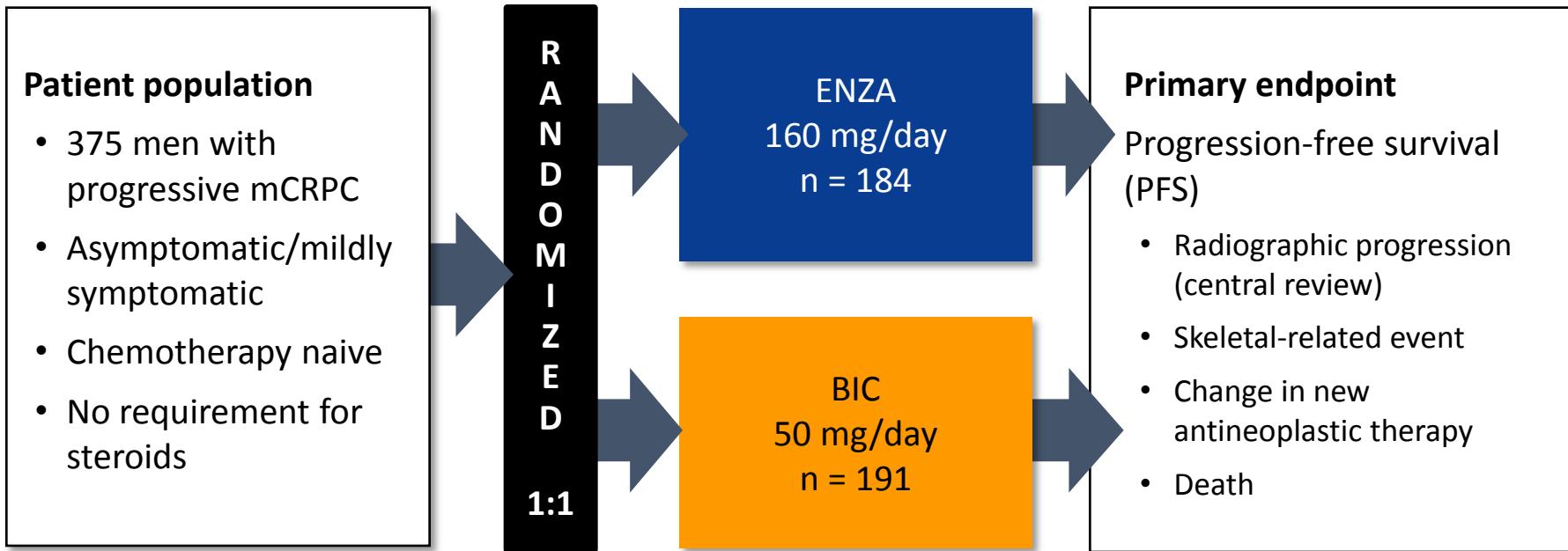
Taxanes²



1. Antonarakis ES et al. N Engl J Med 2014;371:1028-38; 2. Antonarakis ES et al. JAMA Oncol 2015; 1:582-91

**Should We Keep Using “Old”
Hormonal Manipulations Before
Using Next-generation AR-Targeting
Drugs?**

TERRAIN Study Design



TERRAIN trial: NCT01288911

Statistical design

- The final analysis was planned at ≥ 220 progression events with 85% power to detect a target hazard ratio of 0.67 (assuming a median PFS of 9 months vs 6 months¹)
- The data cutoff date was 19 October 2014, with 240 events for the primary efficacy endpoint

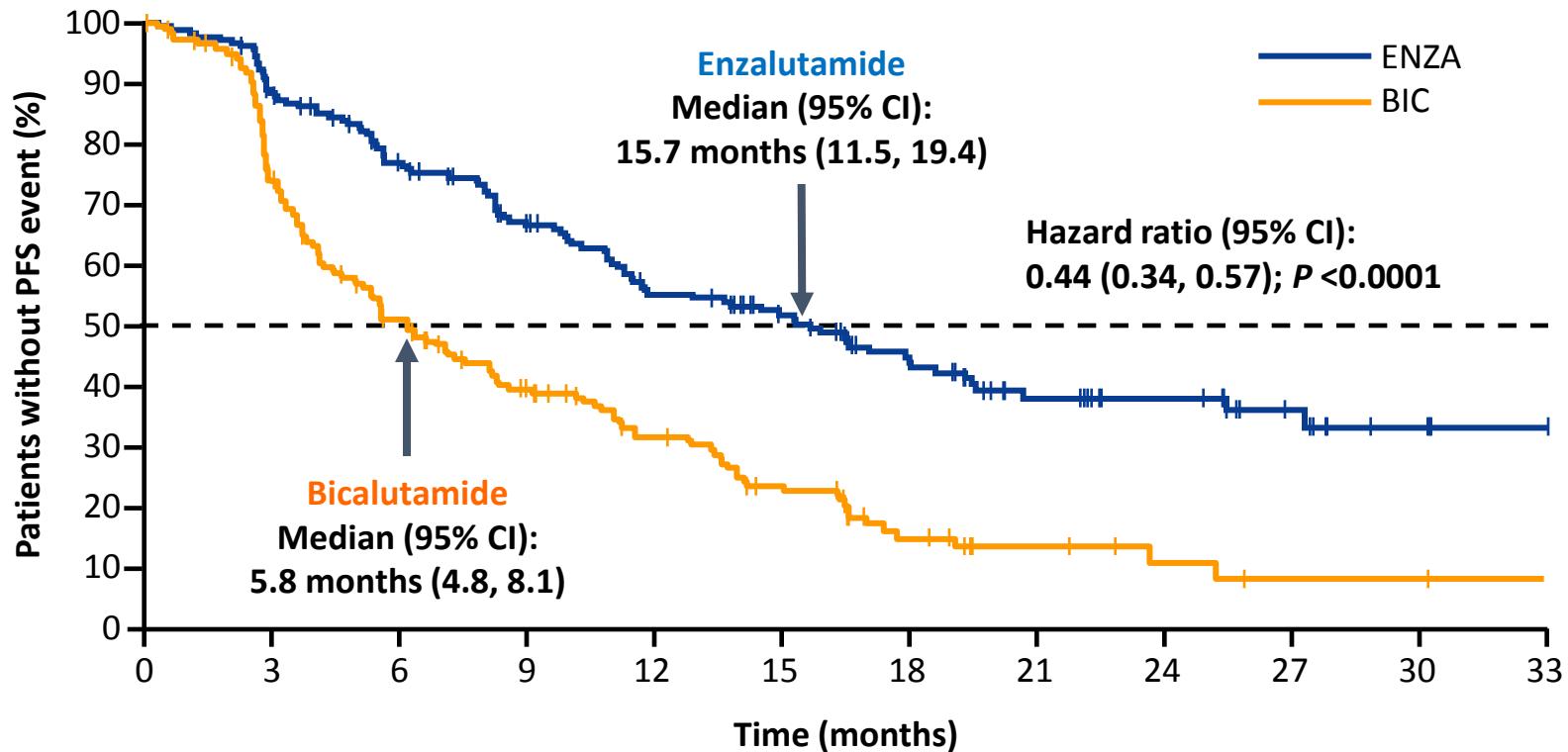
Secondary endpoints

- PSA response
- Time to PSA progression

1. Kucuk O, et al. *Urology*. 2001;58:53-58.

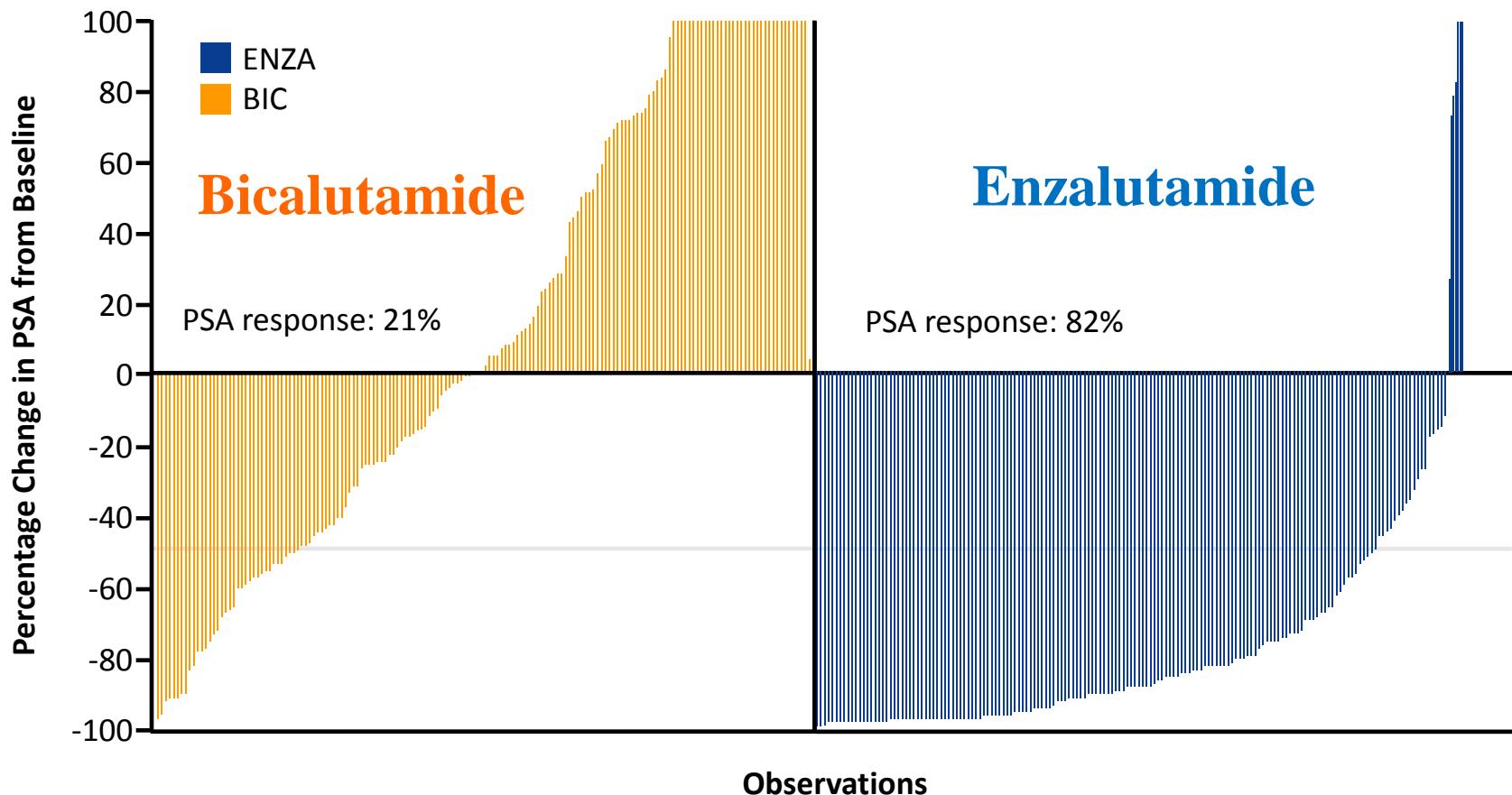
Heidenreich A. EAU 2015. Abstract 234.

Progression-Free Survival in TERRAIN



ENZA	
Patients at risk	184 159 131 107 86 71 52 33 21 13 8 5
BIC	
Patients at risk	191 133 85 61 44 30 13 7 4 2 1

PSA Response by Week 13 with ENZA or BIC



CRPC pre-treated by abiraterone or
enzalutamide:

How to treat?

Sequential use of Enzalutamide and Abiraterone: probably not a good option for most patients (at least post-docetaxel)

Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100)

Y. Loriot^{1*}, D. Bianchini², E. Ileana¹, S. Sandhu², A. Patrikidou¹, C. Pezaro², L. Albiges¹, G. Attard², K. Fizazi¹, J.S. De Bono² & C. Massard¹

Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide

K. L. Noonan¹, S. North², R. L. Bitting³, A. J. Armstrong³, S. L. Ellard⁴ & K. N. Chi^{1*}

¹Department of Medical Oncology, BC Cancer Agency, Vancouver Cancer Centre, Vancouver; ²Department of Medical Oncology, Cross Cancer Institute, Edmonton, Canada; ³Duke Cancer Institute and the Duke Prostate Center, Duke University, Durham, USA; ⁴Department of Medical Oncology, BC Cancer Agency, Cancer Centre for the Southern Interior, Kelowna, Canada

- 38 pts progressing on enzalutamide and docetaxel
- PSA decrease $\geq 50\%$ in 8%
- Median PFS: 2.7 months
- Only 1 partial response (8%)
- 30 pts progressing on enzalutamide and docetaxel
- PSA decrease $\geq 50\%$ in 3%
- Median PFS: 3.5 months
- No objective response

Enzalutamide post-Abiraterone (and post-Docetaxel)

- n=39 pts
- PSA resp: 13%
- **PFS=2.8 months**
- n=35 pts
- PSA resp: 29%
- **PFS<4 months**
- n=61 pts
- PSA resp: 21%
- **PFS=4 months**
- 1 partial resp (3%)

Bianchini D

Eur J Cancer 2014

Schrader AJ, Eur Urol

2014; 65: 30-6

Badrising S, Cancer

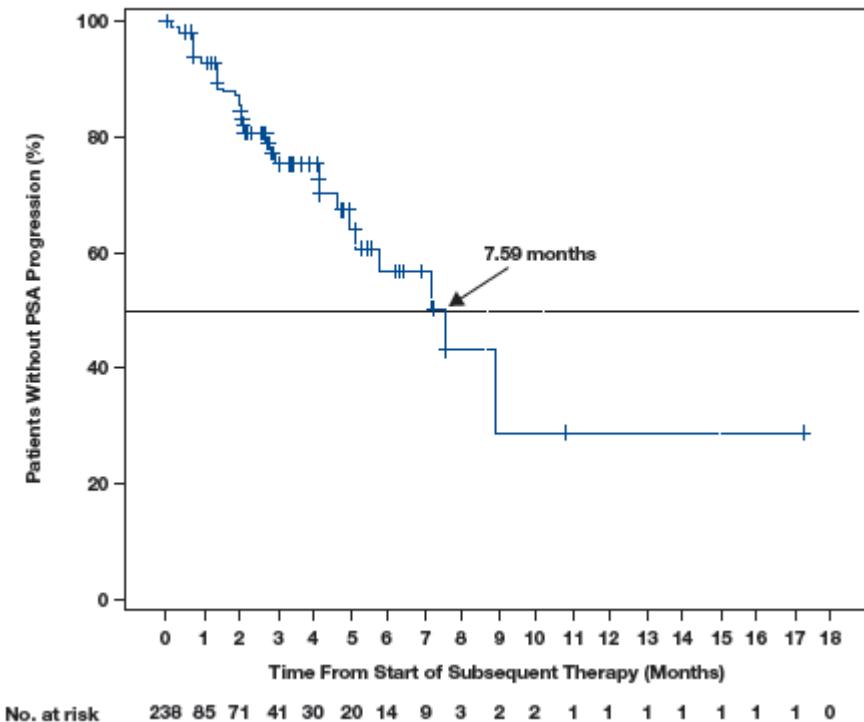
2014; 120: 968-75

Taxane post-Abiraterone (COU-302)

Table 3. Clinical Response on First Subsequent Chemotherapy

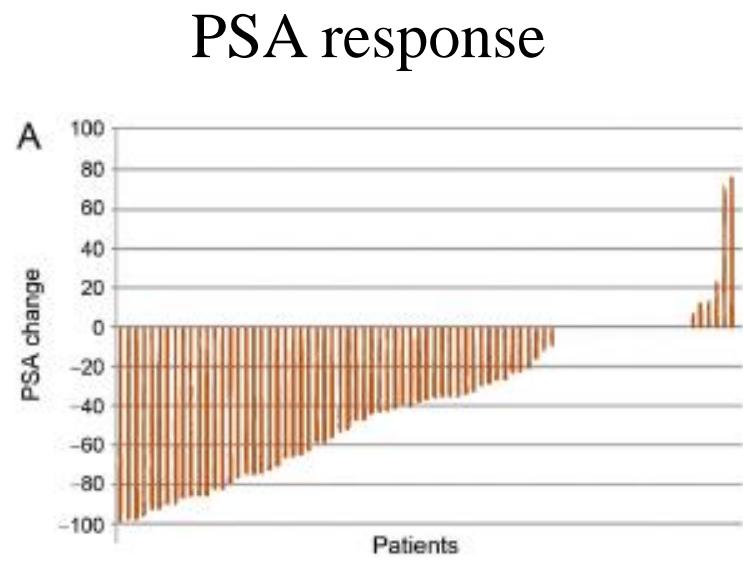
	AA, then taxane chemotherapy as first subsequent therapy
n	265
Exposure to first subsequent chemotherapy	
Treatment duration ^a , median (IQR)	3 months (1.0-5.0)
TTTP ^b on first subsequent chemotherapy, median (95% CI)	7.59 months (4.99, NE)
PSA response based on PCWG2 criteria (per investigator), n (%)	
PSA fall by 50% ^c , n (%)	117 (47)
Confirmed PSA progression	31 (13)
Reason for discontinuation per investigator ^{d,e} , n (%)	
Clinical progression	39 (15)
Radiographic progression	38 (14)
PSA progression	77 (29)
Adverse event	41 (16)
Therapy ongoing	11 (4)
Other	73 (28)

TTTP on First Subsequent Chemotherapy



Cabazitaxel post-Abiraterone (and post-docetaxel)

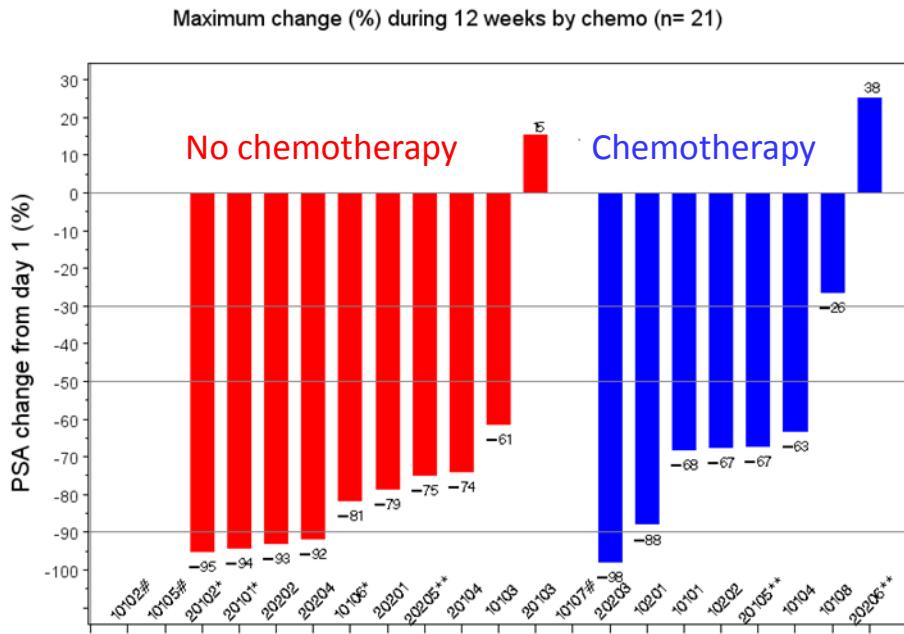
- n=79 pts
- PSA response>30%: **62%**
- PSA response>50%: **35%**
- PFS: 4.4 mo
- OS: 11 mo
- *In vitro*: Caba active against both enza-S and enza-R cells



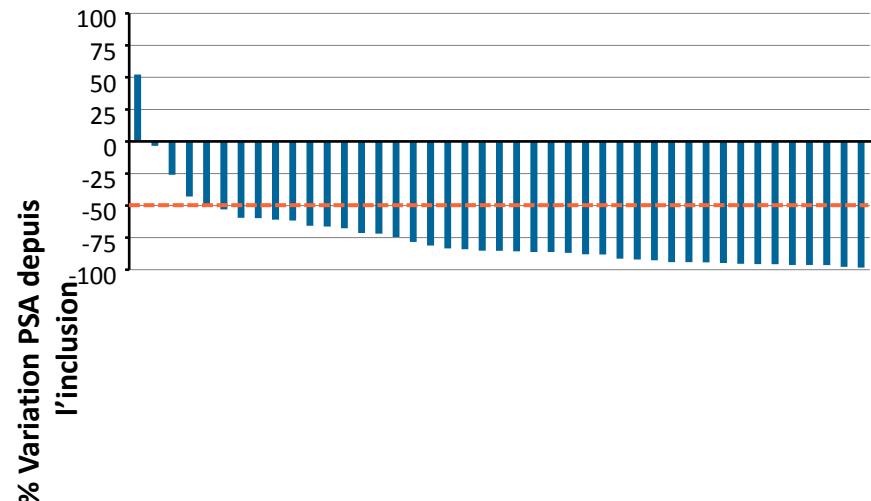
Other drugs targeting the AR axis?

ODM-201 and ARN-509 (AR inhibitor)

ODM-201



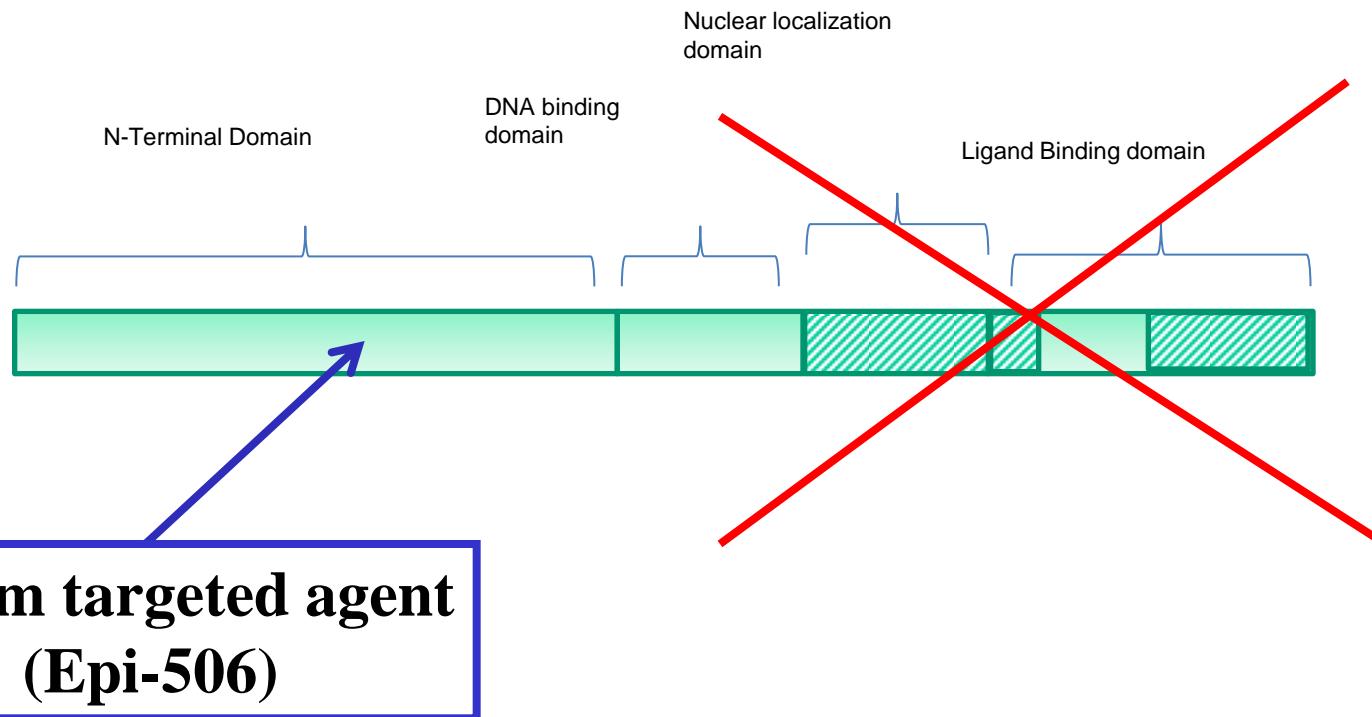
ARN-509



*) New subjects in cohort 2, **) Post Cyp-17i, #) Discontinued subjects, Red: pre-chemo, Blue: post-chemo

Fizazi K, et al. Lancet Oncol 2014; 15: 975-85
Smith MR et al. ASCO GU 2013, Abstract # LBA 7

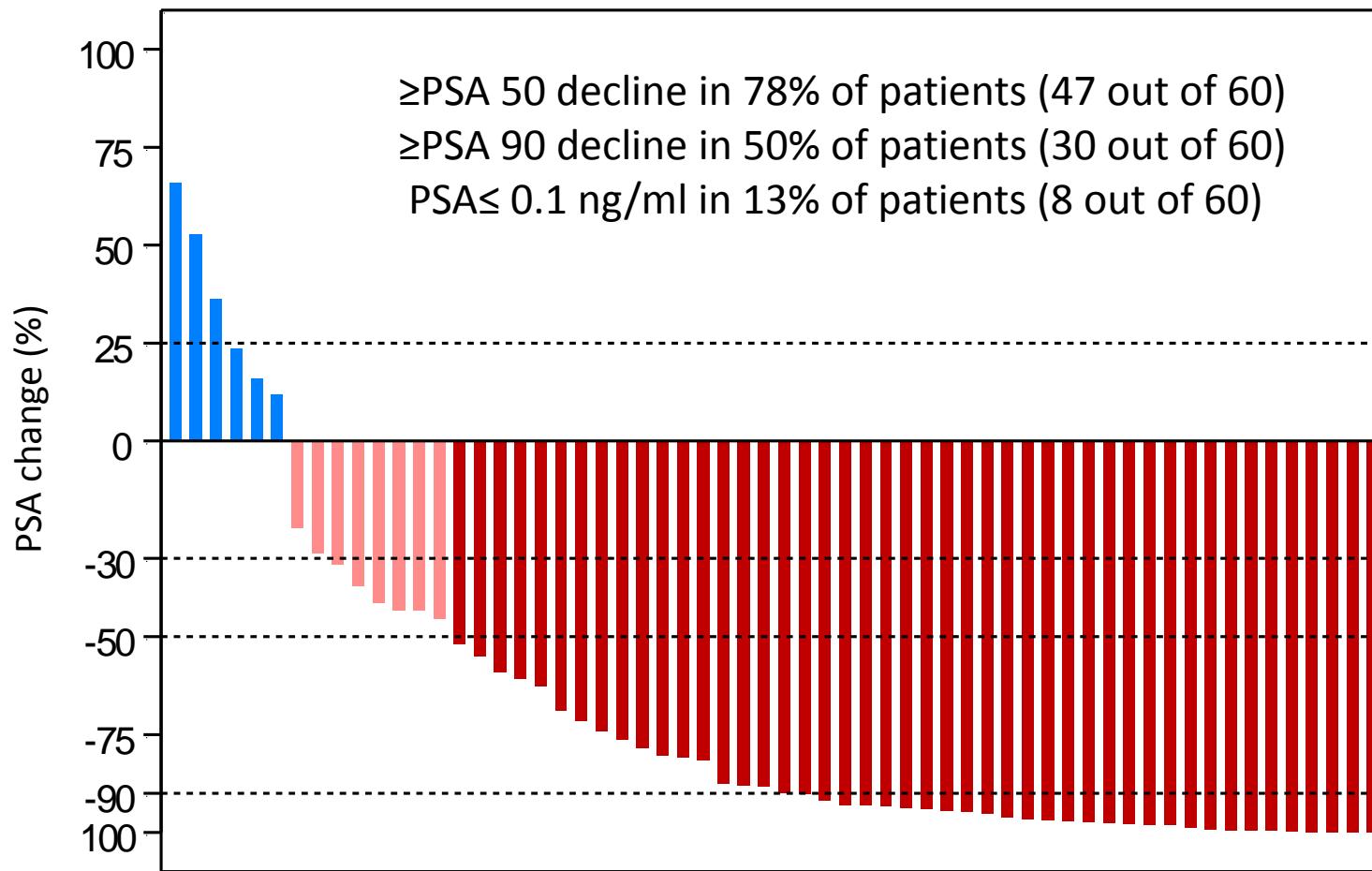
AR splice variants: Toward N-term targeting drugs?



**Splice variant -> AR constitutively active
(no need for androgens)**

Combination of AR pathway
targeting drugs in mCRPC?

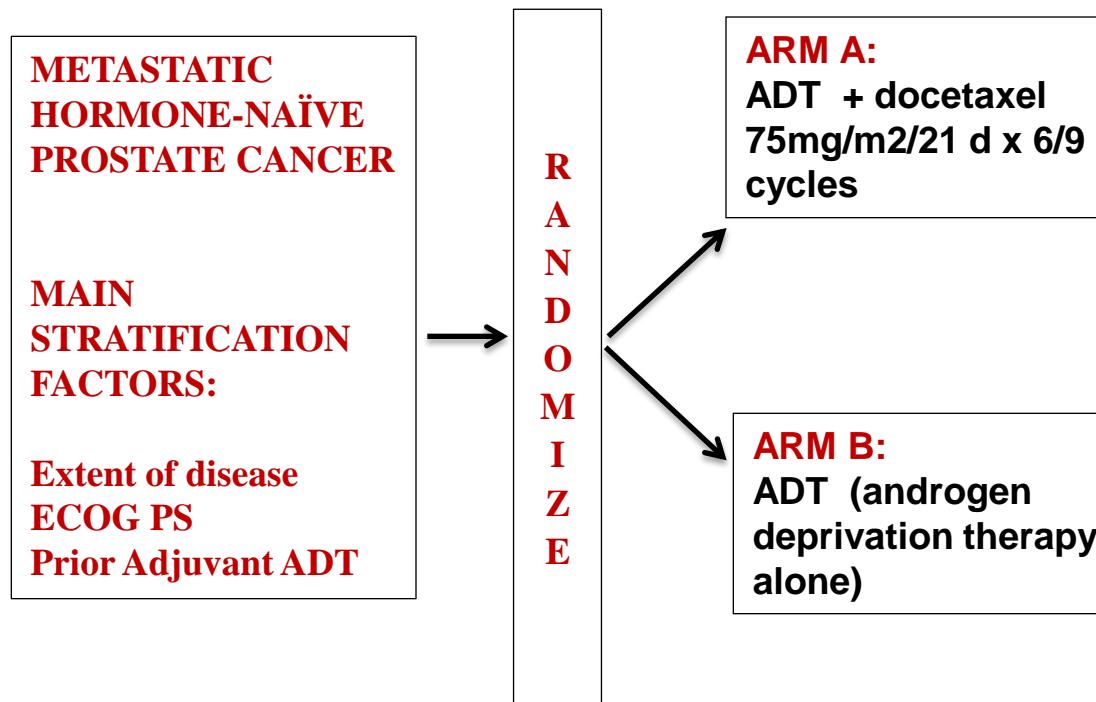
Abiraterone + Enzalutamide Phase I-II trial



Exploratory: association of lack of PSA decline with resistance ($p=0.008$)

But things will soon change again
because many patients
developing CRPC will be likely
pre-treated with docetaxel !

Three phase III trials: GETUG 15, Chaarted and Stampede



GETUG 15
Chaarted

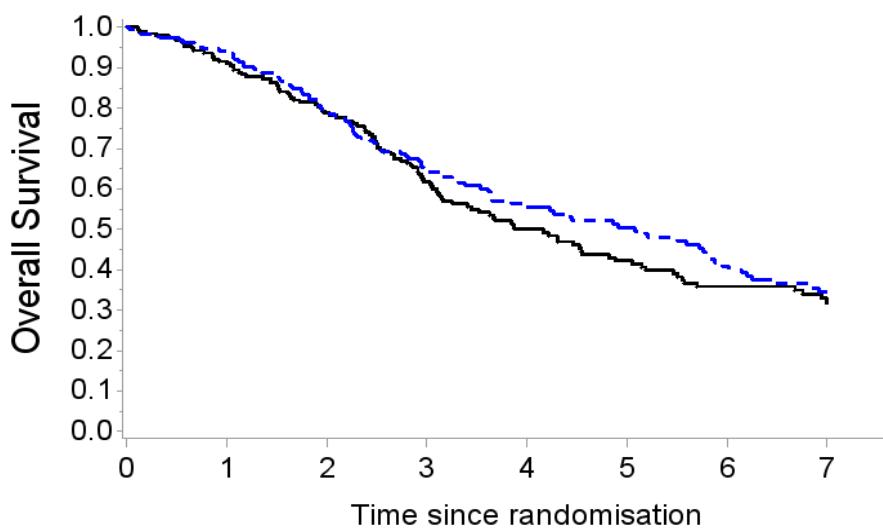
n=385
n= 790

Accrual: 2004-2008
Accrual: 2006-2012

Docetaxel in mHSPC: Overall Survival

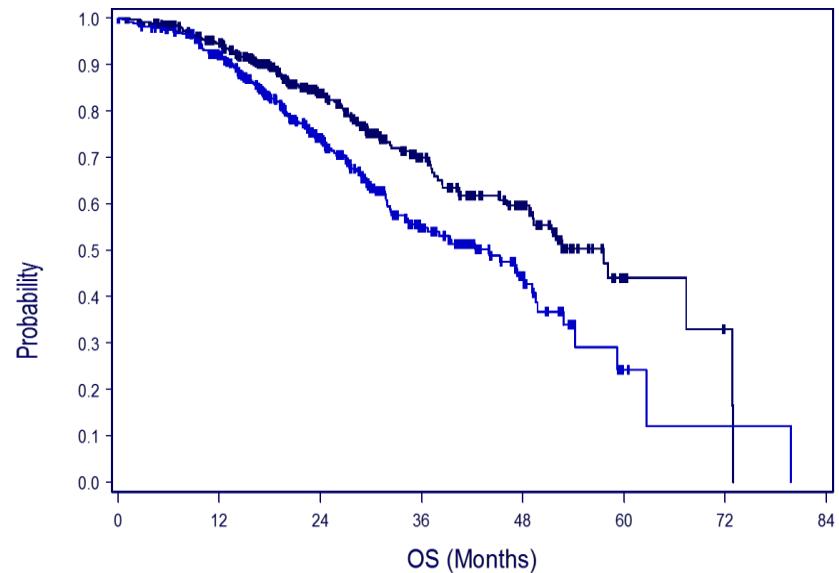
GETUG 15 (1/2 poor-risk pts)

ADT + D: 61 months
ADT: 47 months
HR: 0.9 [0.7–1.2]; $P = .44$



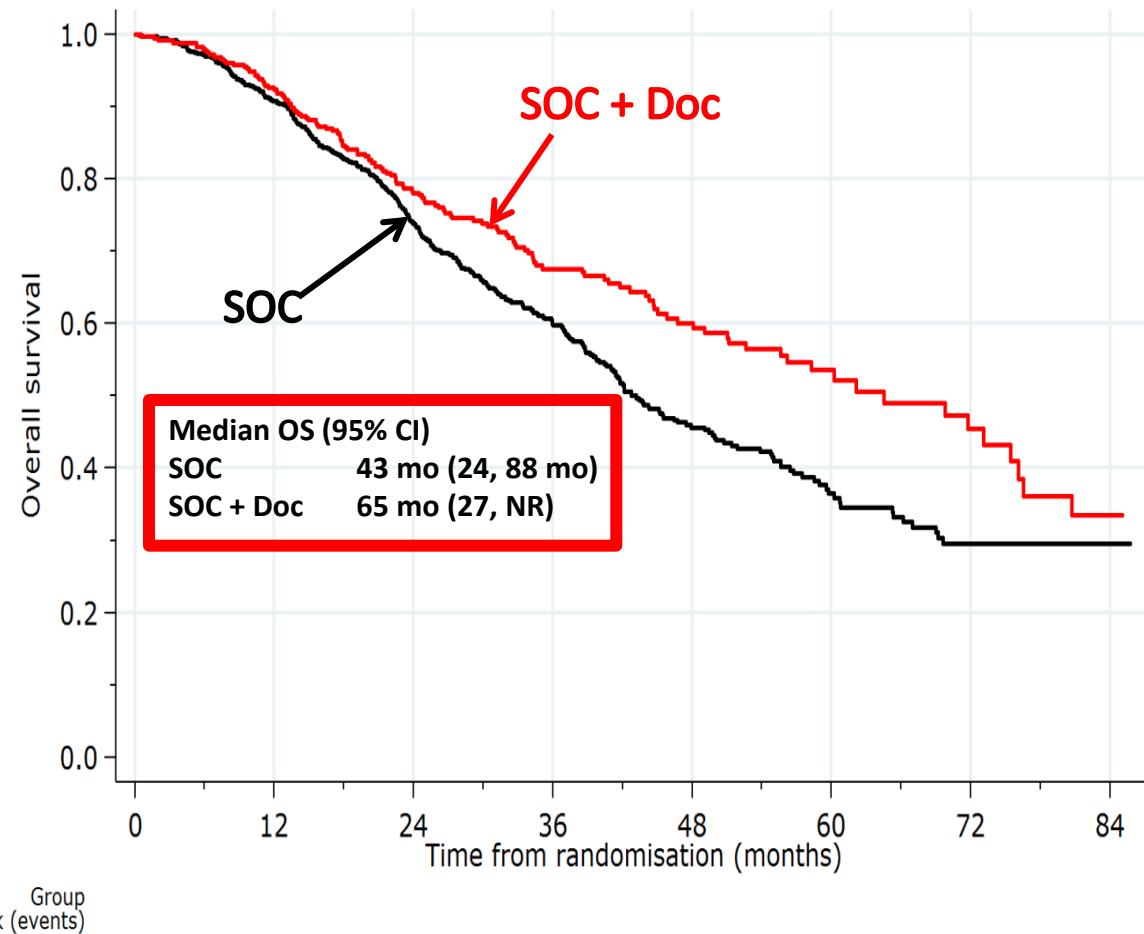
CHAARTED (2/3 poor-risk pts)

ADT + D: 58 months
ADT alone: 44 months
HR = 0.61 (0.47–0.80) $P = .0003$



ADT	193	171	148	105	66	53	43	29
ADT + D	192	175	145	100	70	58	47	27

STAMPEDE: Docetaxel – Survival, M1 Patients



SOC	343 deaths
SOC + Doc	134 deaths
HR (95% CI)	0.73 (0.59, 0.89)
P value	0.002

Non-PH P value 0.23

Restricted mean OS time	
SOC	49.3 mo
SOC + Doc	56.1 mo
Diff (95% CI)	6.8 mo (2.8, 11.0 mo)

M1 docetaxel: Survival

Results based on 2993 men / 1254 deaths

Trial name

CHAARTED

GETUG15

STAMPEDE (SOC +/- Doc)

STAMPEDE (SOC+ZA +/- Doc)

Overall

Favours SOC + docetaxel

.5

1

2

Favours SOC

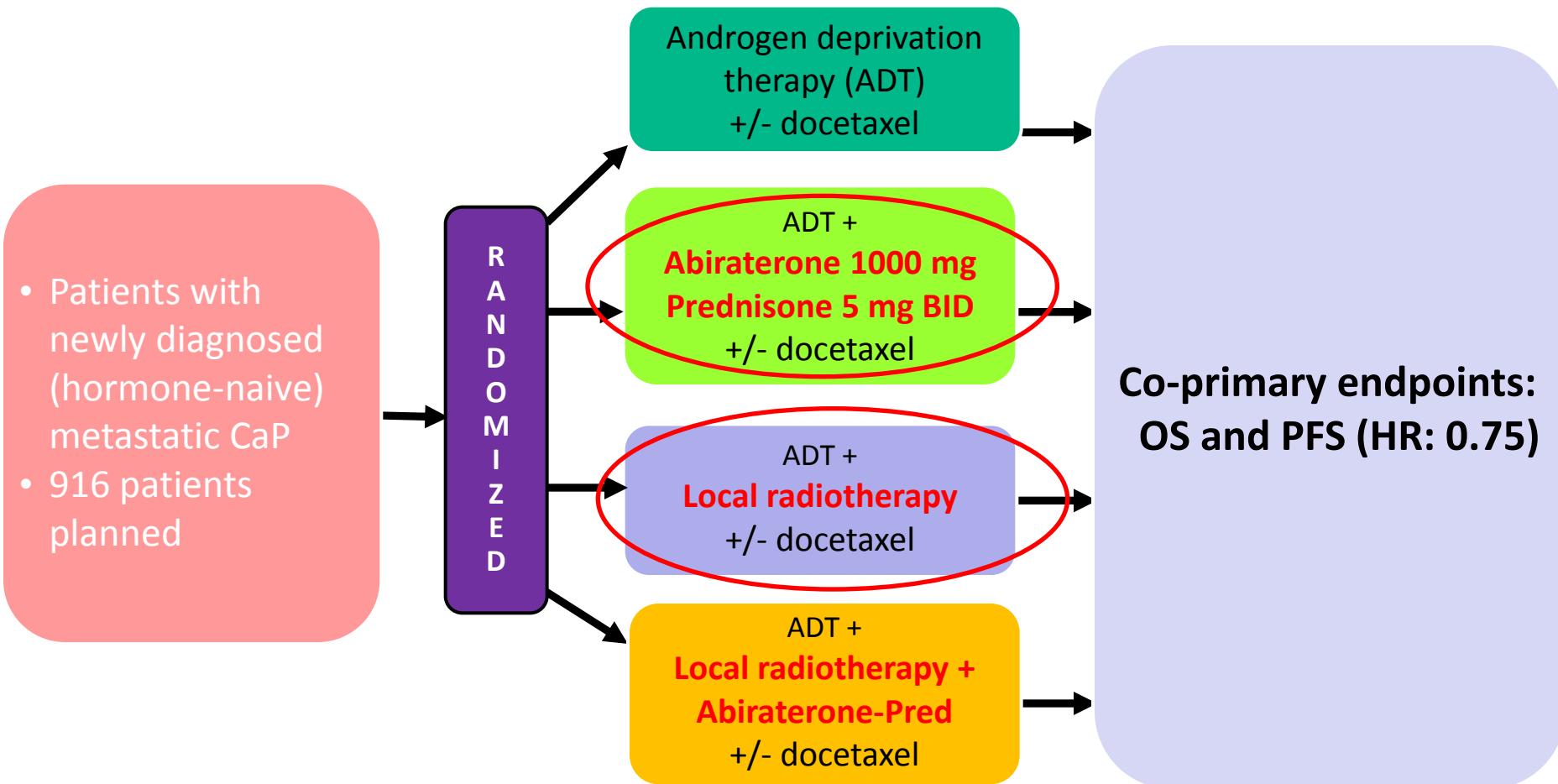


HR=0.77 (0.68, 0.87) p<0.0001

Heterogeneity: $\chi^2=4.80$, df=3, p=0.187, $I^2 = 37.5\%$

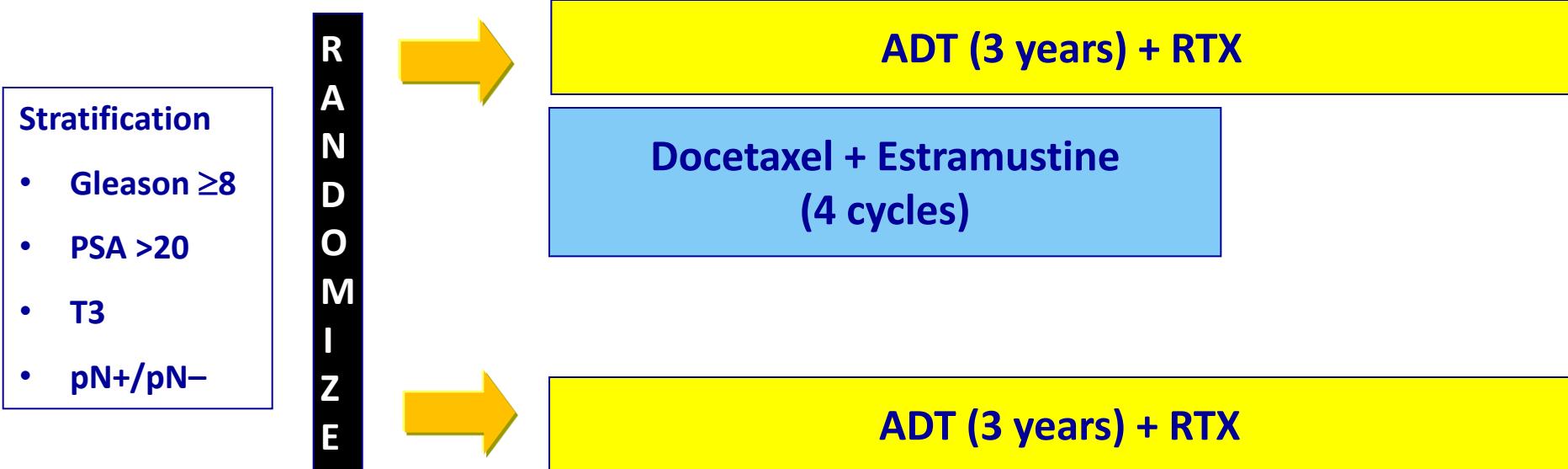
**10% absolute improvement in survival
(from 40% to 50%) at 4 years**

PEACE-1: European Phase III Trial in *de novo* Metastatic Prostate Cancer (revised design)



Study sponsor: Unicancer

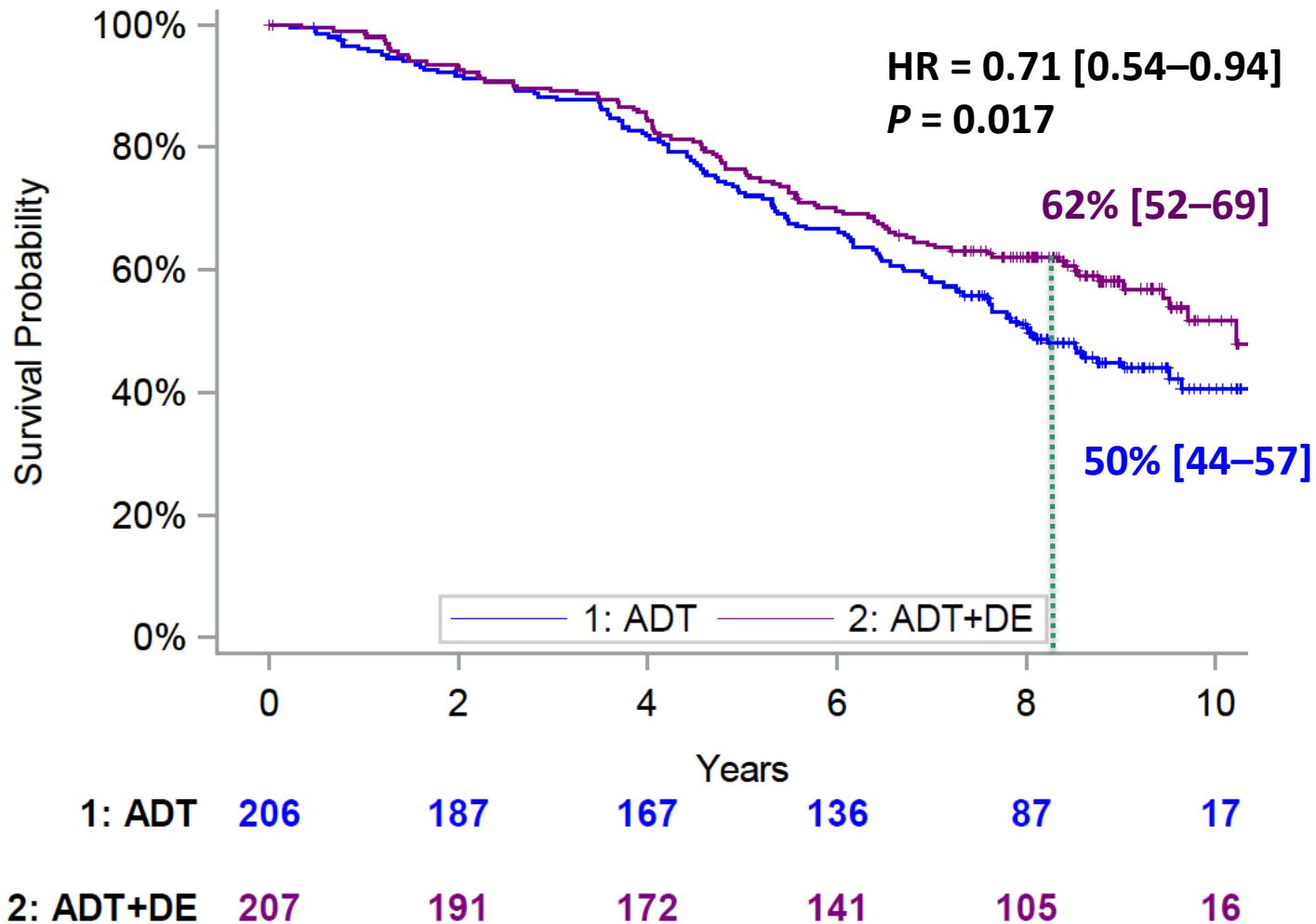
High-Risk localized Prostate Cancer: GETUG 12 Trial



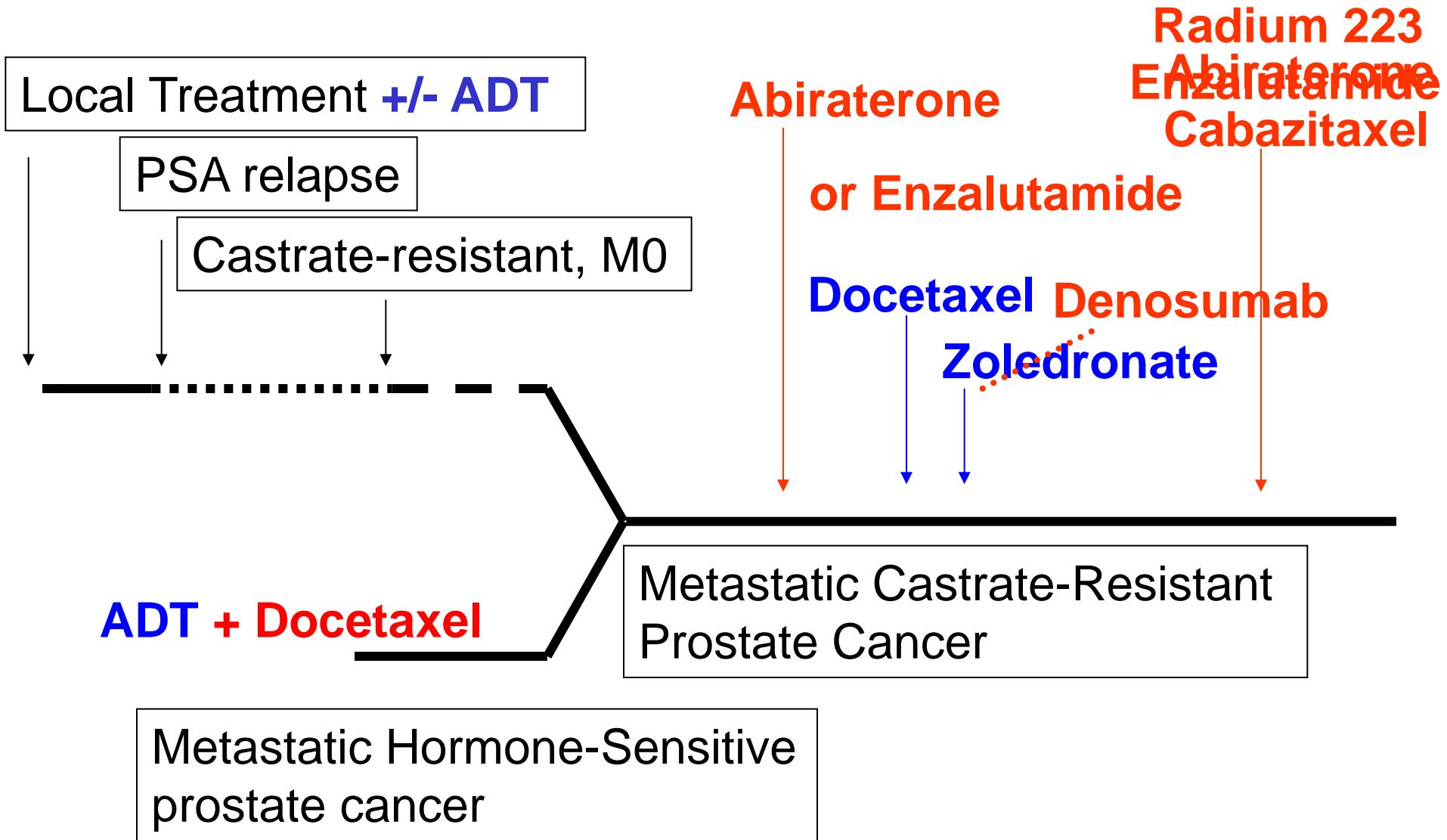
Primary endpoint: Progression-free survival

n = 413 pts (Accrual: 2002–2006)

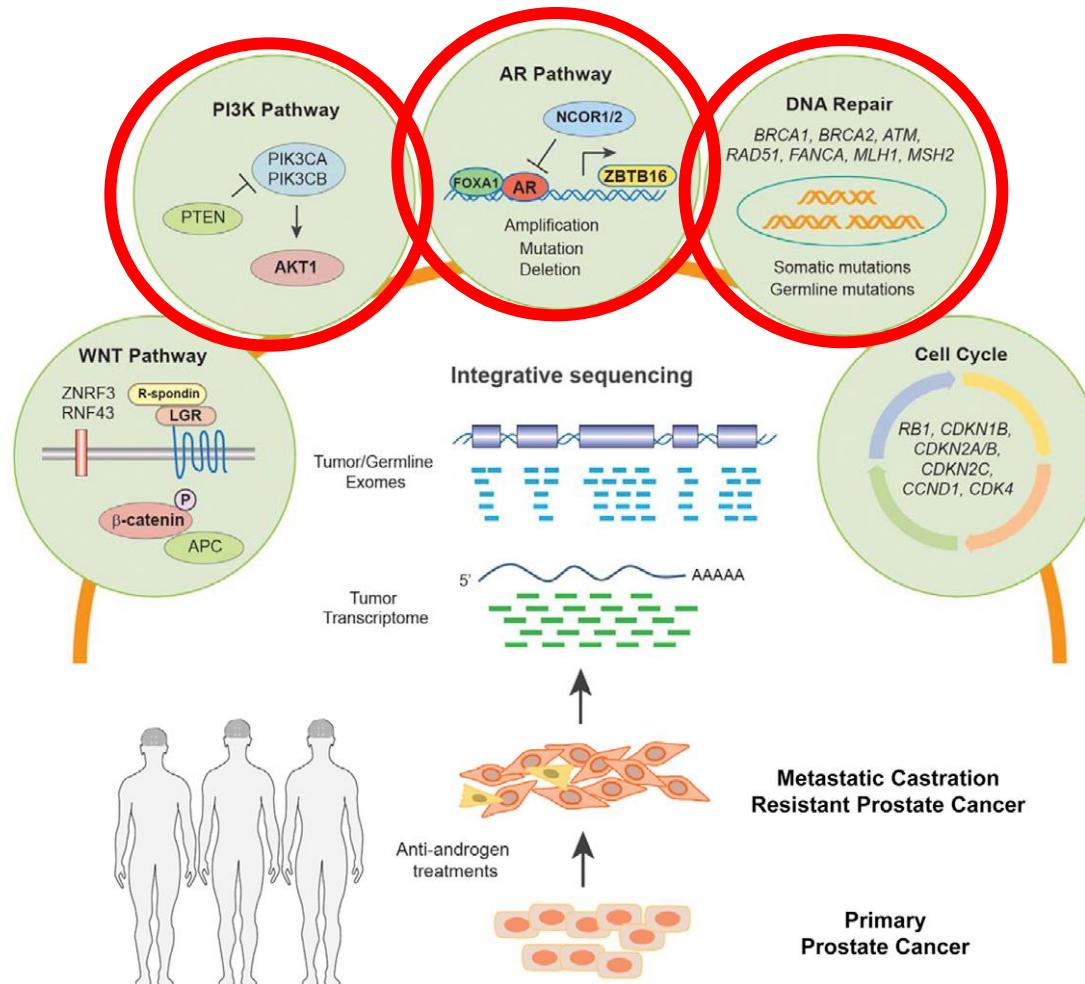
Docetaxel in Localized CaP: Relapse-Free Survival (GETUG 12)



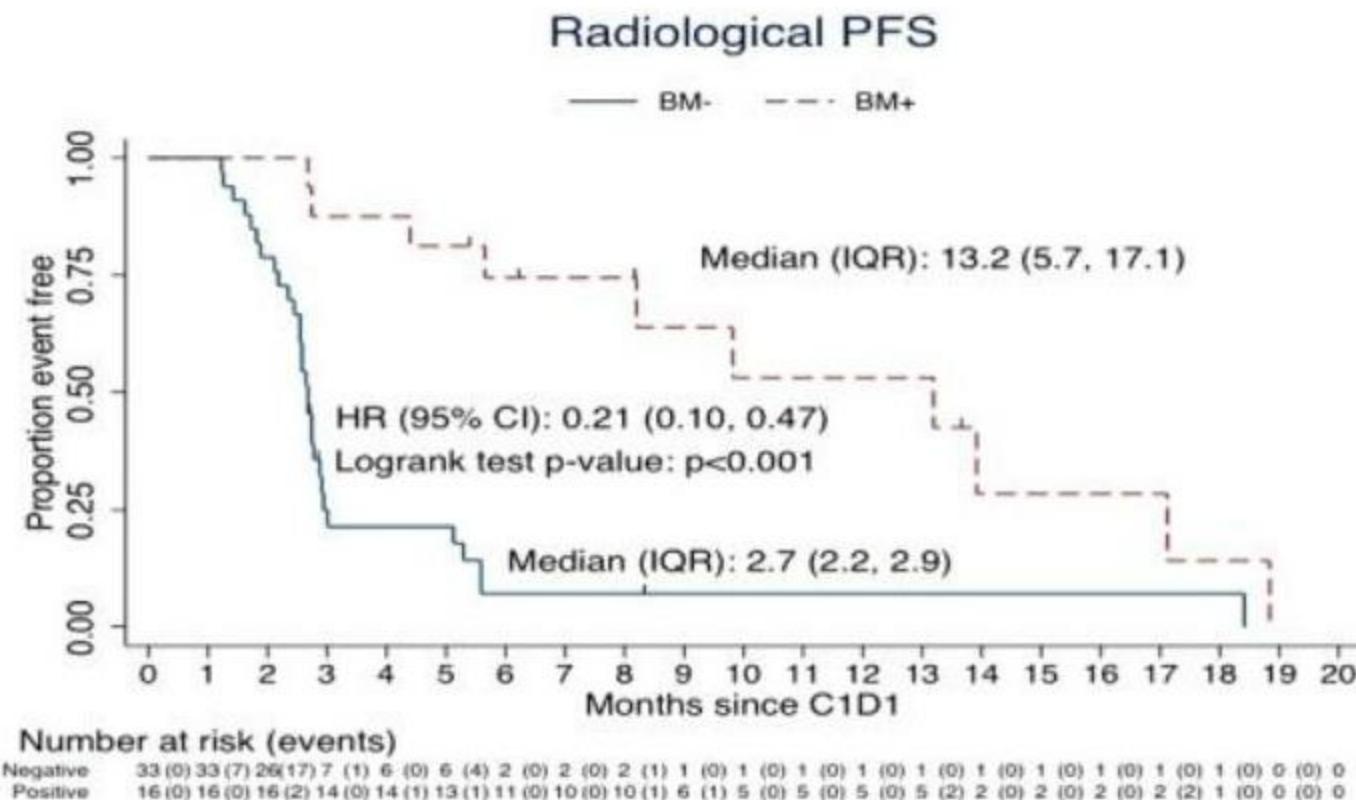
Systemic treatment in 2015



Genomics and new targets in CRPC



Olaparib: response and rPFS are predicted by BRCA2 and ATM



Conclusion

- Docetaxel now a standard treatment in hormone-naïve metastatic prostate cancer
- AR targeting improves overall survival in CRPC (Abiraterone, Enzalutamide)
- Better understanding of the biology:
 - Next generation active compounds (ODM-201, etc)
 - Emerging biomarkers (AR V7)
- New indications currently being explored (M0 CRPC, M1 HSPC)