Optimal Sequence of Treatment for Metastatic Prostate Cancer

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Prostate Cancer is a Continuum of Different Disease Stages

Noncastrate

Diagnoses: 1,100,000

Clinically localized disease

Rising PSA

Clinical metastases: Noncastrate
ADT

Rising PSA or M0: Castrate

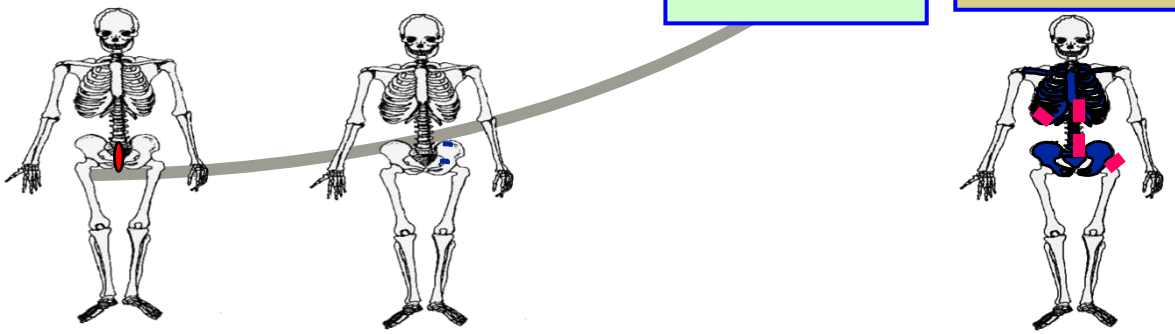
Castration resistant

Deaths: 307,000

Clinical metastases: Castrate
Pre-chemo
Abiraterone
Enzalutamide
Sipuleucel-T
Radium-223

Clinical metastases: Castrate
1st-Line
Docetaxel

Clinical metastases: Castrate
Post-chemo
Abiraterone
Cabazitaxel
Enzalutamide
Radium-223

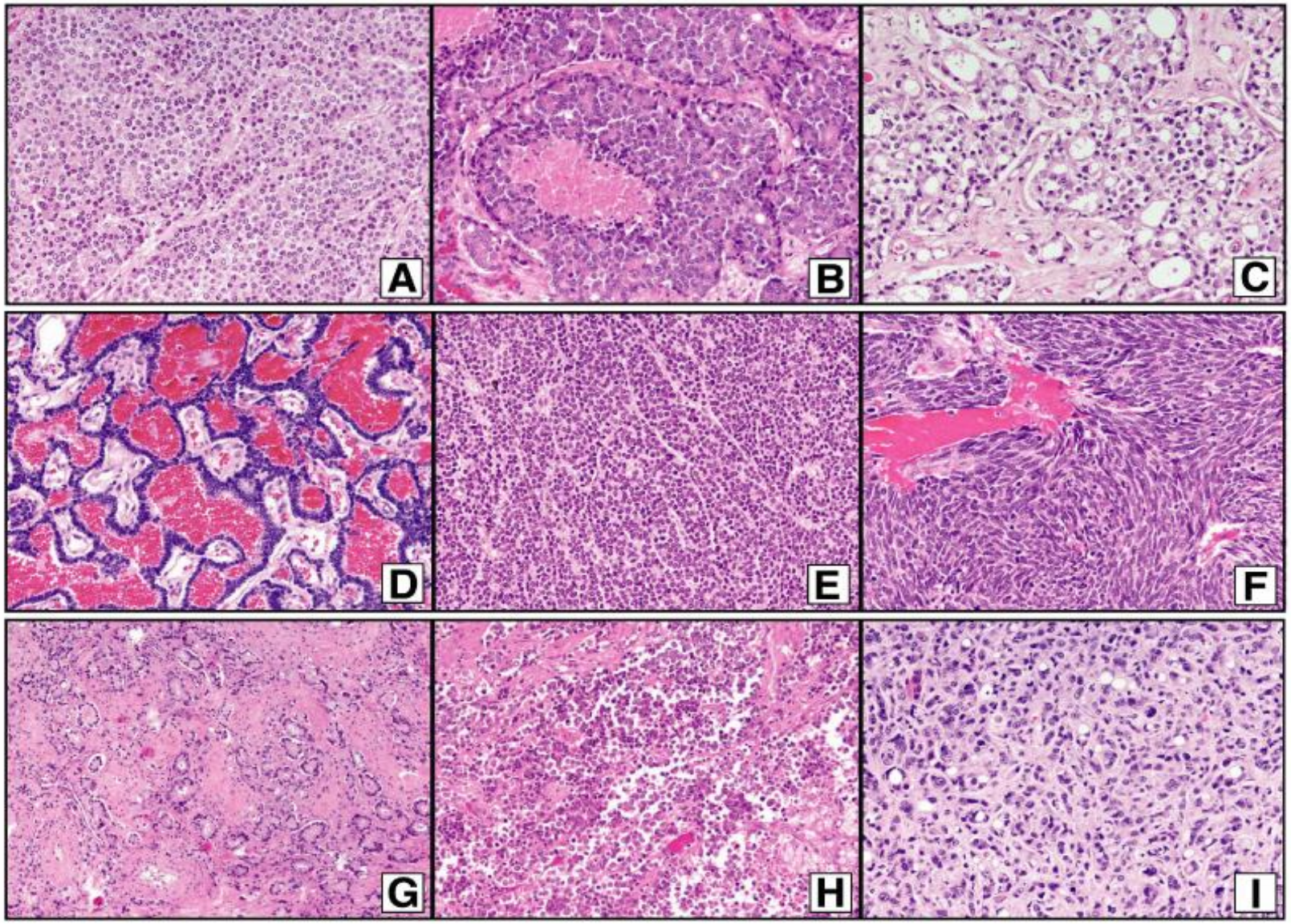


Most common cause of cancer in men

With detectable metastases: deaths from cancer exceed those from other causes

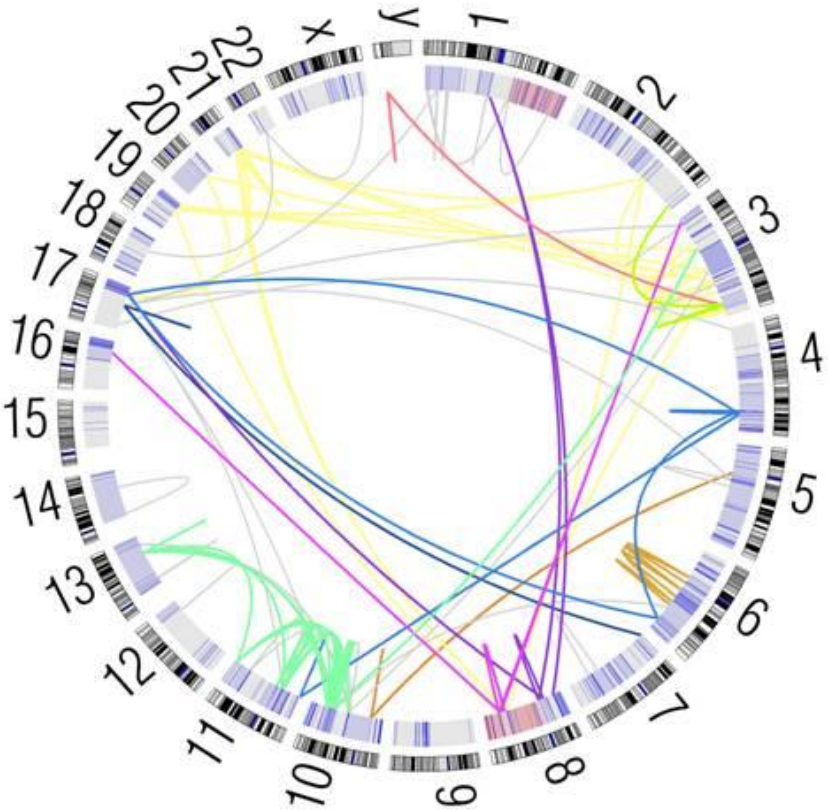
Scher HI. Urology 2000;55:323–7; Jemal A. CA Cancer J Clin 2011;61:69–90
Ferlay A et al. Eur J of Cancer 2013;49:1374– 140
http://globocan.iarc.fr (accessed September 2014)

CRPC is clinically and pathologically heterogeneous



Shah RB et al, Cancer Res 2004 Dec 15;64(24):9209-16

Chained rearrangements are common in prostate cancer ("**chromoplexy**")



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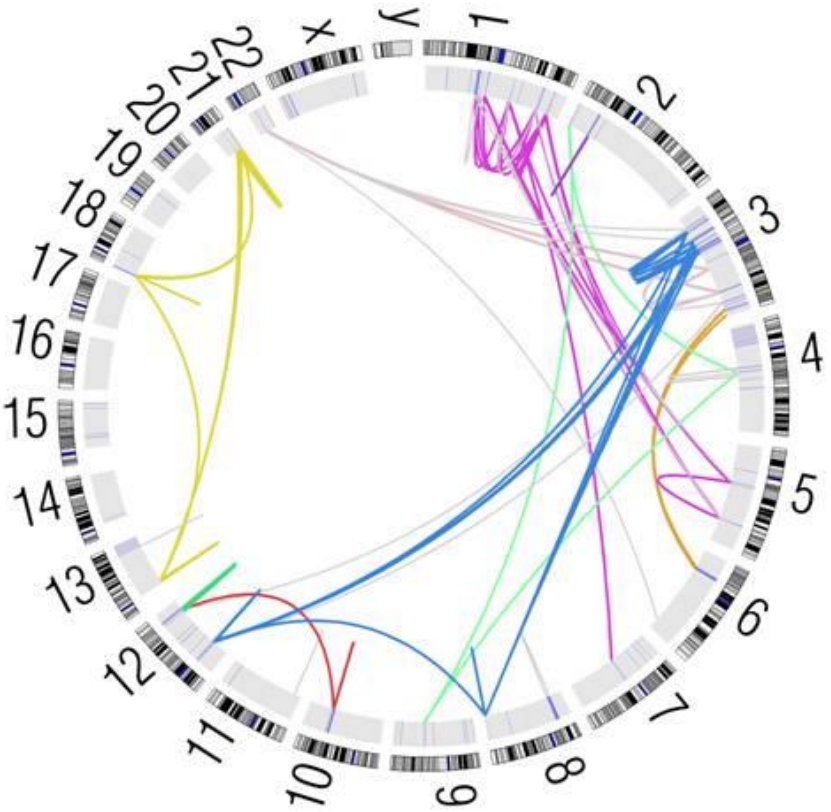


P09-1042

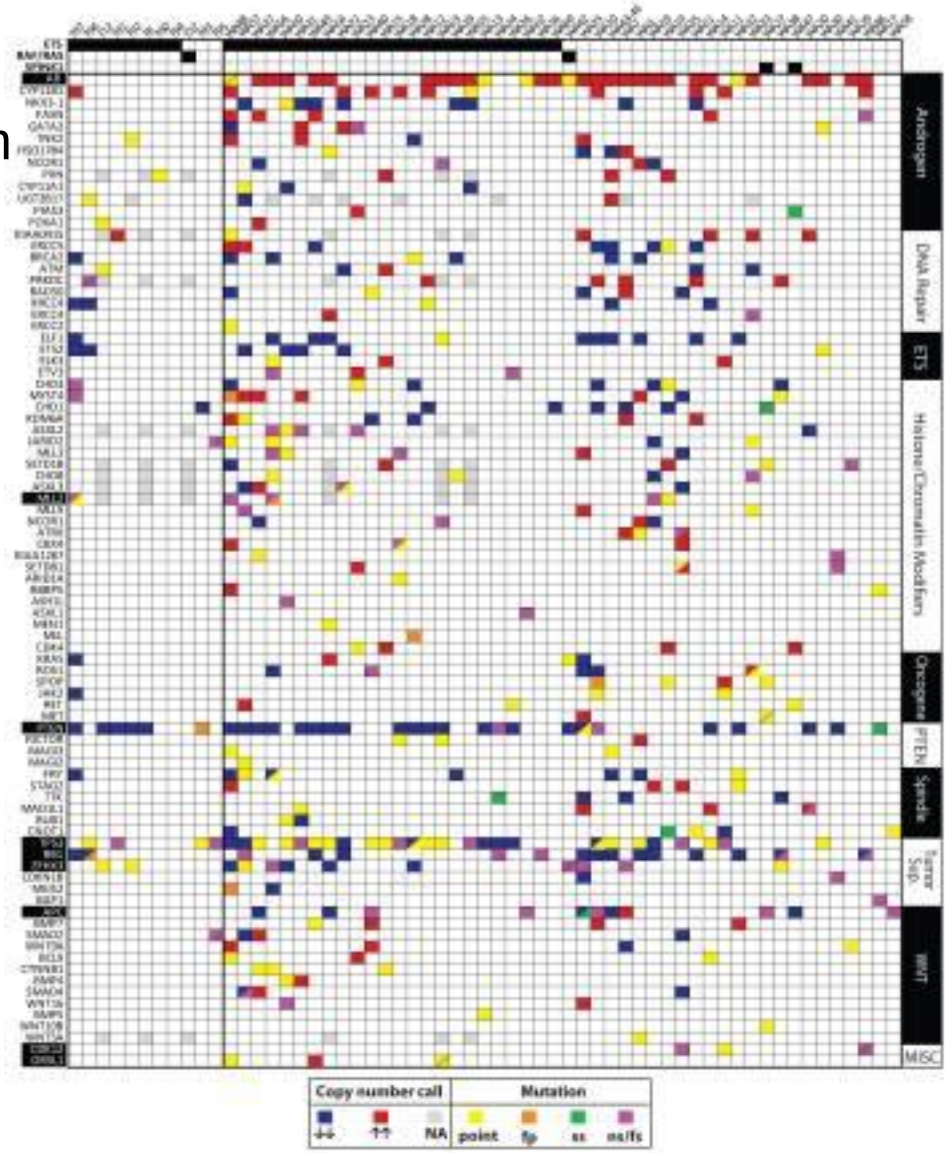
Baca at al., *Cell* (2013)

Genomic Complexity in CRPC: May represent a distinct set of druggable targets

- 50 patients: Rapid Autopsy Program
- Prostate carcinogensis involves the hijacking/alteration of multiple processes/pathways.

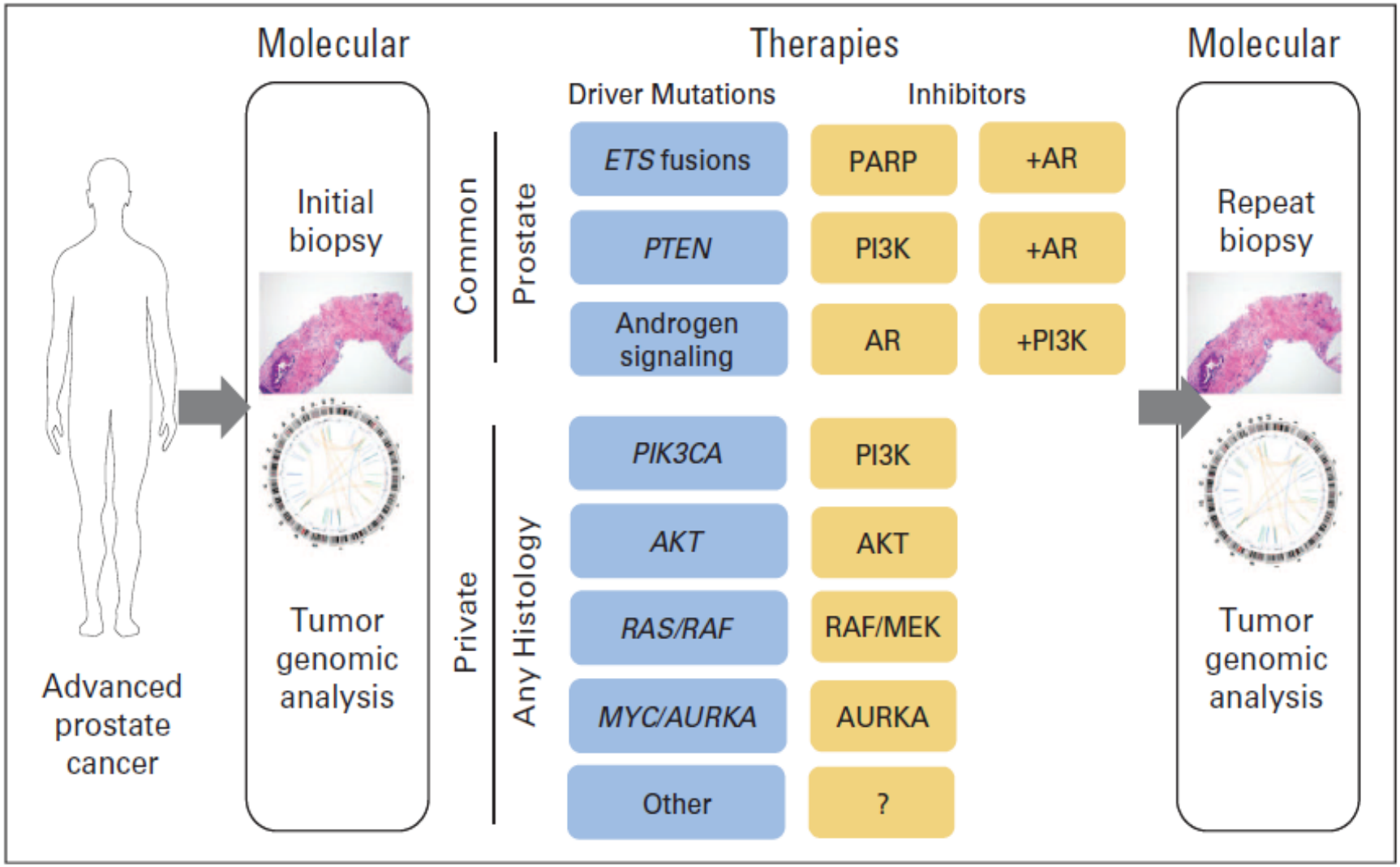
- <u>Next Generation Sequencing</u>
- DNA repair
- AR signaling
- ETS gene rearrangements
- PTEN loss & PI3K/AKT⇧
- P53 mutation

- 9 genes significantly mutated + 3 others without described roles in prostate cancer



Grasso AS et al, Nature 2012 July 12 487 (7406) 349-243

Advancing Precision Medicine for Prostate Cancer Through Genomics



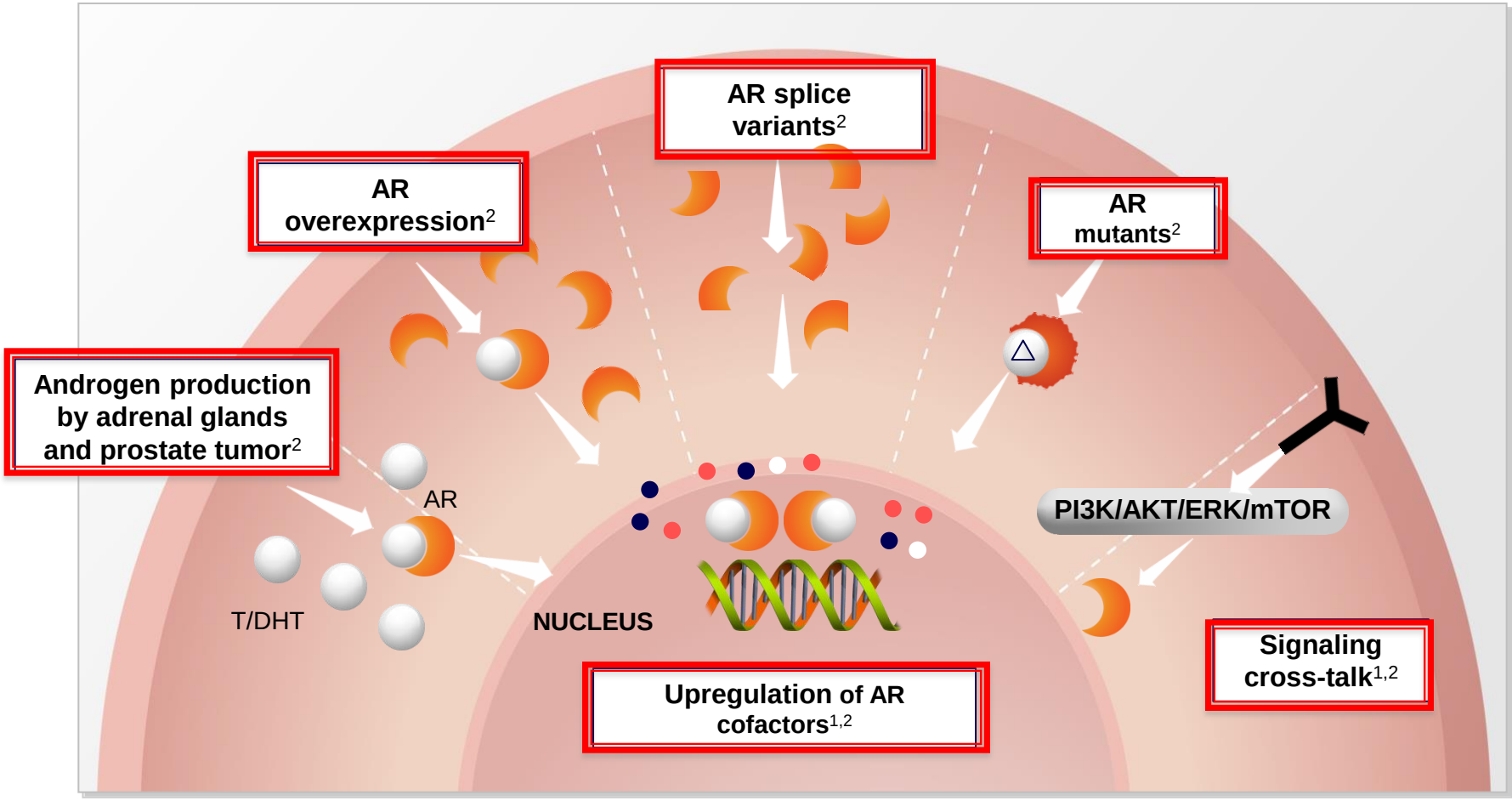
Roychowdhury S, Chinnaiyan A. J Clin Oncol. 2013;31(15):1866-73

Examples of Genomic Alterations in Prostate Cancer

GENE	Alteration type	Frequency	Potential for treatment
PTEN	Loss	50%	PI3K inhibitors
Androgen Receptor	Mutation; Amplification	50% 50%	AR antagonists, ↓Androgen synthesis
ETS transcription factors	Rearrangement	50%	PARP inhibitors
Aurora Kinase	Amplification	5%	Neuroendocrine
MYC	Amplification	40%	Neuroendocrine
Rb	Loss	20–60%	
CDK6	Overexpression	50%	CDK4/6 inhibitors
CCND1 (cyclin D)	Amplification	–	CDK4/6 inhibitors
CDKN2A (p16)	Amplification	–	CDK4/6 inhibitors

Roychowdhury S, Chinnaiyan A. J Clin Oncol. 2013;31(15):1866-73
Lim JTE et al., PNAS 2005;102:5156–5161
Beltran H, et al. Eur Urol 2013;63:920–926.

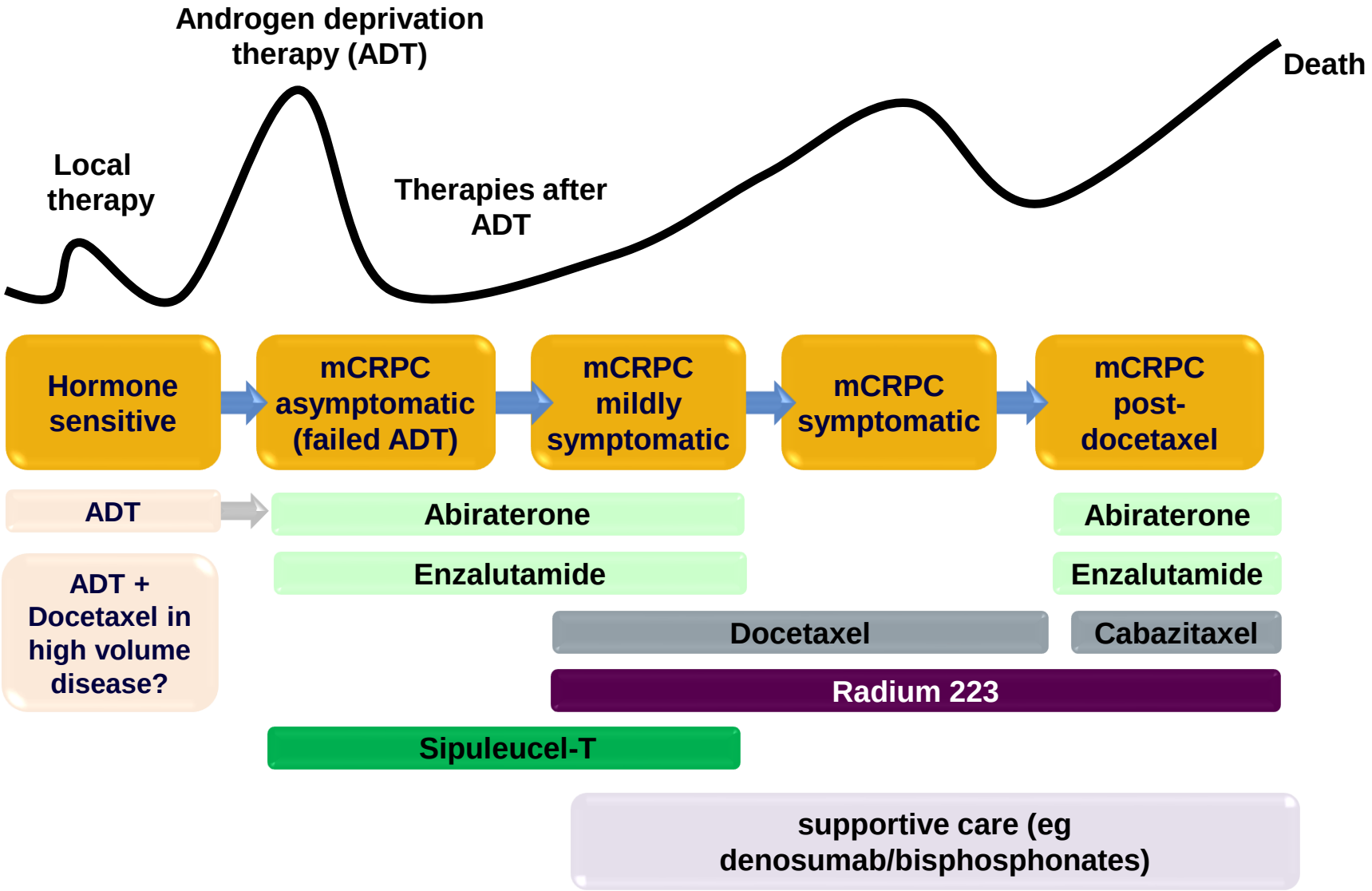
CRPC Remains Driven by Androgen Receptor Signalling – AR Alterations Selected During Therapy



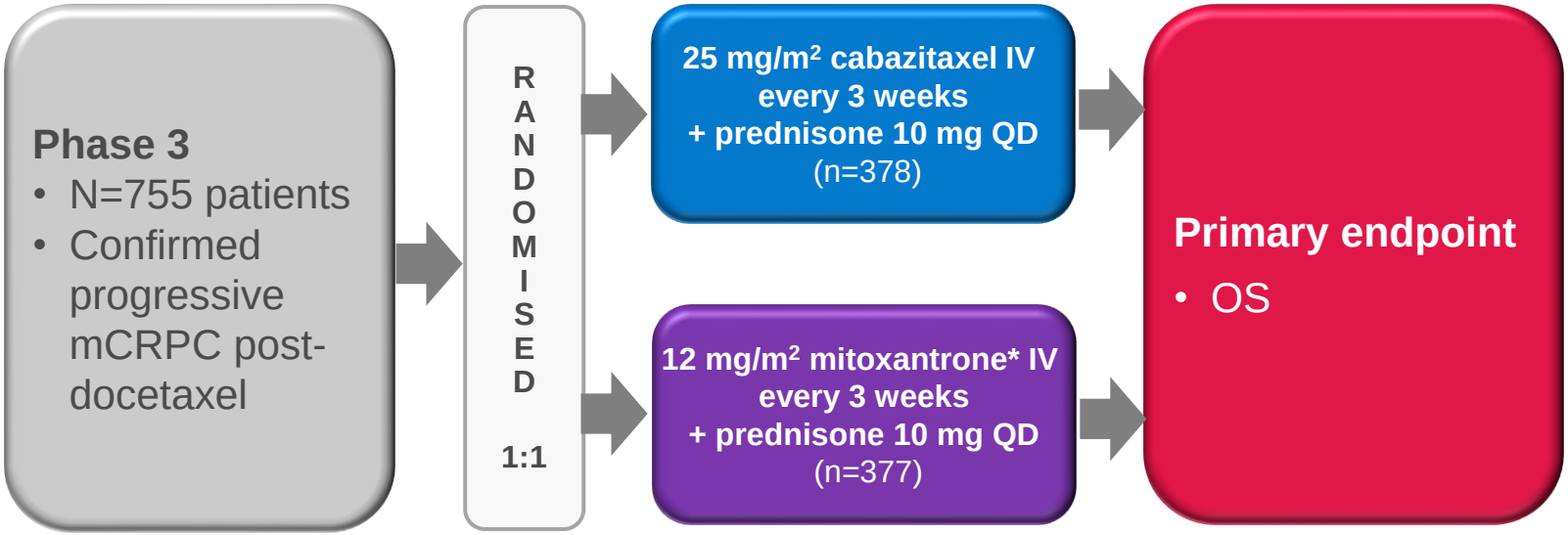
Up to 80% of CRPCs elevated AR gene copy number, 30% high-level amplification of the gene.
AR mutations common 10-30% of the CRPC treated with antiandrogens

[1]Heinlein CA et al. Endocr Rev. 2004;25(2):276-308 [2]Hu R et al. Expert Rev Endocrinol Metab. 2010;5(5):753-764

Current Treatment Paradigm is Evolving



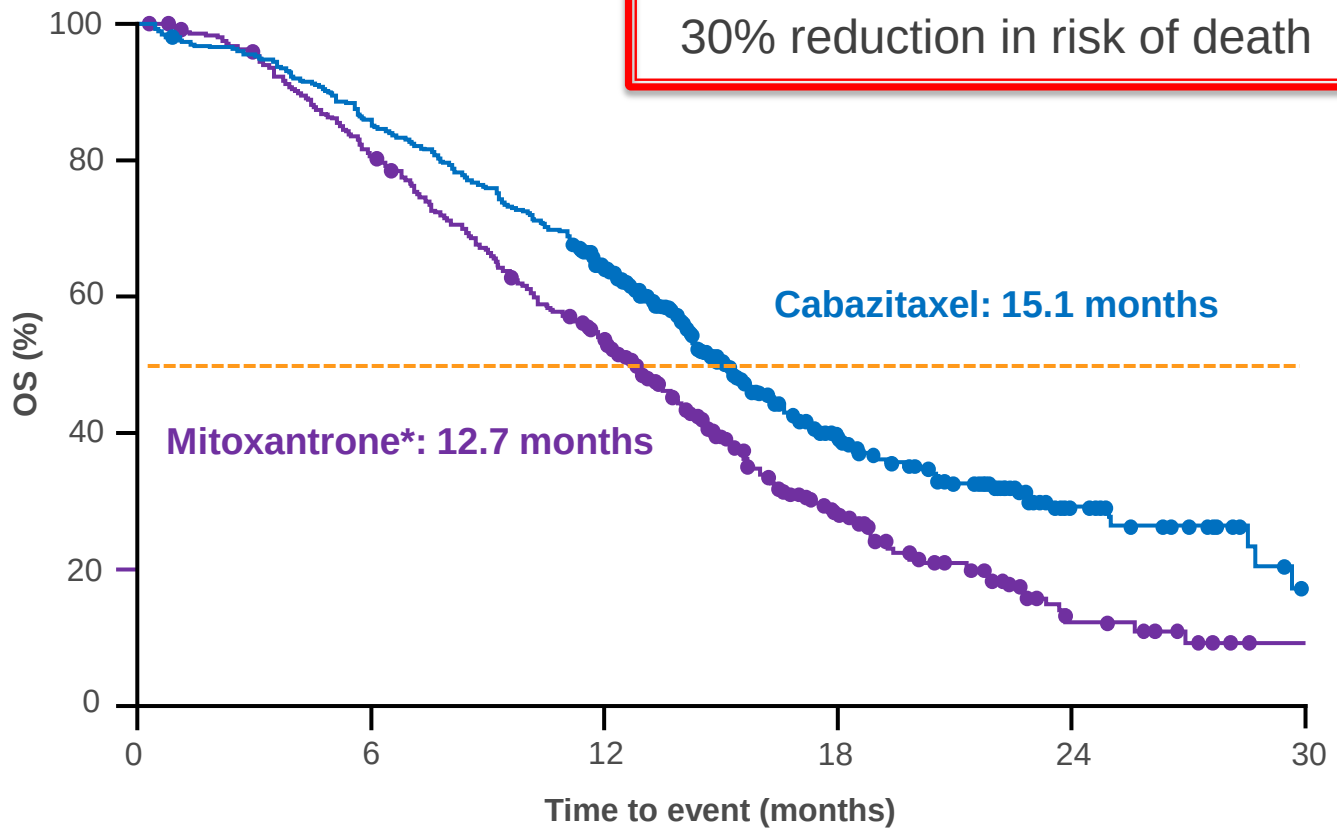
TROPIC: Study design



de Bono J et al. Lancet 2010; 376(9747): 1147-1154

TROPIC Trial Survival (n=755)

HR=0.70 (95% CI: 0.59–0.83); p<0.0001
30% reduction in risk of death

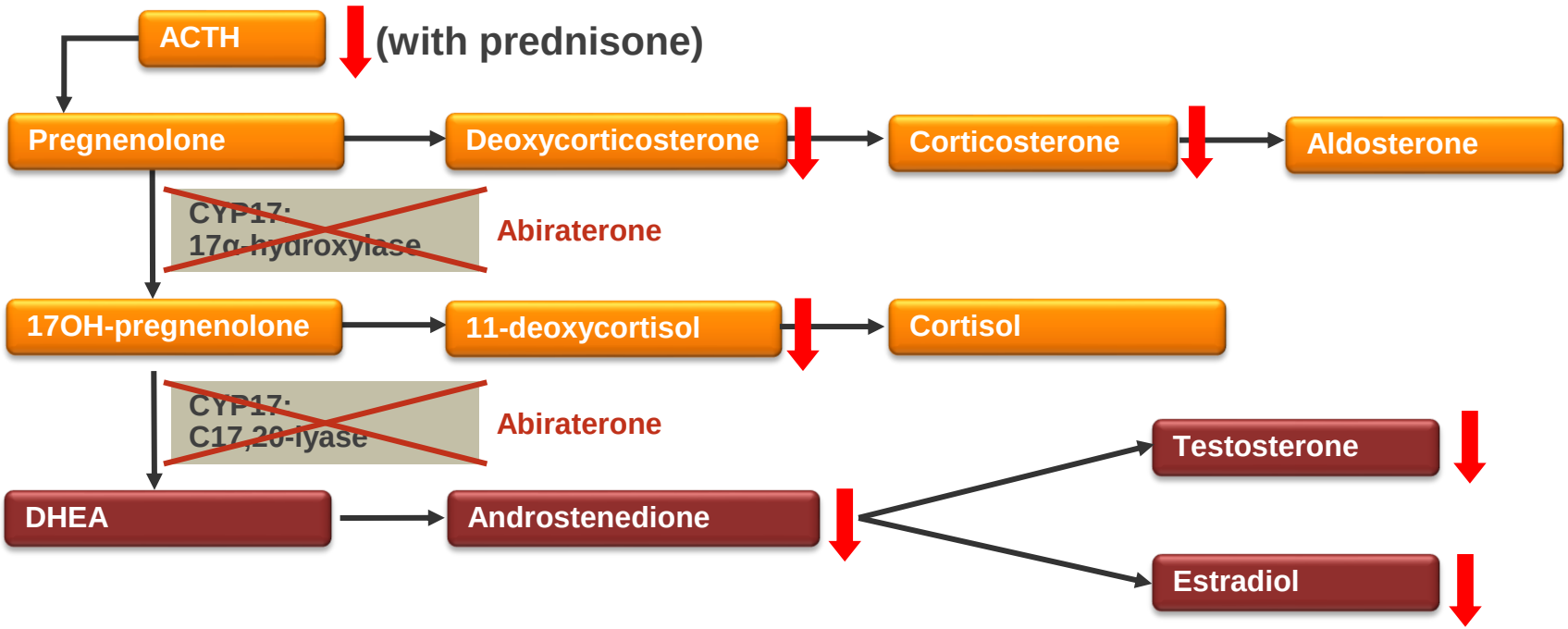


Cabazitaxel, n	378	321	231	90	28	4
Mitoxantrone, n	377	300	188	67	11	1

Median follow-up 13.7 months

de Bono JS et al. Lancet 2010;376:1147-54

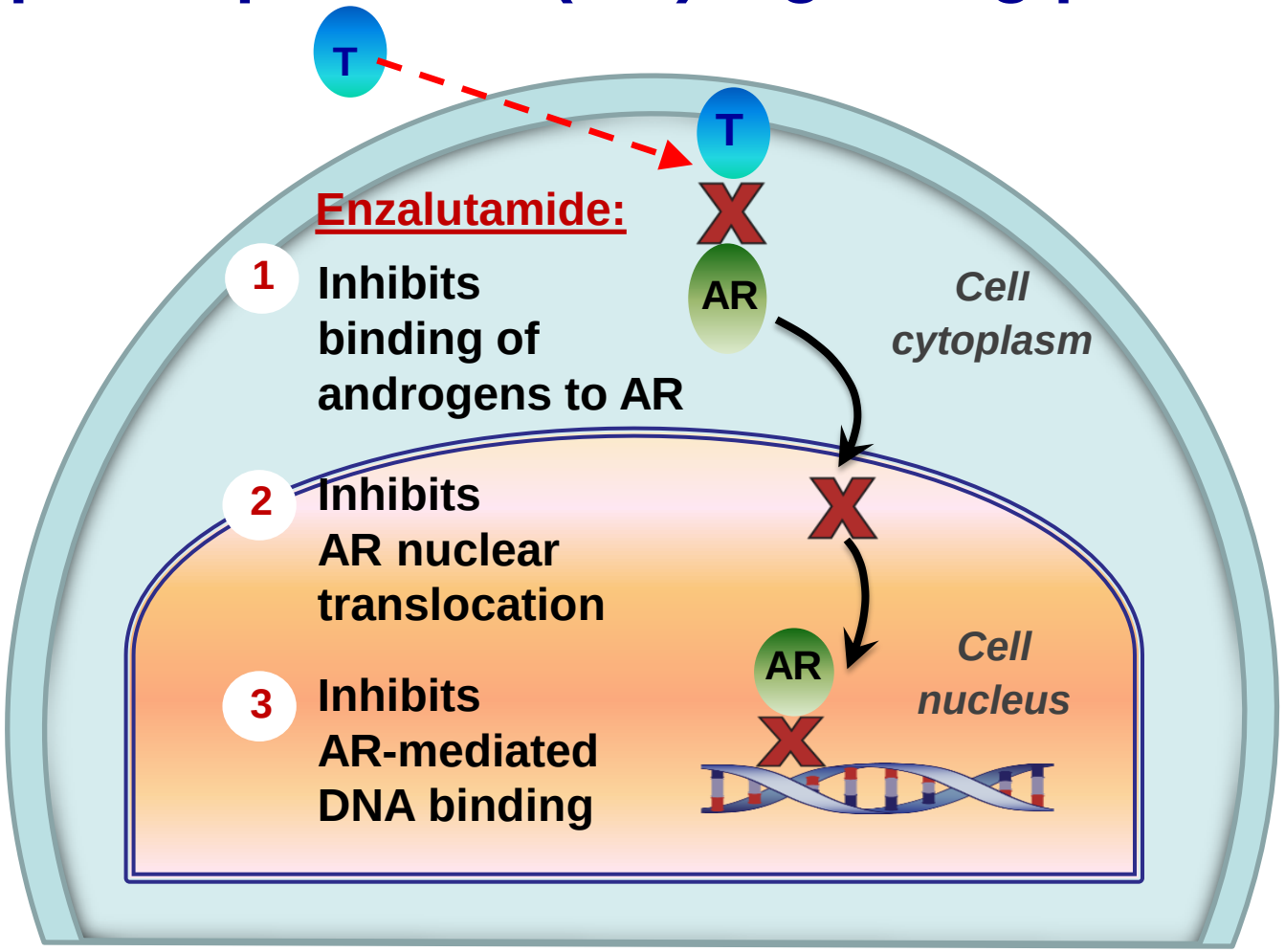
Abiraterone inhibits CYP17: 17α-hydroxylase/17,20-lyase



ACTH=adrenocorticotropic hormone; CYP=cytochrome P450; DHEA=dehydroepiandrostenedione.

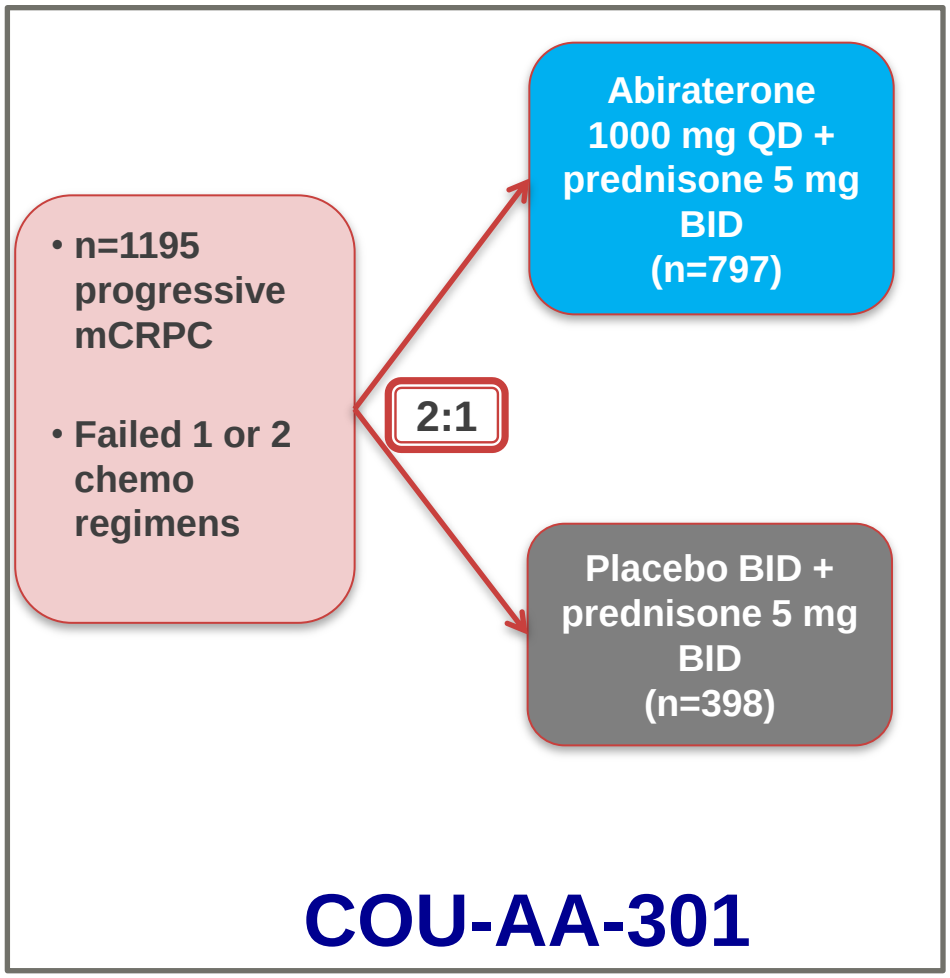
Attard G, et al. J Clin Oncol 2008;26:4563−571

Enzalutamide an AR signalling inhibitor: targets multiple steps in the (AR) signaling pathway

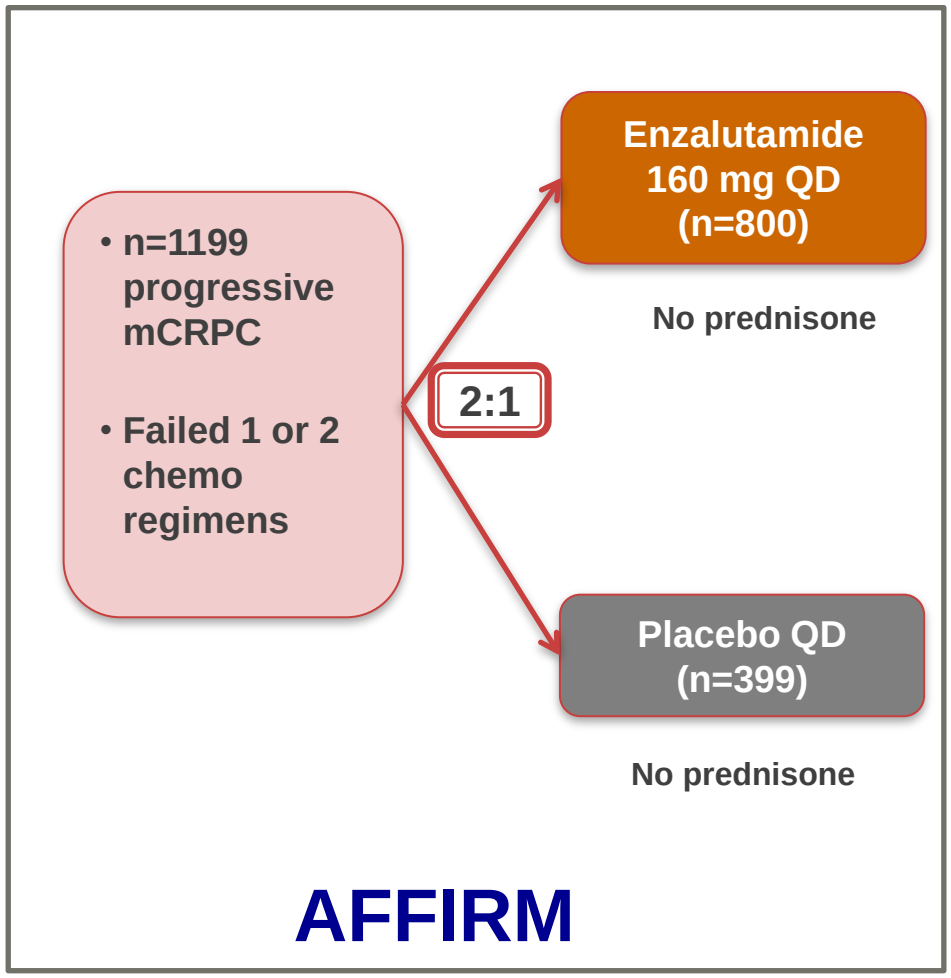


Tran et al. Science. 2009;324:787-790; Scher et al. N Engl J Med. 2012; 367:1187-1197.

Abiraterone and Enzalutamide in mCRPC Phase III Studies Post-docetaxel (Primary Endpoint: OS)

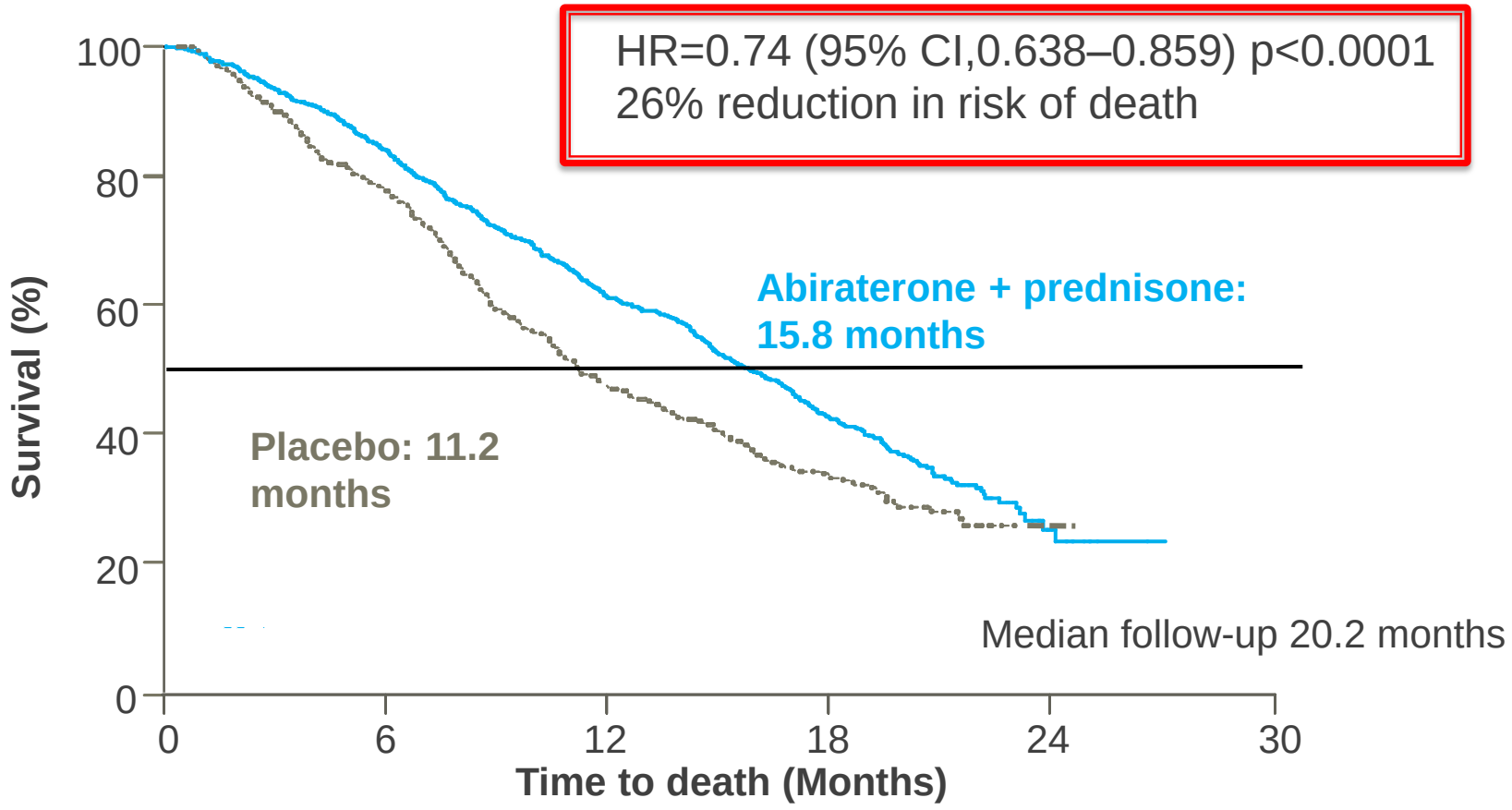


COU-AA-301



AFFIRM

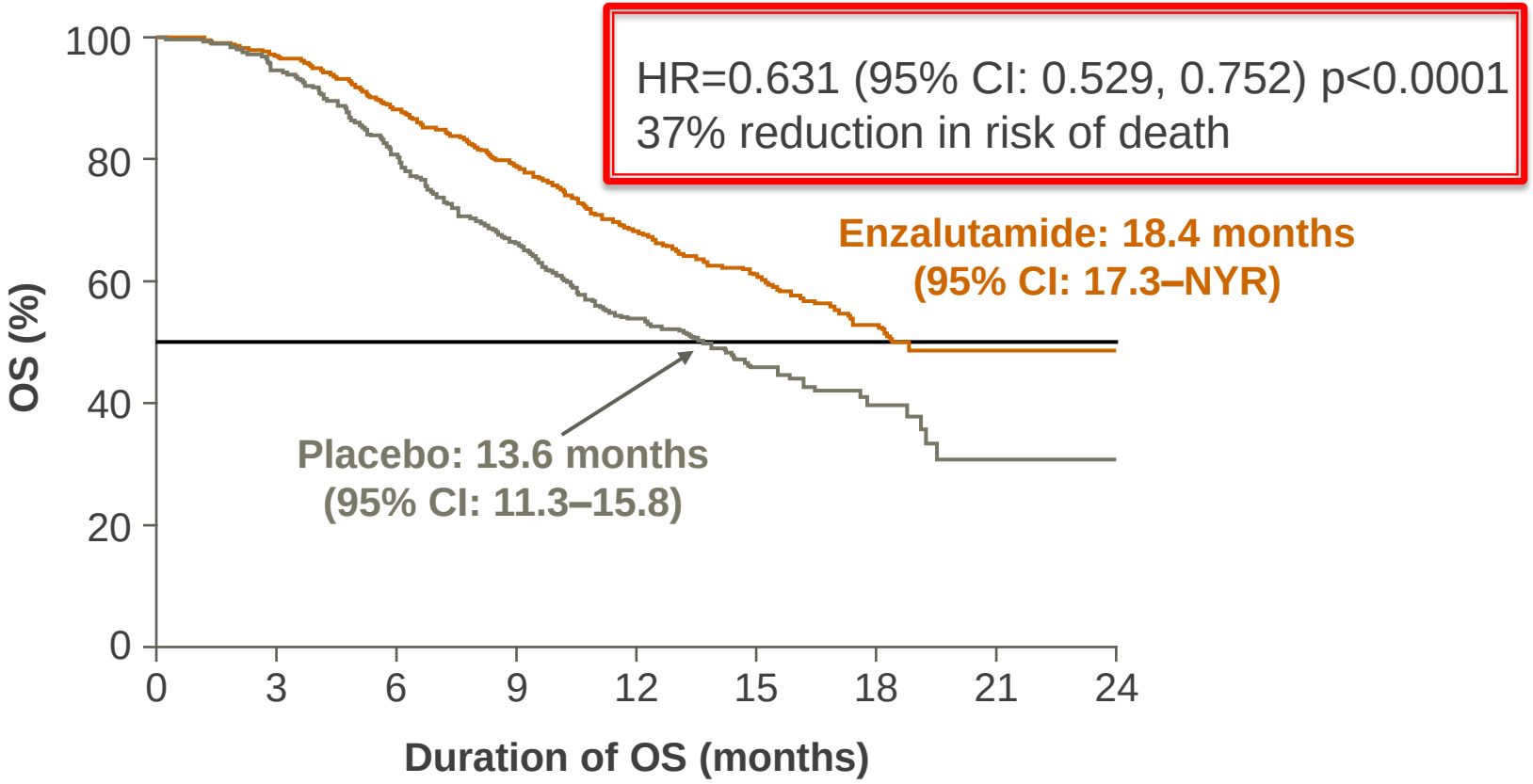
COU-AA-301 Overall Survival
Median Benefit 4.6 Months



Abiraterone (n)	797	657	473	273	15	0
Placebo (n)	398	306	183	100	6	0

[6]de Bono J et al. N Engl J Med 2011;346(21):1995-200
Fizazi K et al. Lancet Oncol 2012;13:983−92

AFFIRM Overall Survival
Median Benefit 4.8 Months

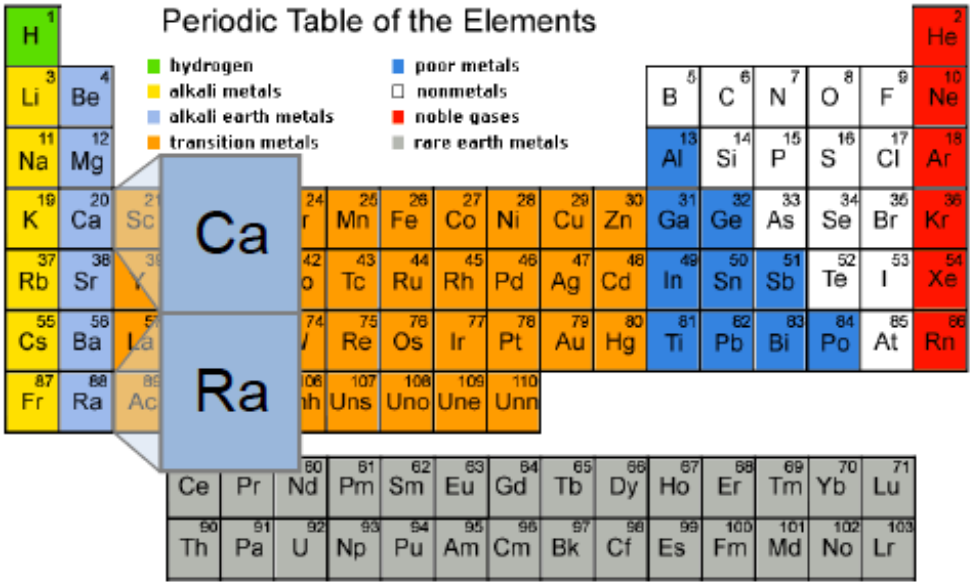


No. at risk:									
Enzalutamide (n)	800	775	701	627	400	211	72	7	0
Placebo (n)	399	376	317	263	167	81	33	3	0

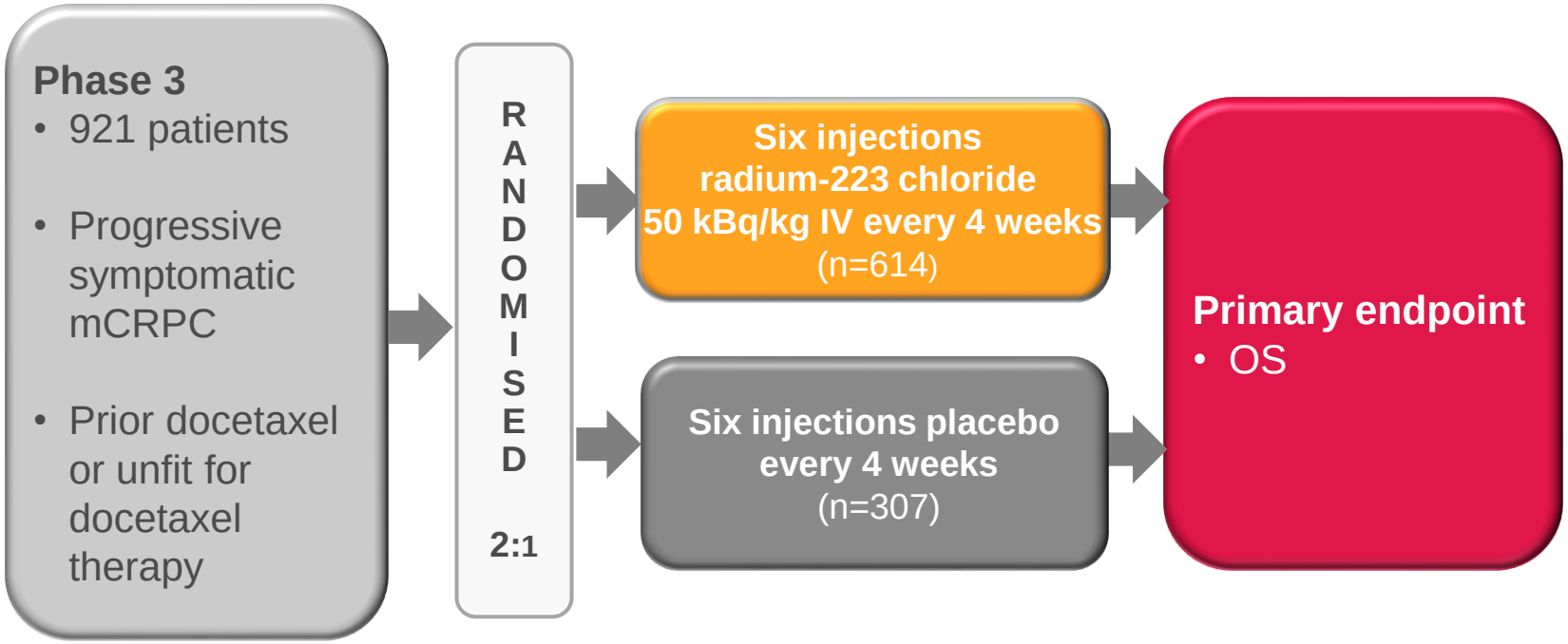
Scher HI et al. N Engl J Med 2012;367:1187–97.

Radium-223: Mechanism of action

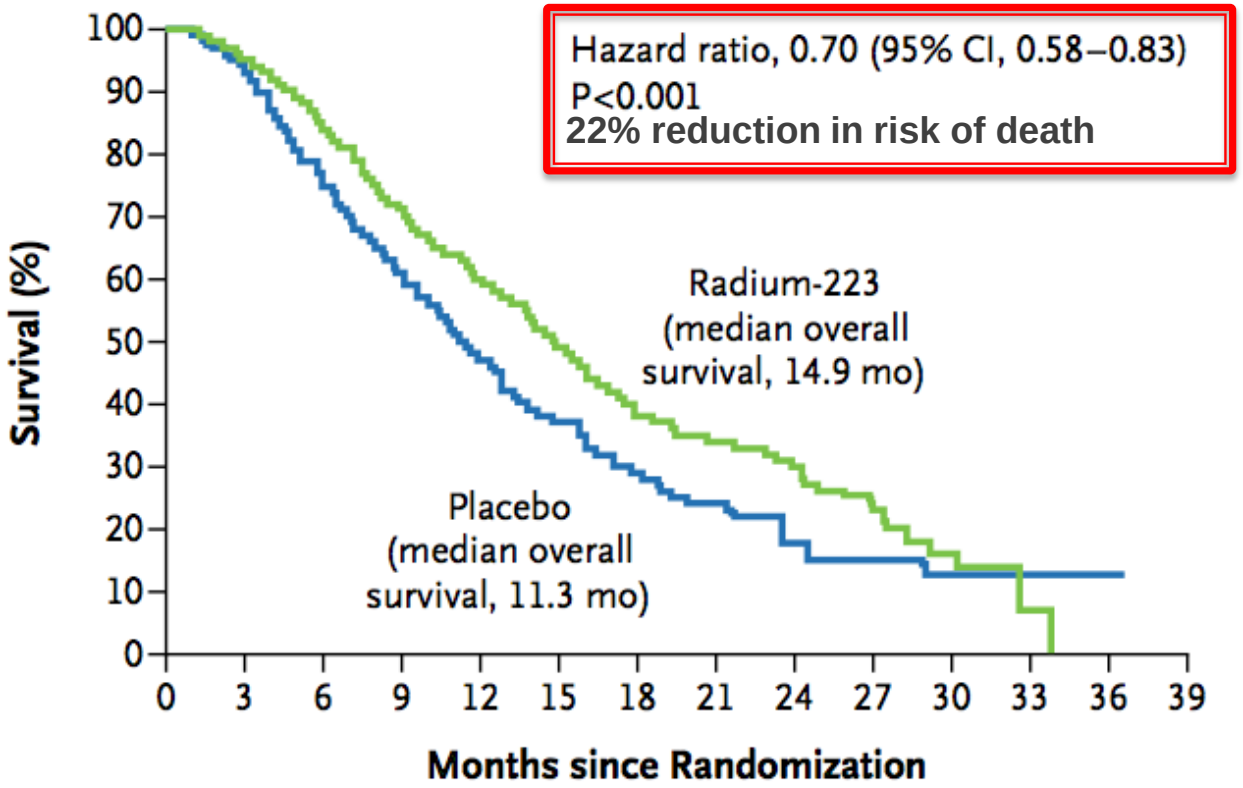
- Calcium mimetic
- Short range of alpha emitter reduces bone marrow exposure
- Selective uptake at bone metastases



Radium-223: ALSYMPCA trial



ALSYMPCA: Overall Survival
3.6 month improvement vs placebo



No. at Risk

Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

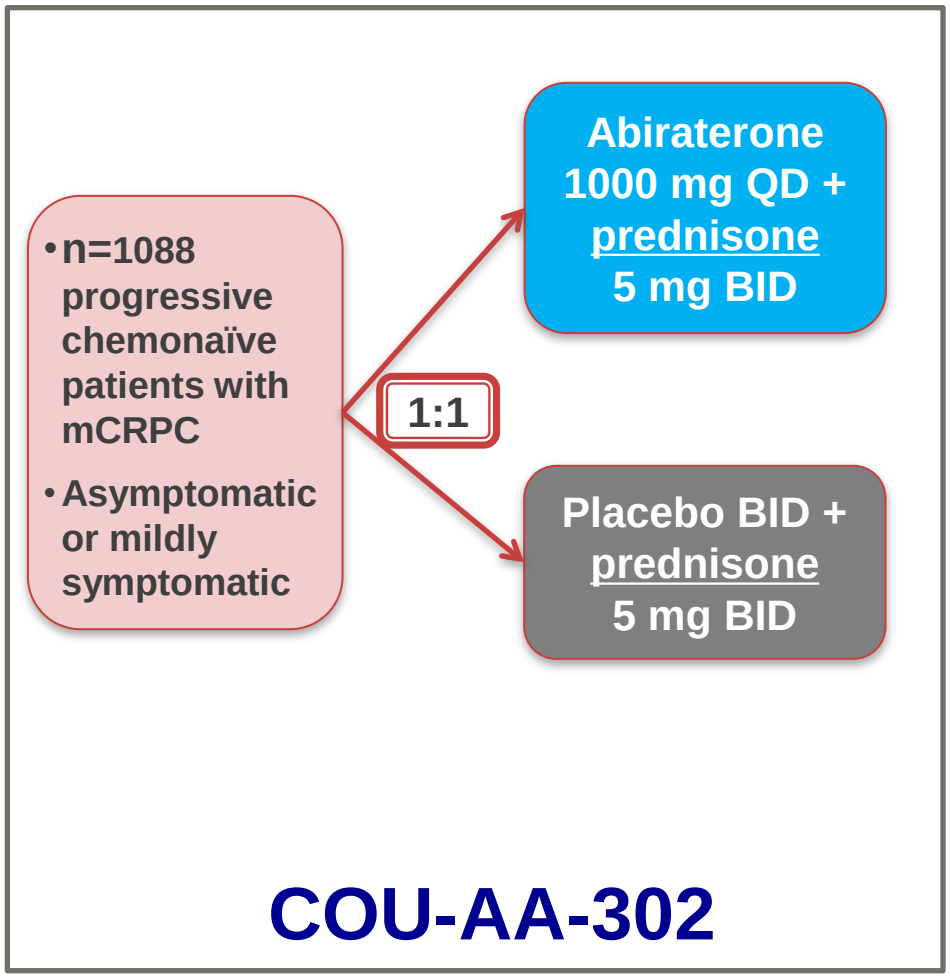
Parker et al. NEJM 2013; 18;369(3):213–23

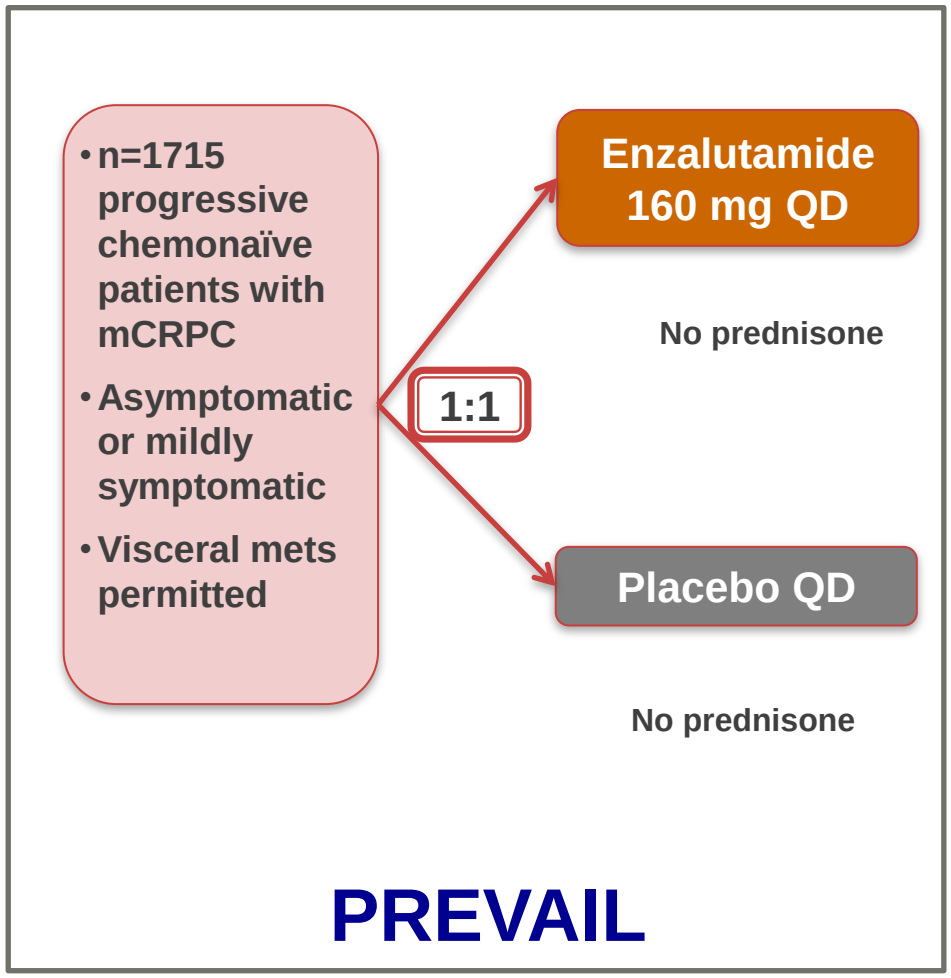
Post-Doc options that improve survival

Treatment	Trial	Visceral disease allowed	HR	Survival (mos)
Cabzitaxel/prednisone vs Mitoxantrone/prednisone	TROPIC[1]	YES	0.70	15.1 vs 12.7
Abiraterone/prednisone vs Placebo/prednisone	COU-301[2]	YES	0.74	14.8 vs10.9
Enzalutamide vs Placebo	AFFIRM[3]	Yes	0.63	18.4 vs 13.6
Radium 223 vs Placebo /BSC	ALSYMCA[4]	No	0.70	14.1 vs 11.3

[1]de Bono et al. Lancet. 2010;376(9747):1147-1154
[2]de Bono et al. N Engl J Med 2011;346(21):1995-200
[3]Scher et al. NEJM 2012;367(13):1187-1197
[4]Parker et al. NEJM 2013;369(2):213-223

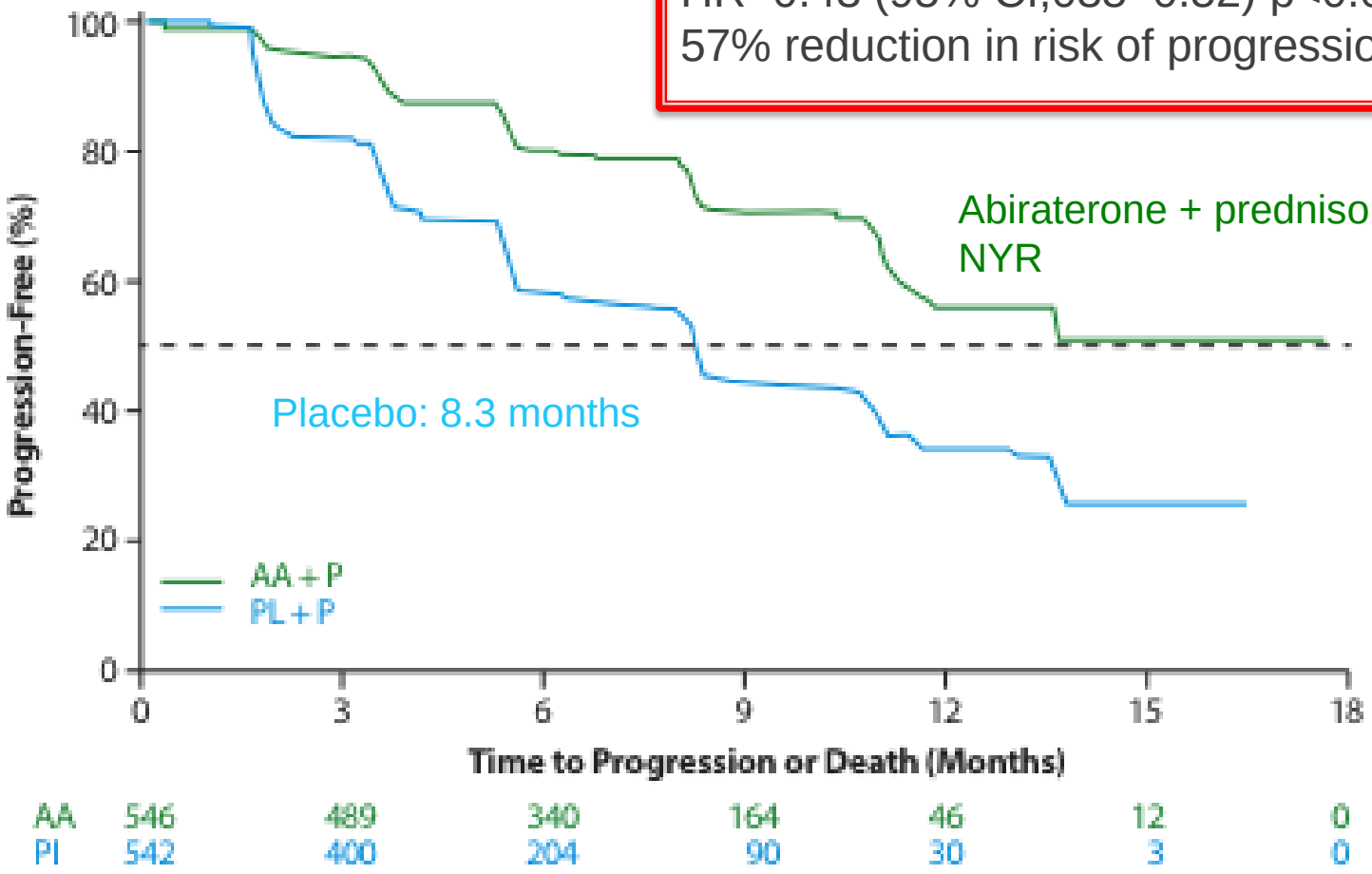
Abiraterone and Enzalutamide in mCRPC Phase III Studies Pre-docetaxel (Primary Endpoint: rPFS and OS)





COU-AA-302: Interim Analysis Results of rPFS

HR=0.43 (95% CI,035–0.52) p<0.0001
57% reduction in risk of progression

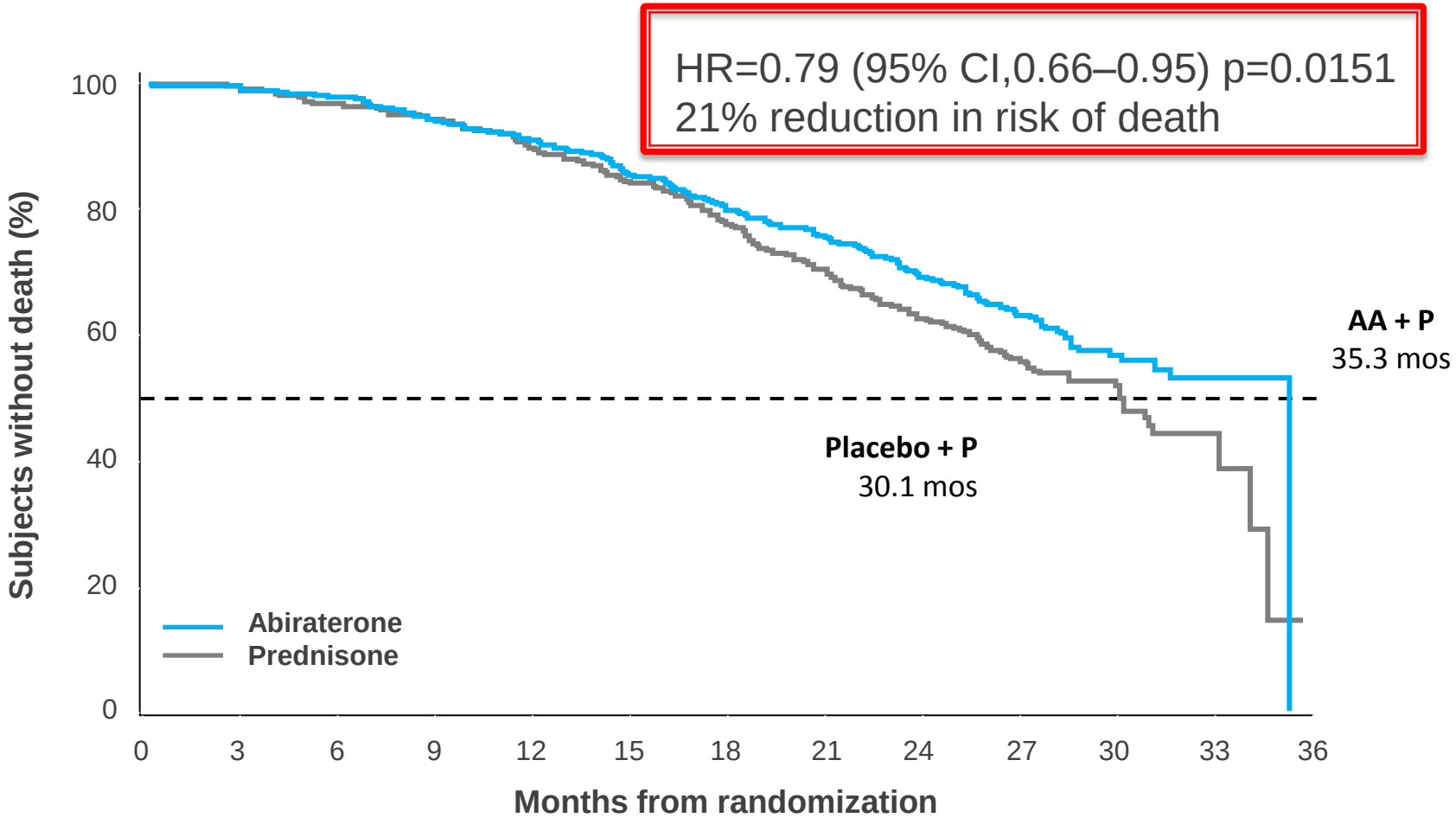


Data cutoff 12/20/2010

rPFS: Radiological progression-free survival

Ryan C et al. N Engl J Med 2013;368:138–48

COU-AA-302: Overall survival 3rd Interim Preplanned Analysis – Median Benefit 5.2 Months

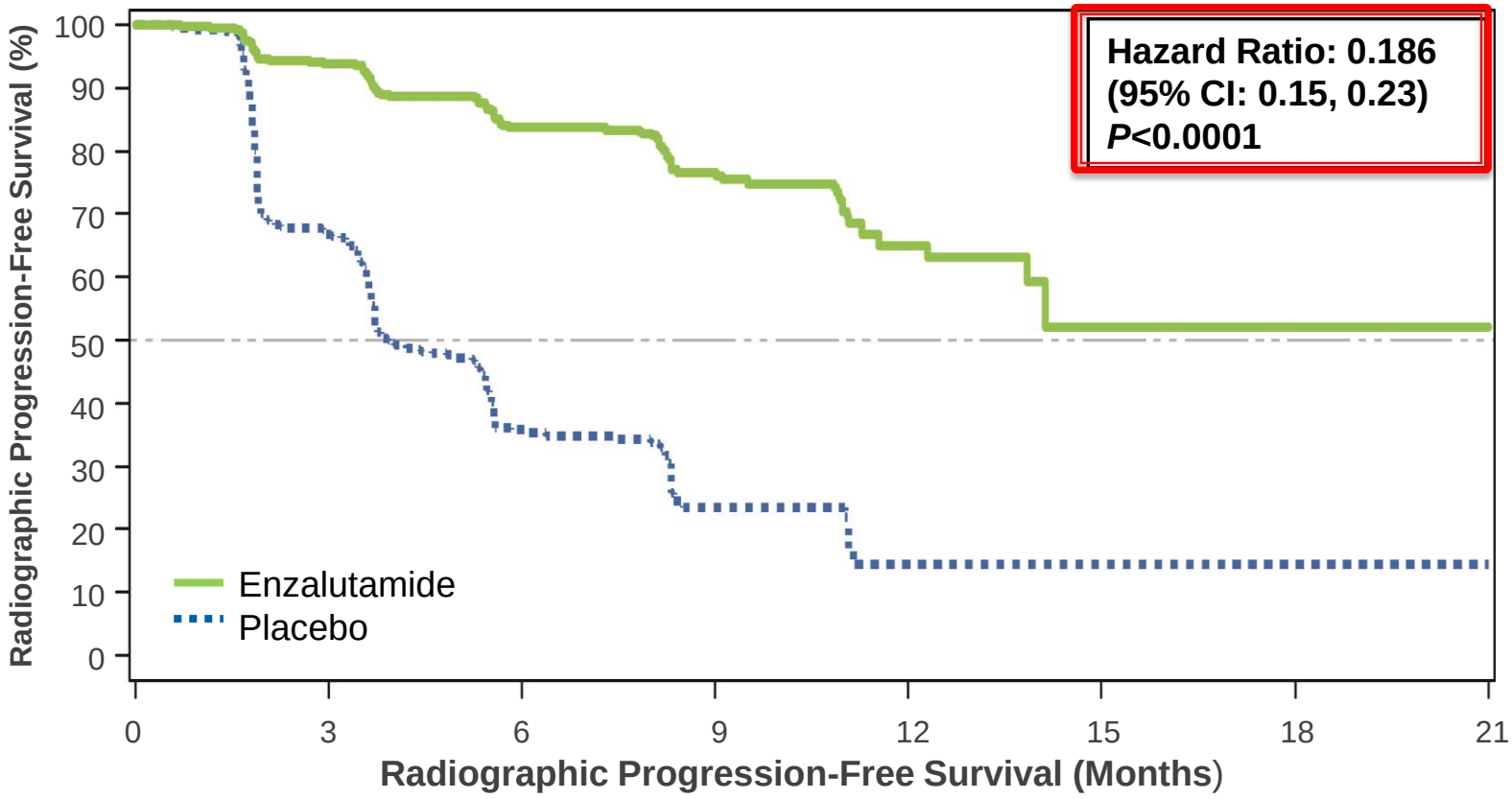


Abiraterone	546	538	524	503	482	452	421	393	333	175	68	15	0
Prednisone	542	534	508	492	465	437	400	361	283	153	67	9	0

IA3 data : [a]Prespecified significance level by O'Brien-Fleming Boundary = 0.0035

Rathkopf DE et al. J Clin Oncol 2013;31(Suppl 6:abstr 5) ASCO GU; Mulders P. Poster 97; EAU 2013

PREVAIL: Enzalutamide 81% Decrease in Risk of Progression



Patients at Risk

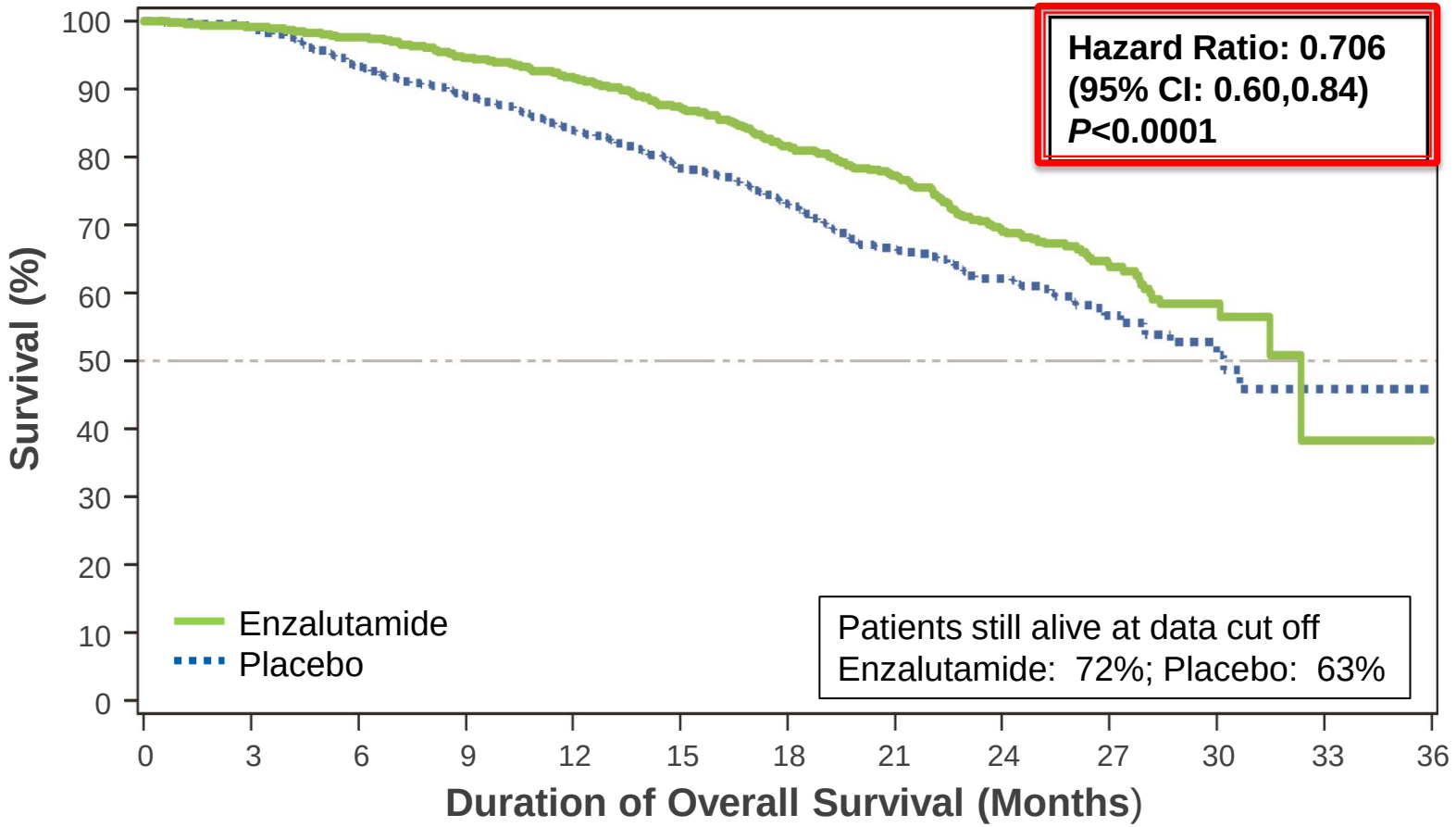
Enzalutamide	832	514	256	128	34	5	1	0
Placebo	801	305	79	20	5	0	0	0

Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4)

NYR = Not Yet Reached

Beer TM et al.N Engl J Med. 2014 Jul 31;371(5):424-33

Enzalutamide Reduced Risk of Death by 29%



Patients at Risk

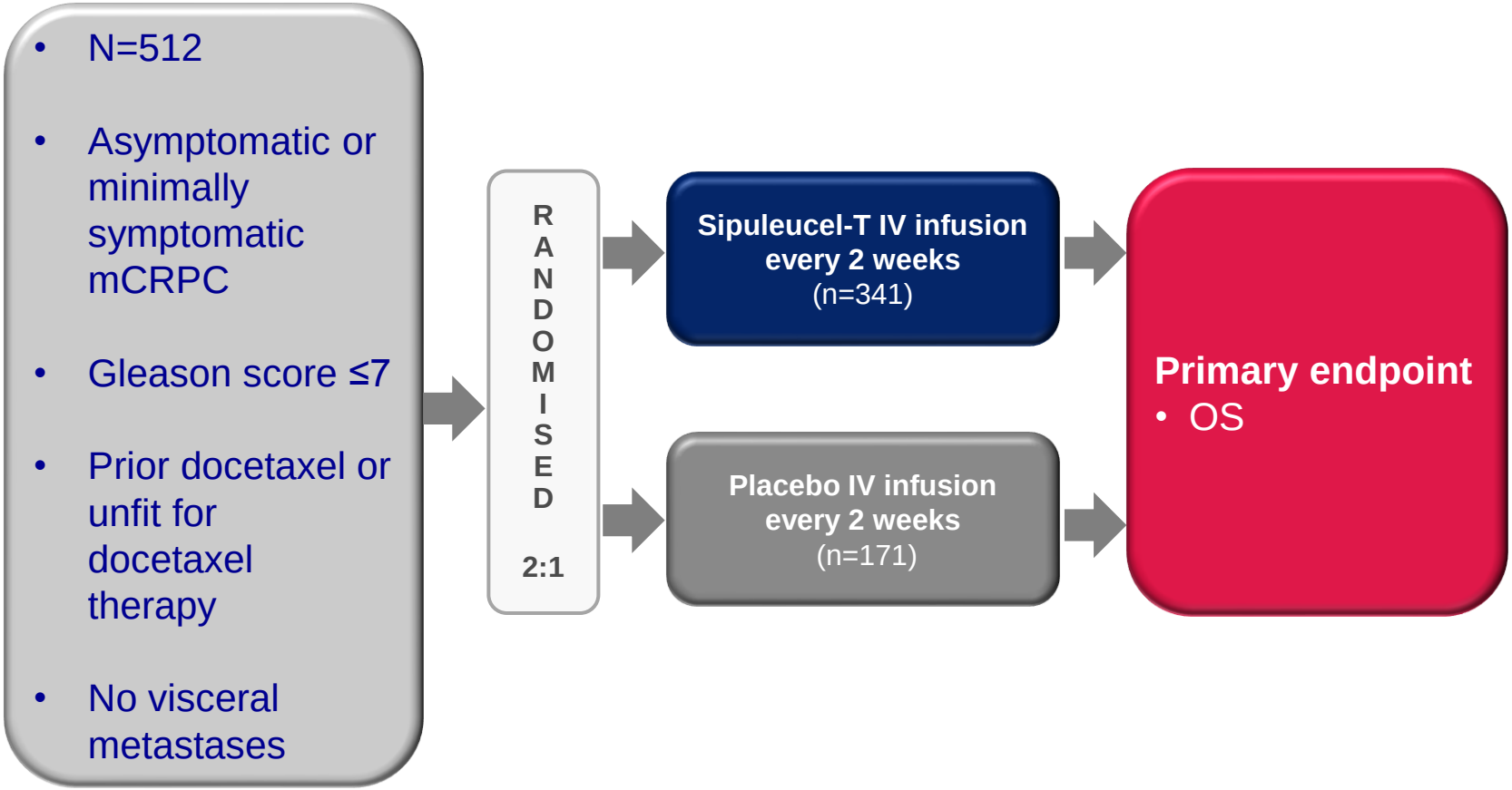
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

NYR = Not Yet Reached

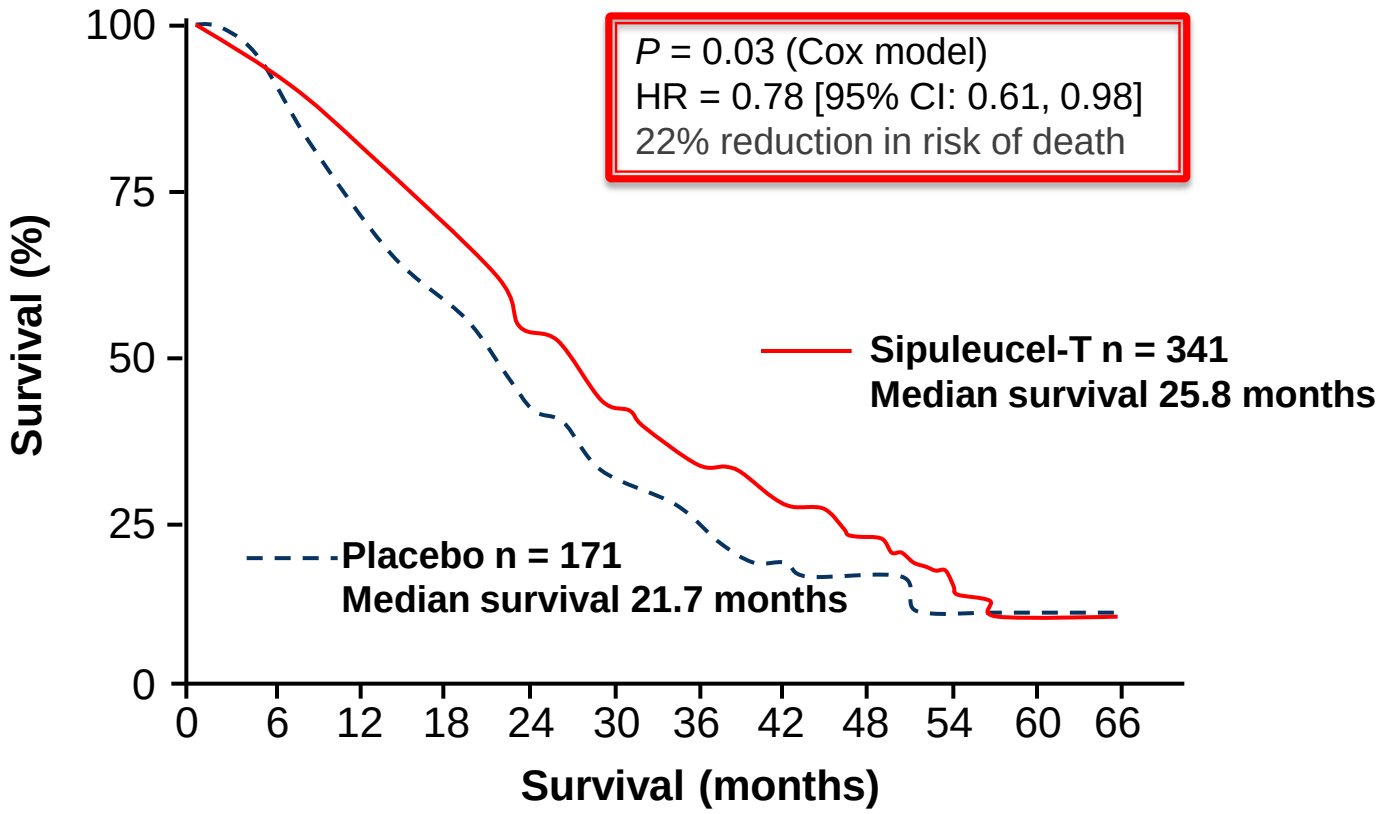
Beer TM et al.N Engl J Med. 2014 Jul 31;371(5):424-33

Sipuleucel-T: The IMPACT trial



Kantoff P et al. New Engl J Med 2010; 363(5): 411-422

IMPACT: Overall Survival
4.1 month improvement vs placebo



IMPACT overall survival: primary endpoint
Intent-to-treat population

Kantoff et al. New Engl J Med 2010; 363(5): 411-422

Front-line options that improve survival

Treatment	Trial	Visceral disease allowed	HR	Survival (mos)
Docetaxel/prednisone vs Mitoxantrone/prednisone	TAX 327[1]	YES	0.79	18.9 vs 16.5
Sipuleucel-T vs control	IMPACT[2]	No	0.78	25.8 vs 21.7
Abiraterone/prednisone vs Placebo/prednisone	COU-302[3]	No	0.75	NYR vs 27.2
Enzalutamide vs Placebo	PREVAIL[4]	Yes	0.70	32.4 vs 30.4
Radium 223 vs Placebo/BSC	ALSYMCA[5]	No	0.70	16.1 vs 11.5

[1]*Tannock et al. N Engl J Med 2004;351(15):1502-1512*

[2]*Kantoff et al. N Engl J Med 2010;363(5):411-422*

3 Ryan et al. N Eng J Med 2013;368:138–48

[4] *Beer et al. N Engl J Med 2014*

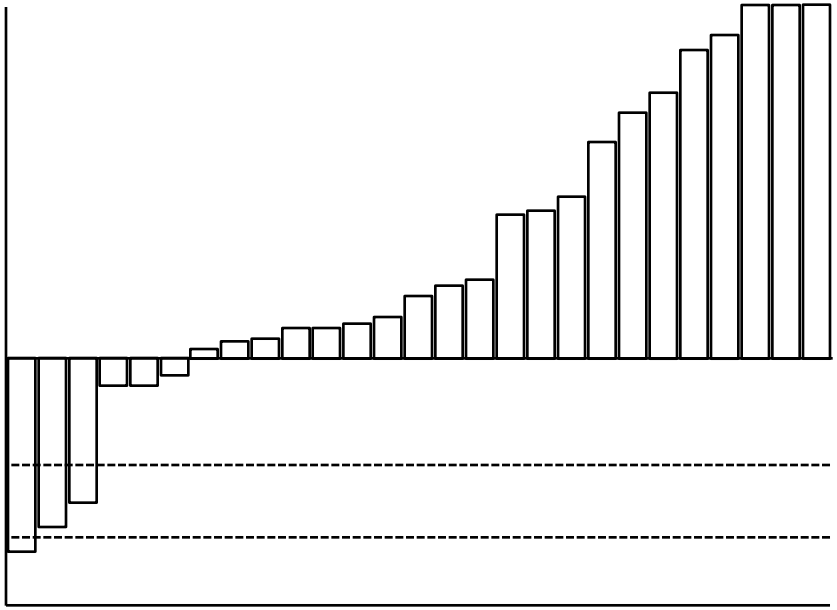
[5]*Parker et al. NEJM 2013;369(2):213-223*

Which drug for which patient?

- How can therapies for mCRPC best be utilized?
- Is there an optimal sequence of therapies?
- Not all patients respond to AR-targeted agents
- Is there cross resistance among therapies?
- None of these new therapies have been directly compared to each other
- Separation of trials into pre and post docetaxel is artificial
- No prospective sequencing trials

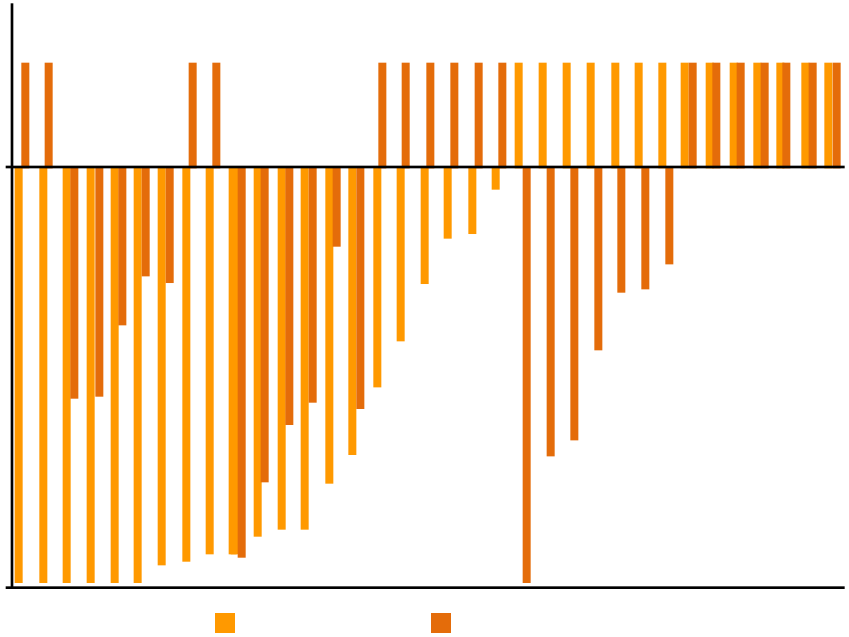
Does Progression on Enzalutamide Decrease the Efficacy of Abiraterone, and Vice Versa?

Abiraterone after enzalutamide[1]



PSA decline >50% = 3%

Enzalutamide after abiraterone[2]



PSA decline >50% = 29%

1. Noonan KL, Ann Oncol. 2013;24(7):1802-1807.

2. Schrader AJ, et al. Eur Urol. 2014 Jan;65(1):30-6.

Does Abiraterone Decrease the Efficacy of Docetaxel ?

	TAX327[1] DOC q3w N=1006	Mezynski[2] ABI→ DOC q3w N=35	Schweizer[3] DOC N=95	Schweizer[3] ABI→ DOC N=24
PSA decrease ≥50%	45%	26%	63%	38%
Median PFS, months	7.7	4.6	6.7	4.1
Median OS, months	19	12.5	NA	NA

Small Retrospective studies

Tannock IF, et al. N Engl J Med. 2004;351(15):1502-1512. 2. Mezynski J, et al. Ann Oncol. 2012;23(11):2943-2947
3. Schweizer MT , et al. Eur Urol. 2014 Oct;66(4):646-52

Does Progression on Abiraterone Decreases the Efficacy of Enzalutamide ?

	AFFIRM[1] DOC→ENZA N=1199	Schrader[2] DOC→ABI→ENZ N=35
PSA decrease ≥50%	54%	29%
Median PFS, months	8.3	4.9
Median OS, months	18.4	8.4 if PSA ↓ ≥50% 6.4 if PSA↓ <50%

Small Retrospective study

Scher HI, et al. N Engl J Med. 2012;367(13):1187-1197. 2. Schrader AJ, et al. Eur Urol 2014 Jan;65(1):30-6.

Does Progression on Enzalutamide Decreases the Efficacy of Abiraterone ?

	COU-AA-301[1-2] DOC→ABI N=1195	Loriot[3] DOC→ENZ→ABI N=38	Noonan[4] DOC→ENZ→ABI N=30
PSA decrease ≥50%	38%	8%	3%
Median PFS, months	5.6	2.7	3.5
Median OS, months	15.8	7.2	11.5

Small Retrospective studies

1. *De Bono JS, et al. N Engl J Med. 2011;364(21):1995-2005. 2. Fizazi K, et al. Lancet Oncol. 2012;13(10):983-992. 3. Loriot Y, et al. Ann Oncol. 2013;24(7):1807-1812. 4. Noonan KL, et al. Ann Oncol. 2013;24(7):1802-7*

Does Prior AR Targeted Agent Decrease the Efficacy of Cabazitaxel?

	TROPIC[1-2]	Pezaro[3]	Angelergues[4]	
Abiraterone or enzalutamide	**none**	**Before CBx N = 89**	**Before CBx N = 42**	**After CBx N = 27**
PSA decrease ≥50%	**39.2%**	**49%**	**42.9%**	**48.1%**
Partial Response RECIST	**14.4%**	**20%**		
Median PFS, months			**5.1**	**10.5**
Median OS, months	**29.4**		**38.2**	**66.2**

Small Retrospective studies

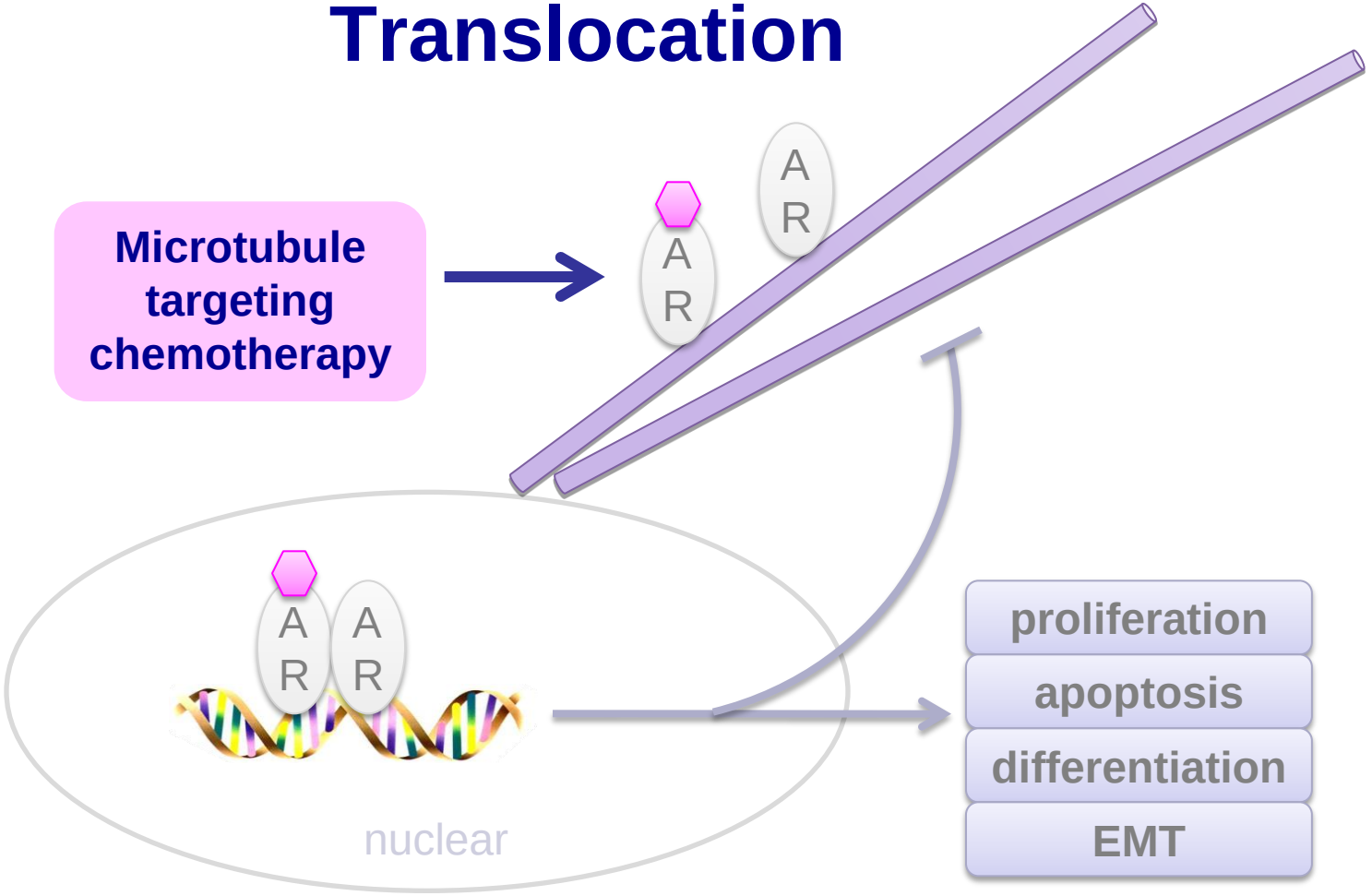
1. De Bono JS, et al. Lancet. 2010;376(9747):1147-1154. 2. Sartor S, et al. J Clin Oncol. 2011;29(15S): Abstract 4525.
3. Pezaro CJ, et al. J Clin Oncol. 2013;31(Suppl 6): Abstract 155.
4. Angelergues A, et al. J Clin Oncol. 2013;31(Suppl 6): Abstract 5063

Retrospective Trials on Sequential Therapy

SEQUENCE	Authors	N° pts	PSA response	RR	PFS	OS
ABI → ENZA	Bianchini	39	12.8	4.3	2.8	NR
	Schrader	35	28.6	2.9	4.0	7.1
	Schmid	35	10	2.8	3.1	7.5
	Badrising	61	21	NA	3.0	7.9
	Thomsen	24	NA	NA	NA	4.8
	Thomson	23	39.1	NA	2.8	8.5
	Roeder	24	NA	NA	NA	4.8
	Vera-Badillo FE	26	27	NA	4.9	NA
	Sandhu	23	17.3	NA	2.3	NA
	Scholz	63	NA	NA	NA	NA
	Stevenson	75	NA	NA	3.96	NA
ENZA → ABI	Noonan	30	3	11	3.85	12.5
	Loriot	38	8	8	2.7	7.2
ABI → CABA	Albiges	39	56	15	NA	NA
	Sella	24	31.5	15.3	NA	8.2
	Sonpavde	36	NA	NA	7.1	11.8
CABA → ABI	Sonpavde	77	NA	NA	10.4	18.2
ABI/ENZA → CABA	Pezaro	41	39	14	4.6	15.8

Courtesy of O. Cafffo with modifications

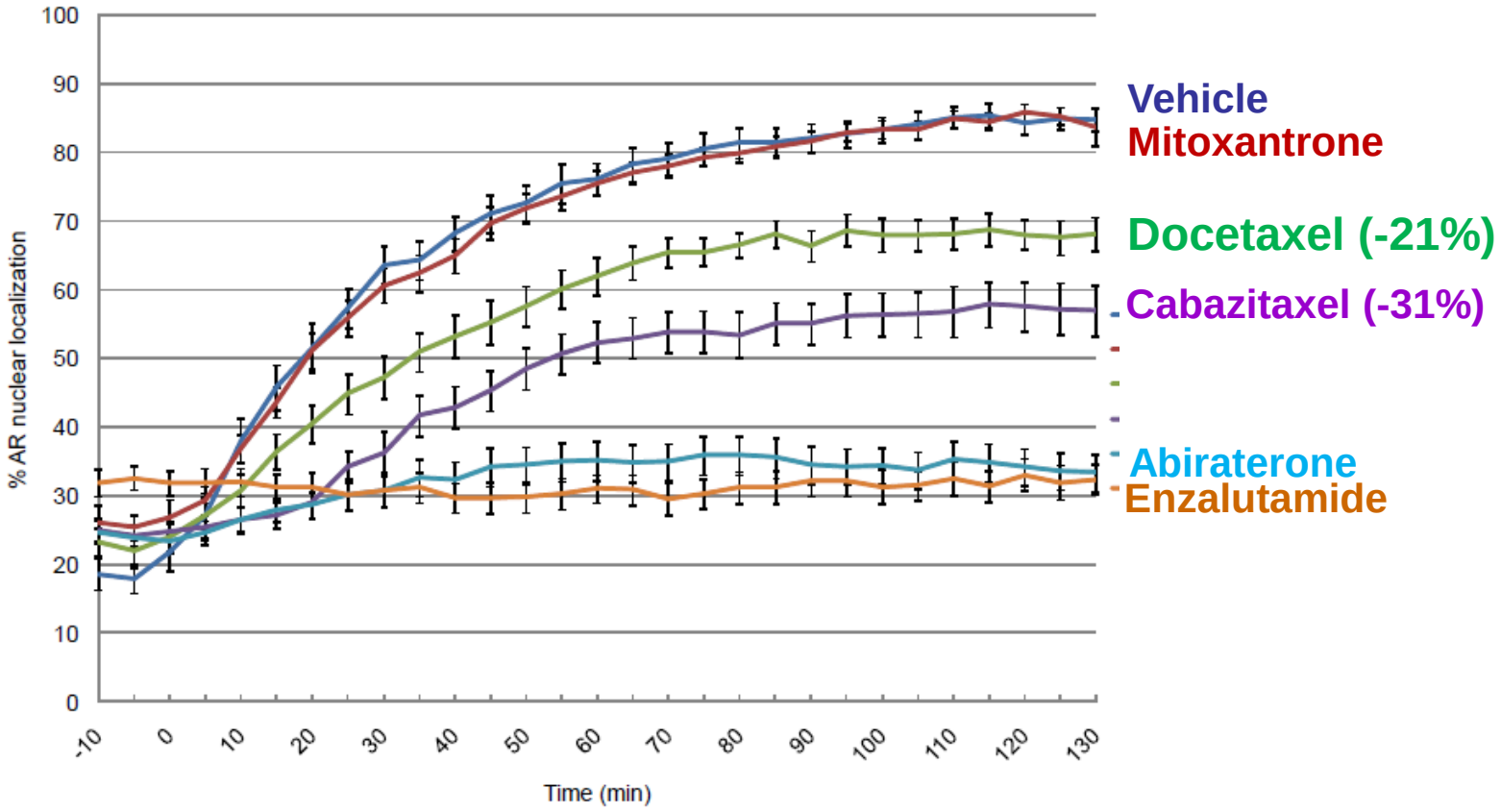
Microtubules Facilitate AR Nuclear Translocation



Androgens Inhibit Tubulin Expression in Prostate Cancer Cells

Zhu et al. Cancer Res 2010;70:7992
Thadani-Mulero M. Cancer Res 2012;72:4611

Inhibition of AR Nuclear Translocation



van Soest R et al. Eur J Cancer. 2013;49(18):3821-30

Response to therapy according to prior duration of ADT

Hormonal therapy[1]

- Retrospective analysis in 108 patients with metastatic PCa

Duration of response	<16 months	≥16 months	p value
↓ PSA ≥50%	18%	58%	0.01
Median TTP, months	3.0	5.0	<0.043

Docetaxel[2]

- 188 patients with mCRPC in two prospective databases

Duration of response	≤1 year	>1 year	p value
↓ PSA ≥50%	67%	81%	0.10
Median TTP, months	6.1	7.8	0.04

*Including abiraterone, ketoconazole, hydrocortisone, DES and bicalutamide).

1. Loriot Y, *et al. J Clin Oncol* 2012;30(Suppl): abstract 213.
2. Huillard O, *et al. J Clin Oncol* 2013;31(Suppl): abstract 5075.

Benefit with enzalutamide irrespective of duration of prior response to ADT

- *Post-hoc* analysis post-chemotherapy AFFIRM trial

Duration of response to ADT	≤12 months		12–26.9 months		>26.9 months	
	ENZ	Placebo	ENZ	Placebo	ENZ	Placebo
Time to radiographic progression, median (months)	5.7	2.8	8.3	2.8	11.0	3.0
HR (95% CI)	0.44 (0.33–0.60)		0.42 (0.31–0.58)		0.33 (0.23–0.46)	
OS, median (months)	15.4	9.1	NYR	14.7	NYR	15.5
HR (95% CI)	0.49 (0.34–0.70)		0.69 (0.47–1.01)		0.54 (0.35–0.82)	

de Bono JS, *et al.* ECC 2013; Poster presentation P369.

OS and rPFS with abiraterone according to baseline Gleason score

- *Post-hoc* analysis Phase 3 COU-AA-301 and COU-AA-302 trials

	Gleason score <8			Gleason score ≥8		
	Median (months)			Median (months)		
	AA + P	P	HR (95% CI)	AA + P	P	HR (95% CI)
mCRPC post-docetaxel						
n	342	161		356	189	
OS	16.3	13.4	0.82 (0.64–1.04)	15.5	10.3	0.61 (0.49–0.76)
rPFS	6.4	5.5	0.70 (0.56–0.86)	5.6	2.9	0.58 (0.48–0.72)
mCRPC chemotherapy-naïve						
n	225	254		263	254	
OS	NYR	31.0	0.72 (0.54–0.97)	31.6	30.0	0.84 (0.64–1.09)
rPFS*	16.5	8.2	0.44 (0.35–0.56)	13.8	8.2	0.61 (0.48–0.77)

Fizazi K, *et al. J Clin Oncol* 2014;32(Suppl): abstract 20.

OS and rPFS with enzalutamide according to baseline Gleason score

- *Post-hoc* analysis Phase 3 AFFIRM and PREVAIL trials

	Gleason score <8			Gleason score ≥8		
	Median (months)			Median (months)		
	ENZ	Placebo	HR (95% CI)	ENZ	Placebo	HR (95% CI)
mCRPC post-docetaxel[1]						
n	360	175		366	193	
OS	18.4	14.8	0.67 (0.51–0.88)	18.2	11.3	0.60 (0.47–0.76)
rPFS	–	–	–	–	–	–
mCRPC chemotherapy-naïve[2]						
n	414	385		424	423	
OS	NYR	30.0	0.66 (0.51–0.85)	31.5	30.2	0.77 (0.60–0.97)
rPFS	14.1	5.3	0.16 (0.11–0.22)	NYR	3.7	0.23 (0.17–0.31)

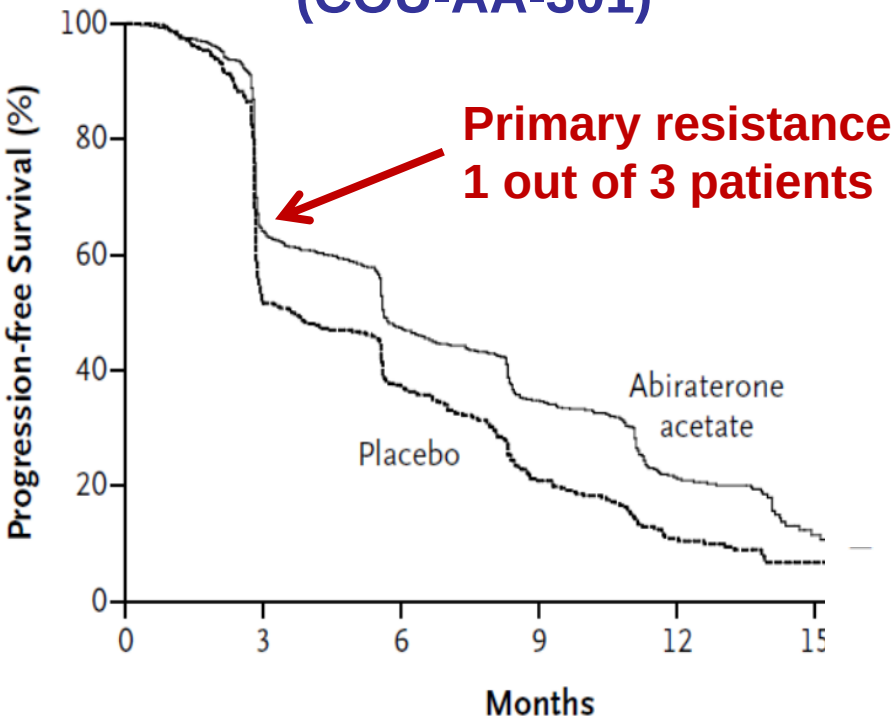
.

1. Data on file: ENZ/13/0074/EU, August 2013.
2. Beer TM, *et al. N Engl J Med* 2014;371:424–33. Suppl. Appendix.

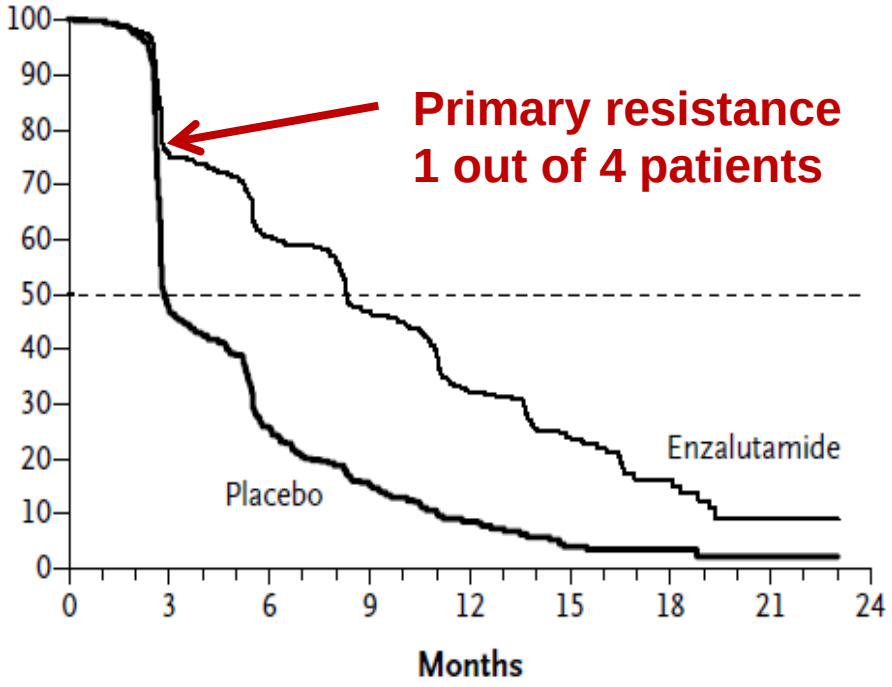
Primary resistance to AR-targeted agents

Radiological progression-free survival

Abiraterone[1] (COU-AA-301)



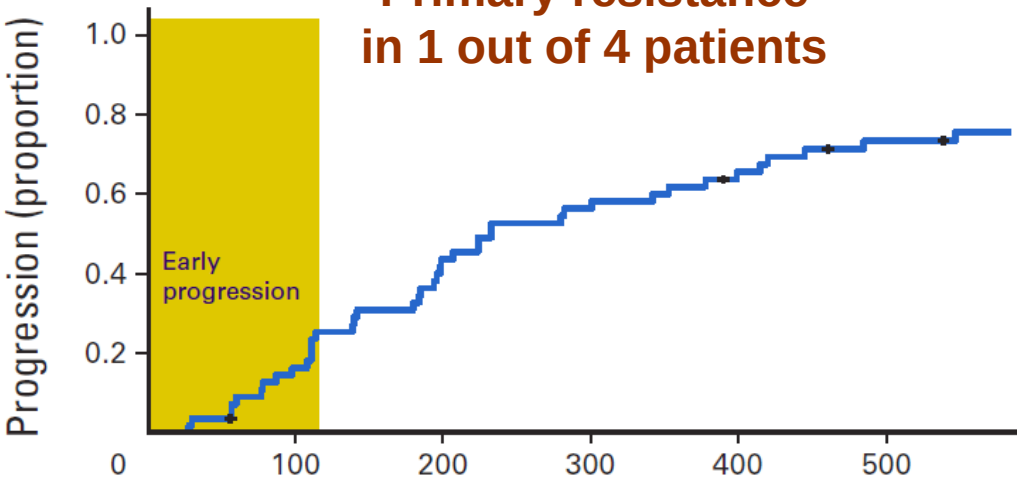
Enzalutamide[2] (AFFIRM)

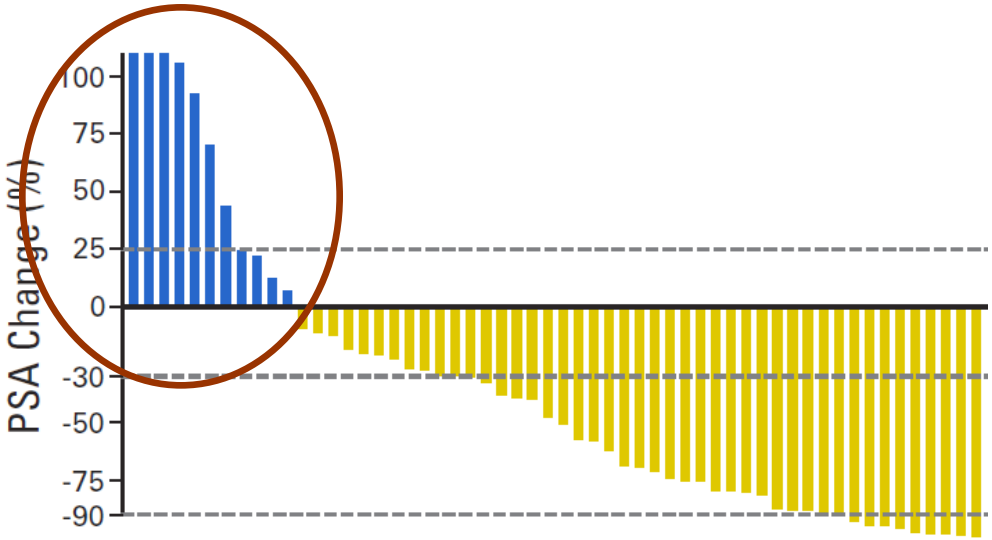


De Bono et al. N Engl J Med 2011; 364: 1995–2005
Scher H et al. N Engl J Med 2012; ;367:1187-97

Who are the non responders to abiraterone?

Primary resistance in 1 out of 4 patients





Who are the NON responders?
(defined as patients treated for ≤4 months)

Bone marrow biopsy:
- Intense AR nuclear expression
- CYP17 expression

YES
82% responders
(12/13)

NO
18% responders
(2/12)

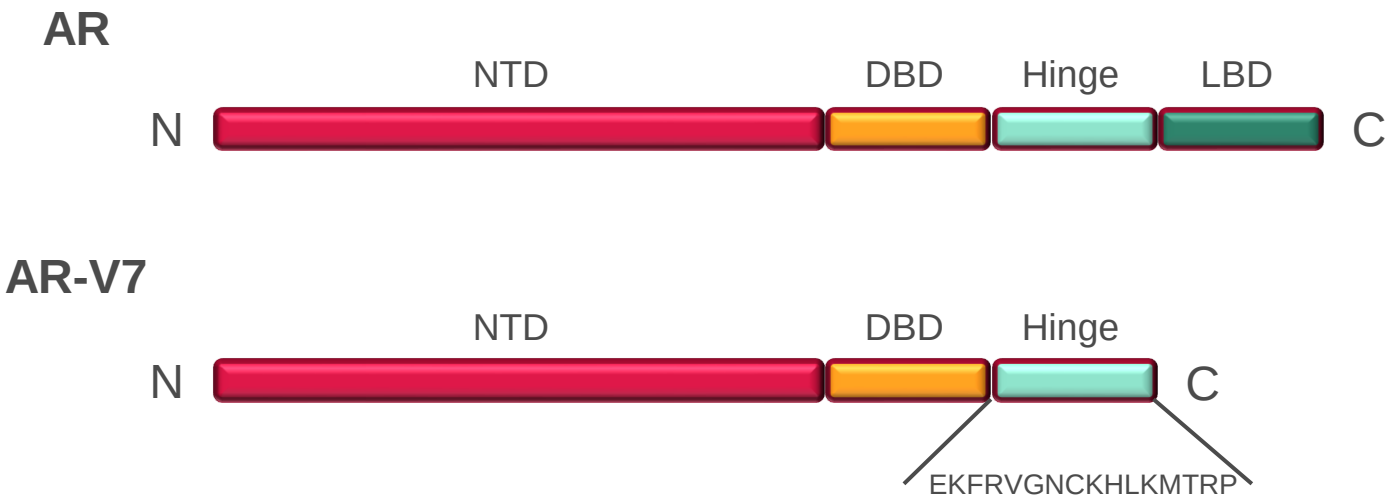
P<0.001

Efstathiou E et al. J Clin Oncol 2011;30:637-43

AR-V7 as a predictor of treatment outcome to enzalutamide and abiraterone in mCRPC

AR-V7 characteristics

- Most abundant splice variant
- Constitutively active
- 20-fold increased expression in mCRPC
- Produces functional protein product unaffected by nonsense-mediated mRNA decay

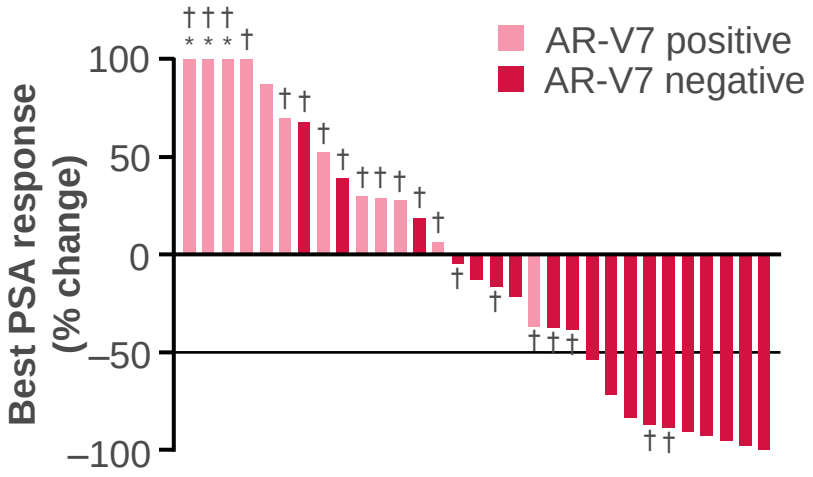


Pelekanou V, et al. Hormones 2013;12:224–35.

PSA responses according to AR-V7 status

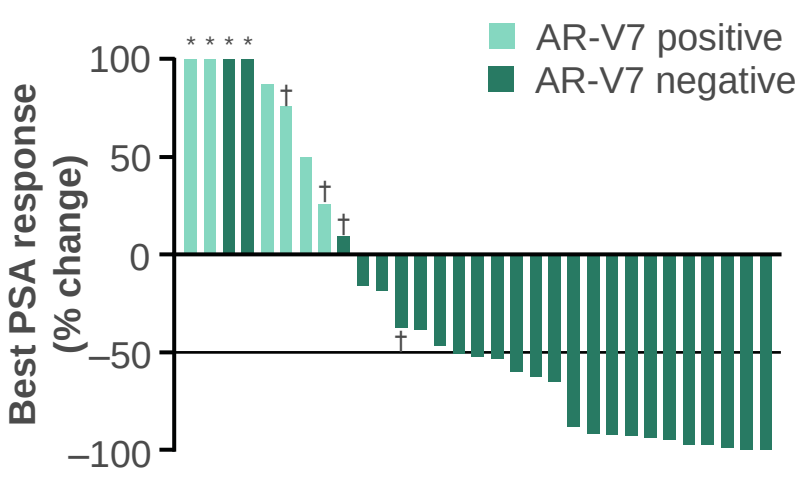
- Patients previously receiving chemotherapy, abiraterone or enzalutamide were included

Enzalutamide



PSA response rate
AR-V7 positive: 0% (95% CI: 0–26%)
AR-V7 negative: 52.6% (95% CI: 29–76%)
p=0.004

Abiraterone

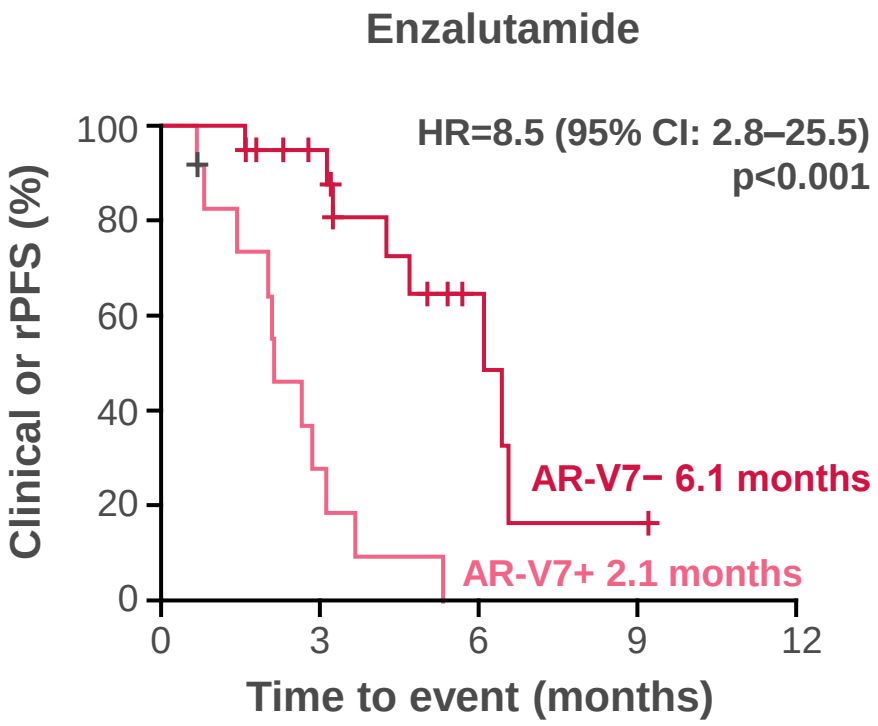


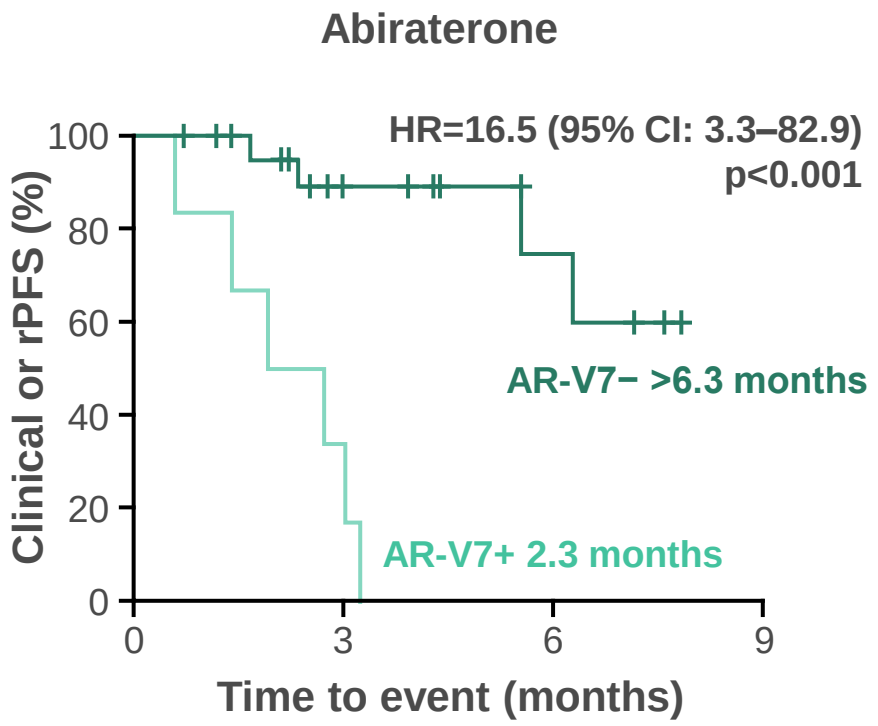
PSA response rate
AR-V7 positive: 0% (95% CI: 0–46%)
AR-V7 negative: 68.0% (95% CI: 46–85%)
p=0.004

*Increase of more than 100% in best PSA response. †Patients in the enzalutamide cohort who had previously received abiraterone and patients in the abiraterone cohort who had previously received enzalutamide.
Antonarakis ES, *et al. N Engl J Med* 2014;371:1028–38.

rPFS according to AR-V7 status

- Prospective biomarker study of 62 patients receiving enzalutamide or abiraterone





Antonarakis ES, *et al. N Engl J Med* 2014;371:1028–38.

AR-V7 associated with primary and acquired resistance to enzalutamide and abiraterone

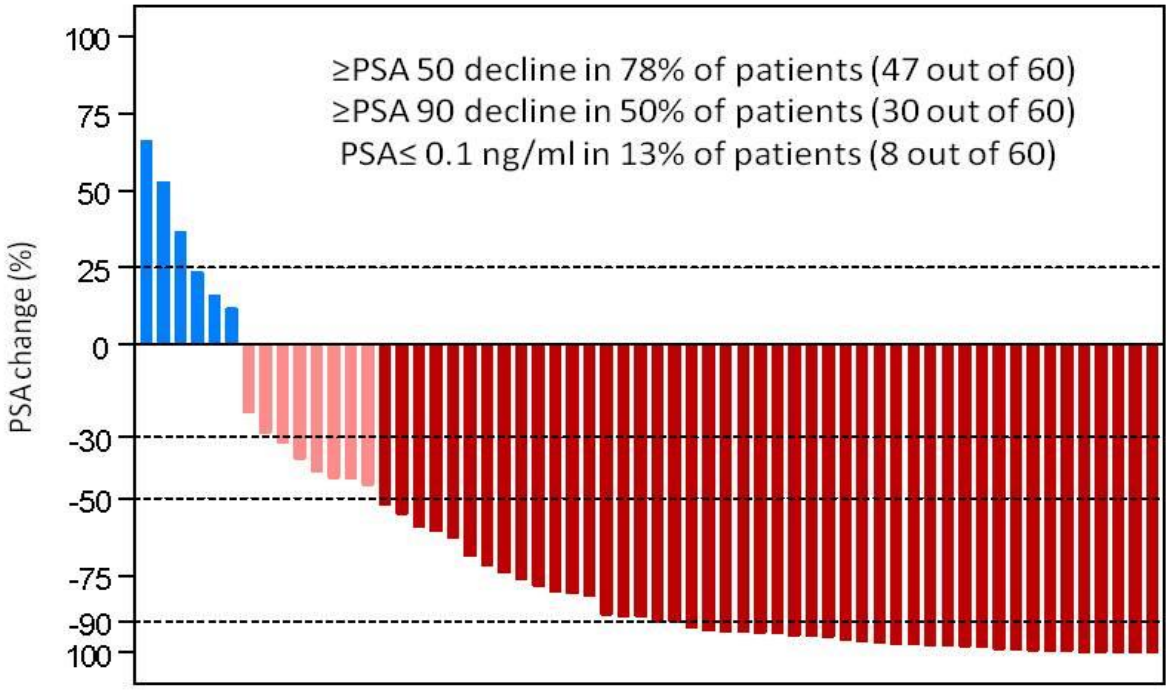
- Prospective biomarker study of 62 patients receiving enzalutamide or abiraterone

Outcome	AR-V7(-) to AR-V7(-) (n=36)	AR-V7(-) to AR-V7(+) (n=6)	AR-V7(+) to AR-V7(+) (n=16)
PSA response, % (95% CI)	68 (52–81)	17 (4–58)	0 (0–19)
PSA PFS, months (95% CI)	6.1 (5.9–NYR)	3.0 (2.3–NYR)	1.4 (0.9–2.6)
PFS, months (95% CI)	6.5 (6.1–NYR)	3.2 (3.1–NYR)	2.1 (1.9–3.1)

Antonarakis E, *et al.* ASCO 2014; oral presentation abstract 2910.

Co-Targeting Androgen Receptor and Androgen Biosynthesis

Maximal PSA Decline

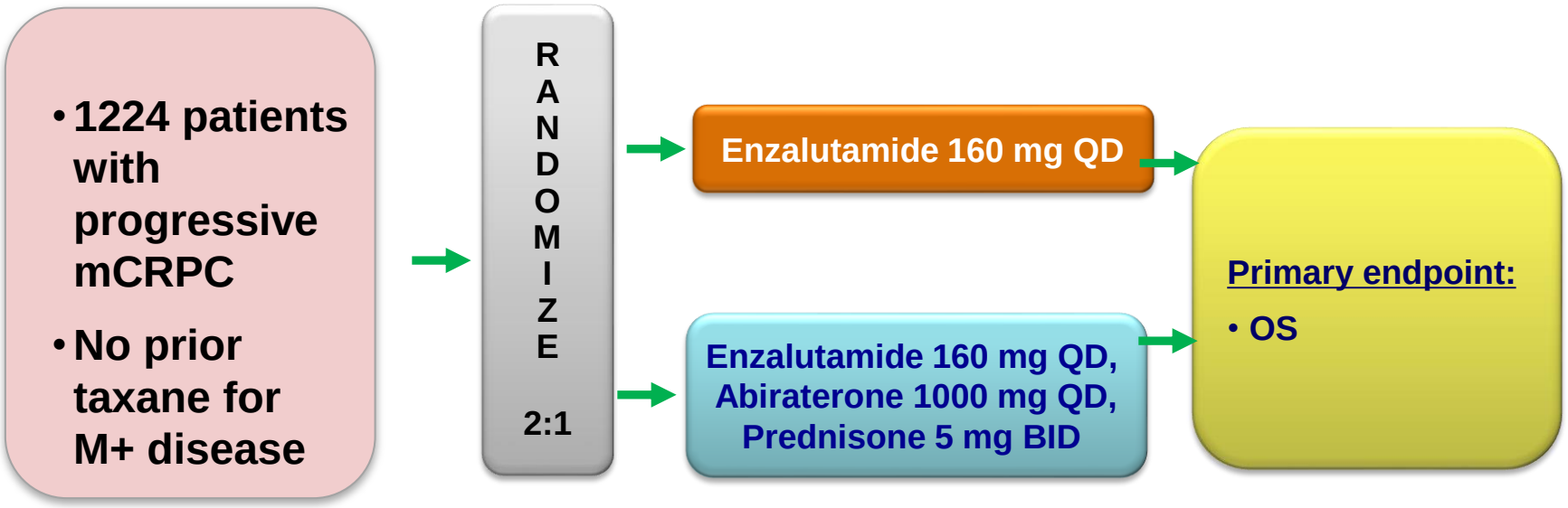


Exploratory: association of lack of PSA decline with primary resistance (p=0.008)

Efstathiou E et al. presented at ASCO 2014, abstract 5000

ALLIANCE Study Design
Phase III Pre-chemo

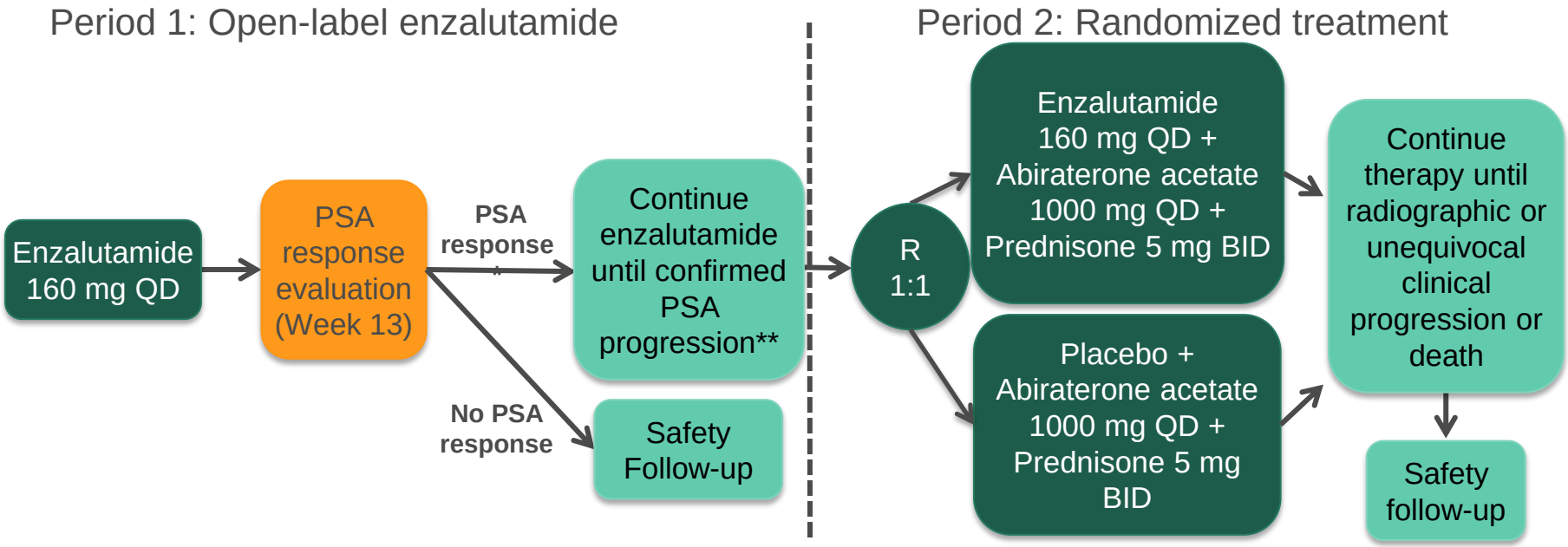
Phase 3 trial of enzalutamide versus enzalutamide, abiraterone + prednisone in mCRPC pre-chemotherapy



Total of 616 deaths, log-rank statistic 90% power (one sided type I error rate of 0.025) to detect HR of 0.77 in favor of arm B

ClinicalTrials.gov:/NCT01949337

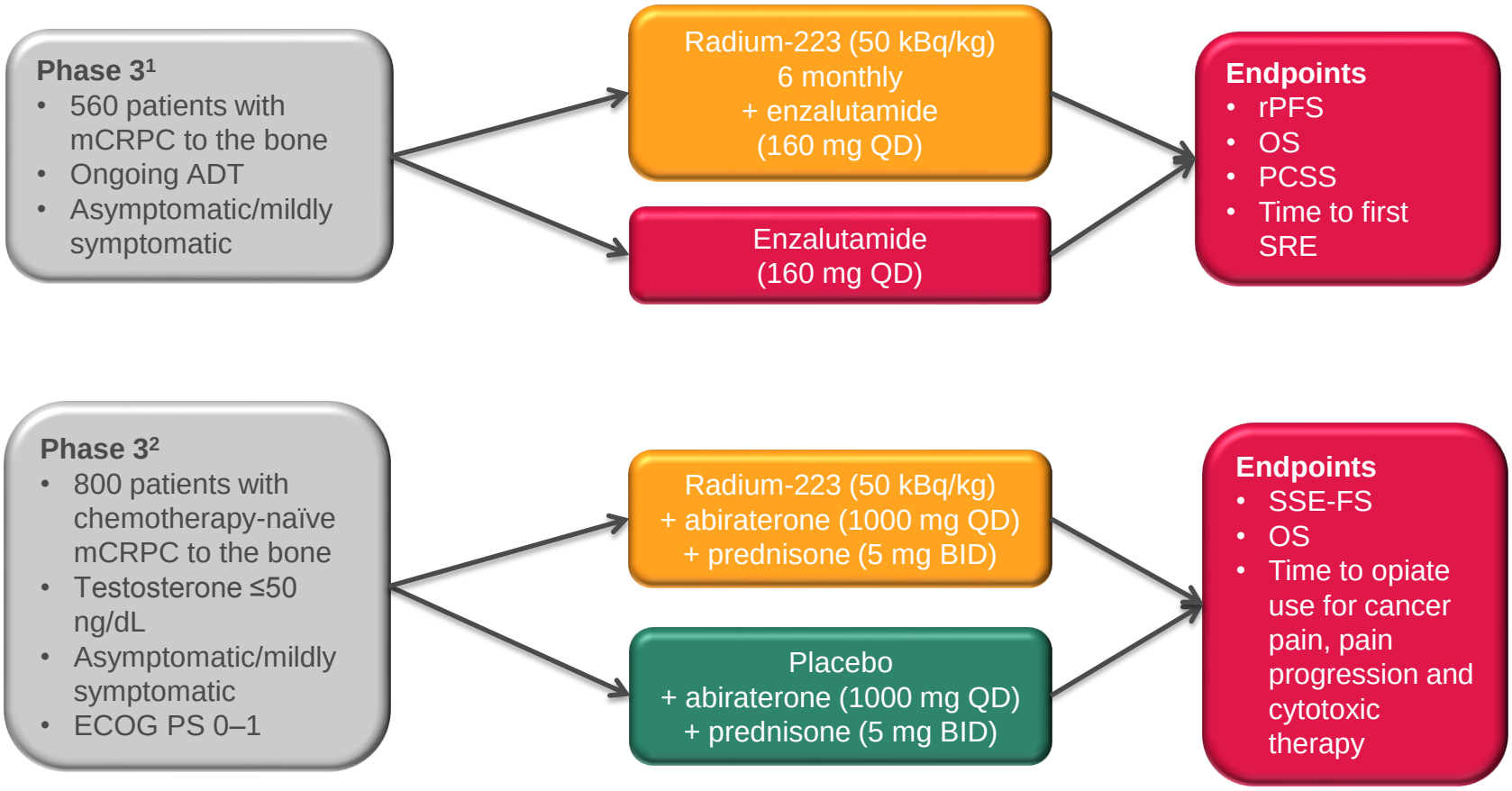
PLATO: Continued enzalutamide treatment in prostate cancer patients



- Phase 4, randomized, double-blind, placebo-controlled study
- Patients with metastatic CRPC (n=500)
  - No prior chemotherapy or prior treatment with abiraterone acetate
- Primary endpoint: progression-free survival (PFS)

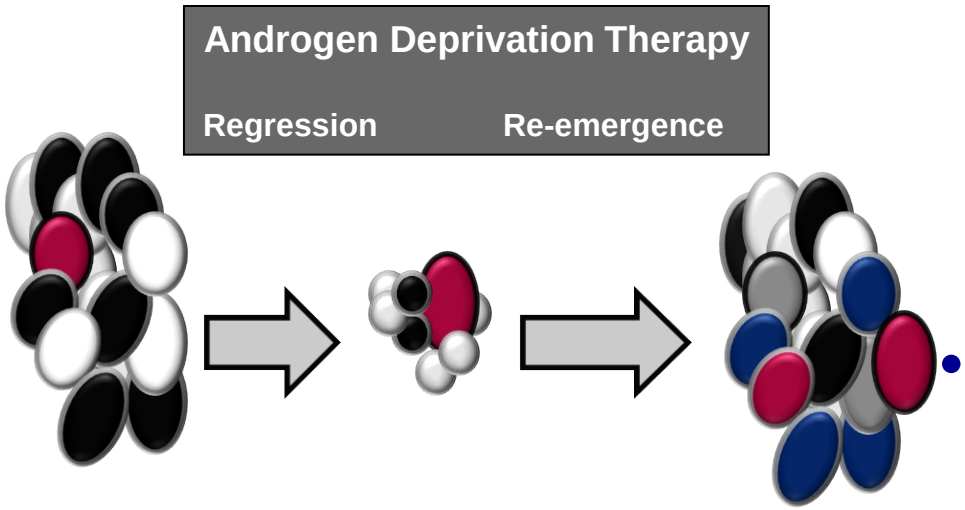
ClinicalTrials.gov:/NCT01995513

Ongoing combination studies: Abiraterone or enzalutamide with radium-223



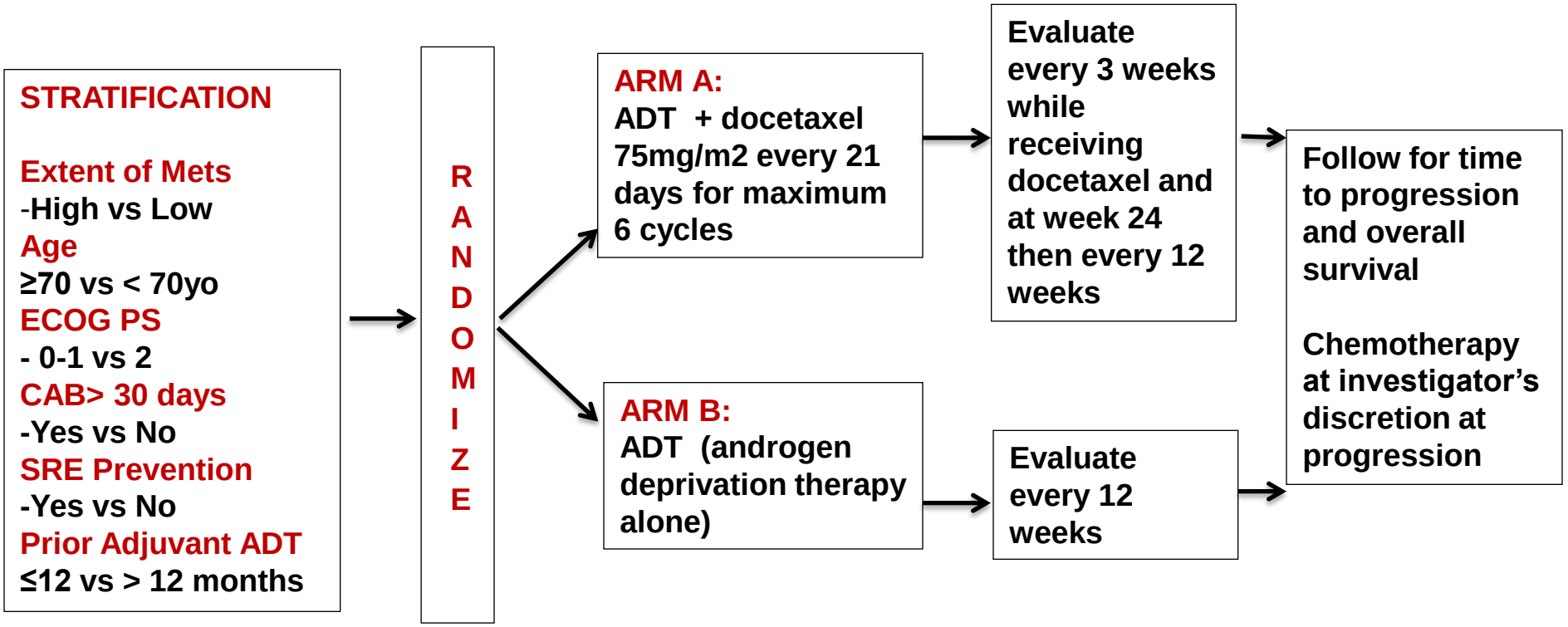
1. NCT02194842. Available at http://clinicaltrials.gov..
2. NCT02043678. Available at http://clinicaltrials.gov..

Early Chemo + ADT



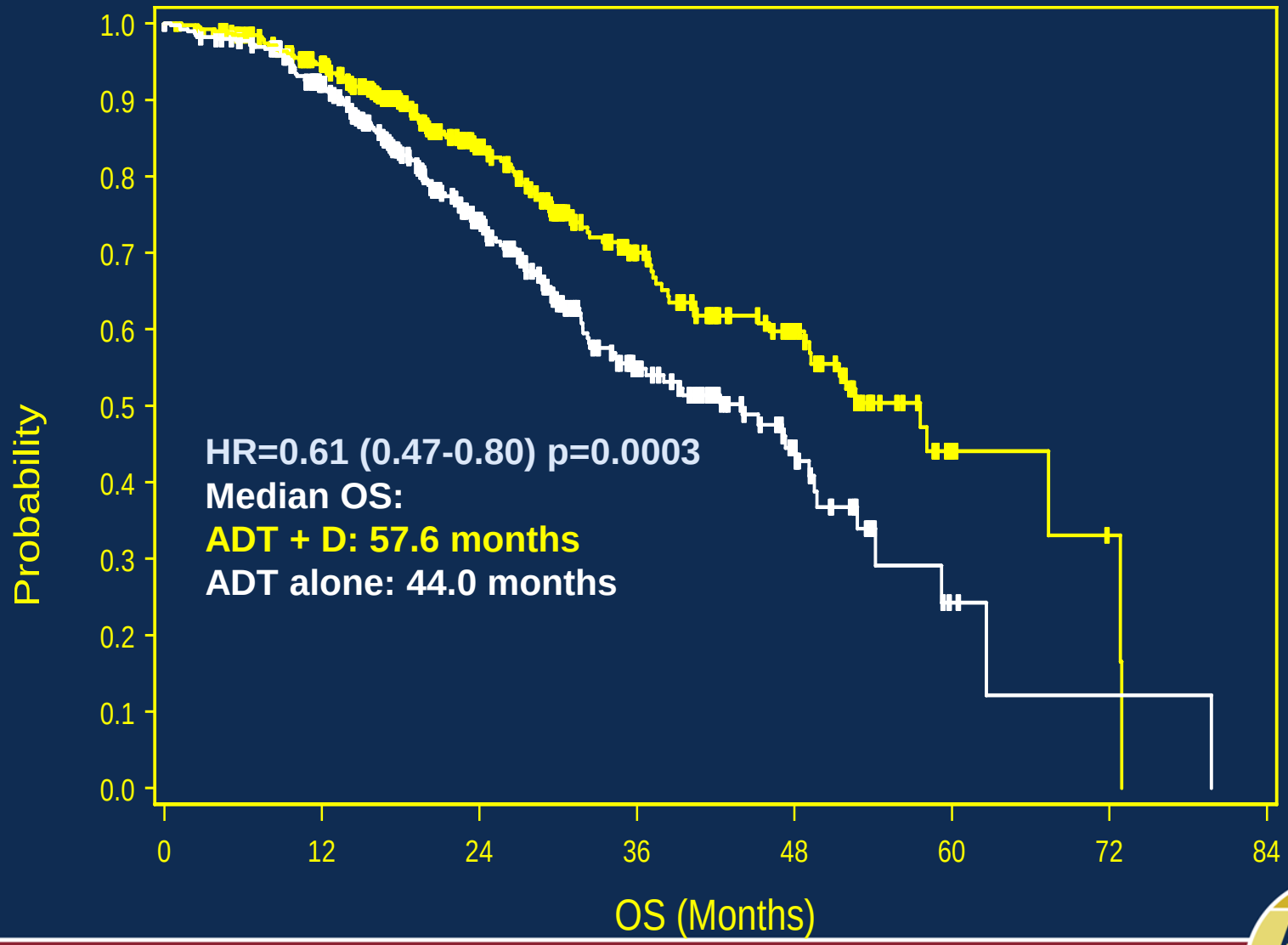
- **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo
- **Con**
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some patients respond for a long time and never need chemo

E3805-CHAARTED Treatment



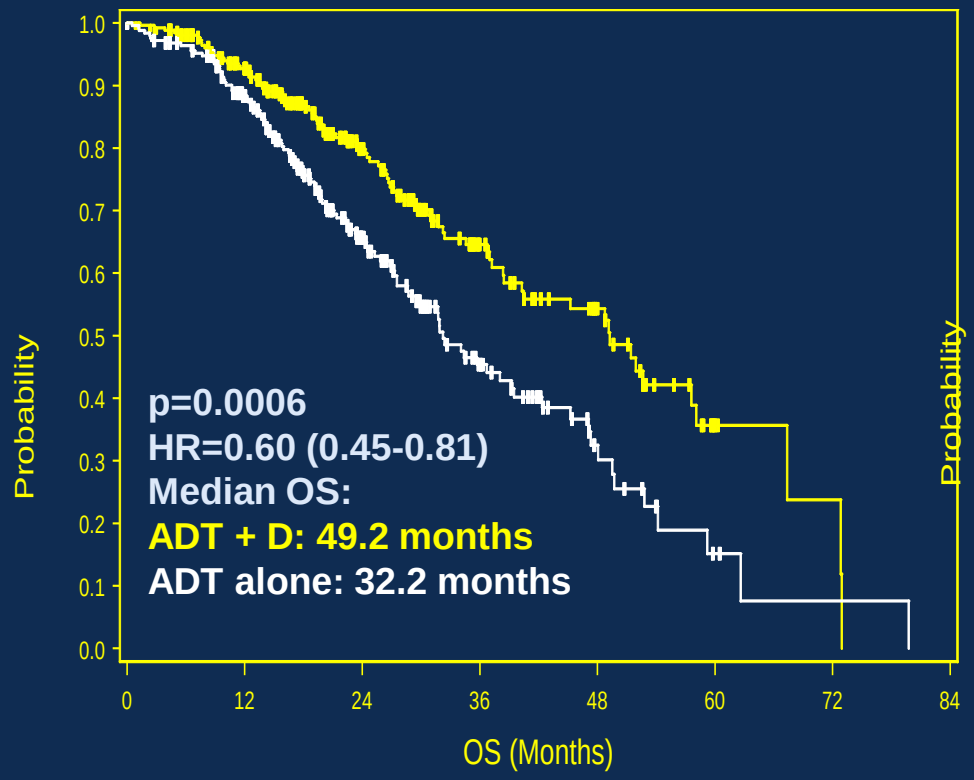
- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Primary endpoint: Overall survival

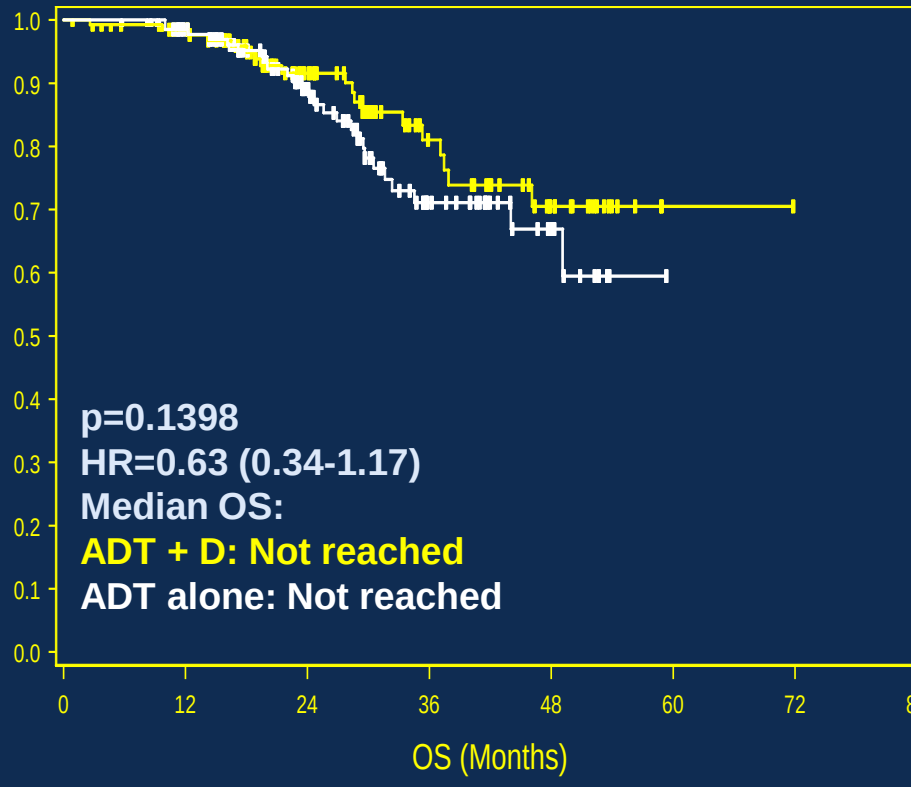


OS by extent of metastatic disease at start of ADT

High volume



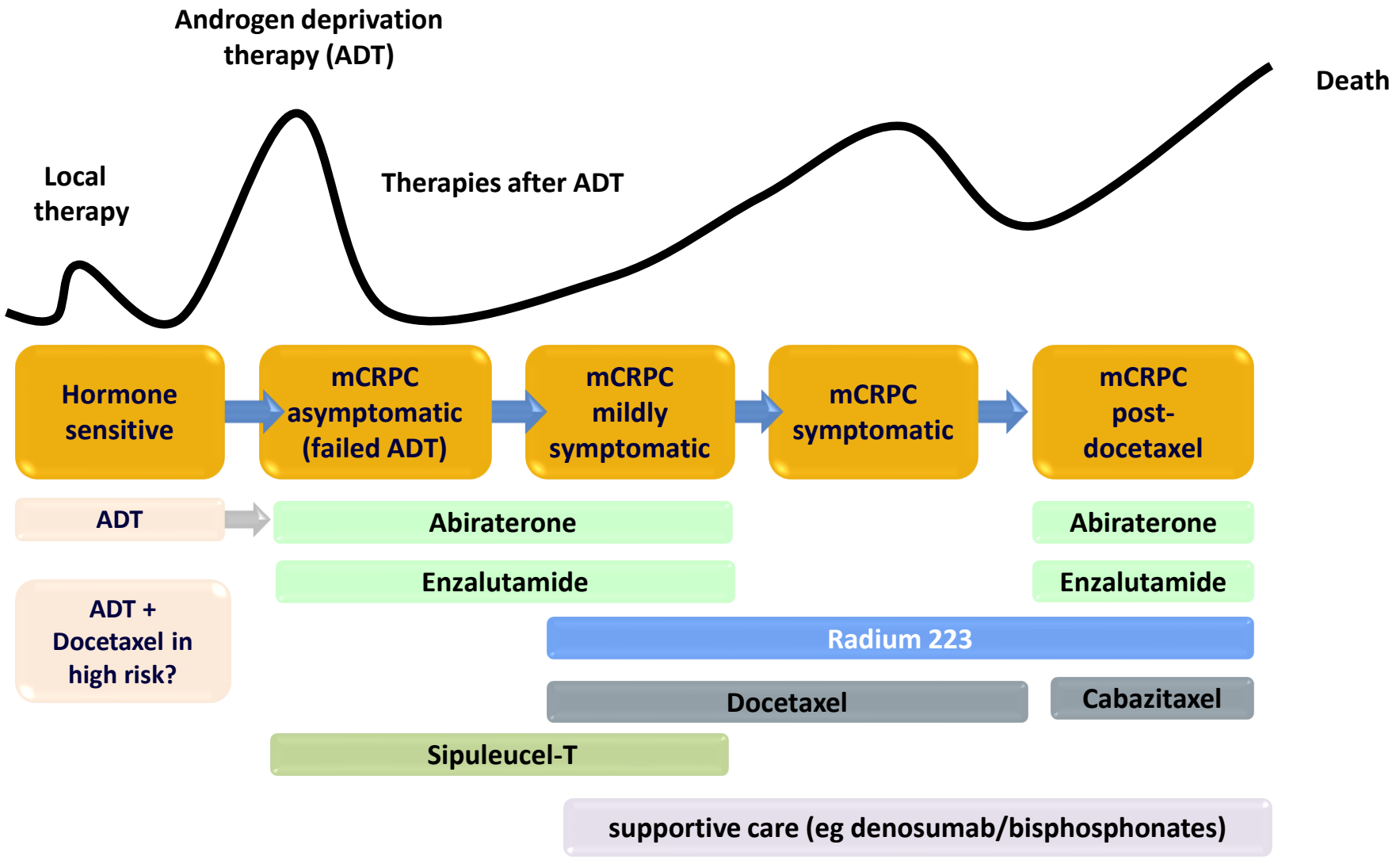
Low volume



In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

Current treatment paradigm is evolving



Therapeutic strategies for metastatic CRPC

- Prostate cancer is a heterogeneous disease
- Unequivocal evidence of continued involvement of the AR signaling axis
- Multiple new treatments available with proven OS benefit
- Evidence of cross resistance among agents targeting AR
- Best sequence and combination is undefined – prospective trials
- Clinical or molecular predictive factors are urgently needed

Thank you