The ROYAL MARSDEN
NHS Foundation Trust

2nd line hormone therapy in prostate cancer

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The Royal Marsden

1st December 2017

Working Together Improving the Management of Advanced Prostate Cancer

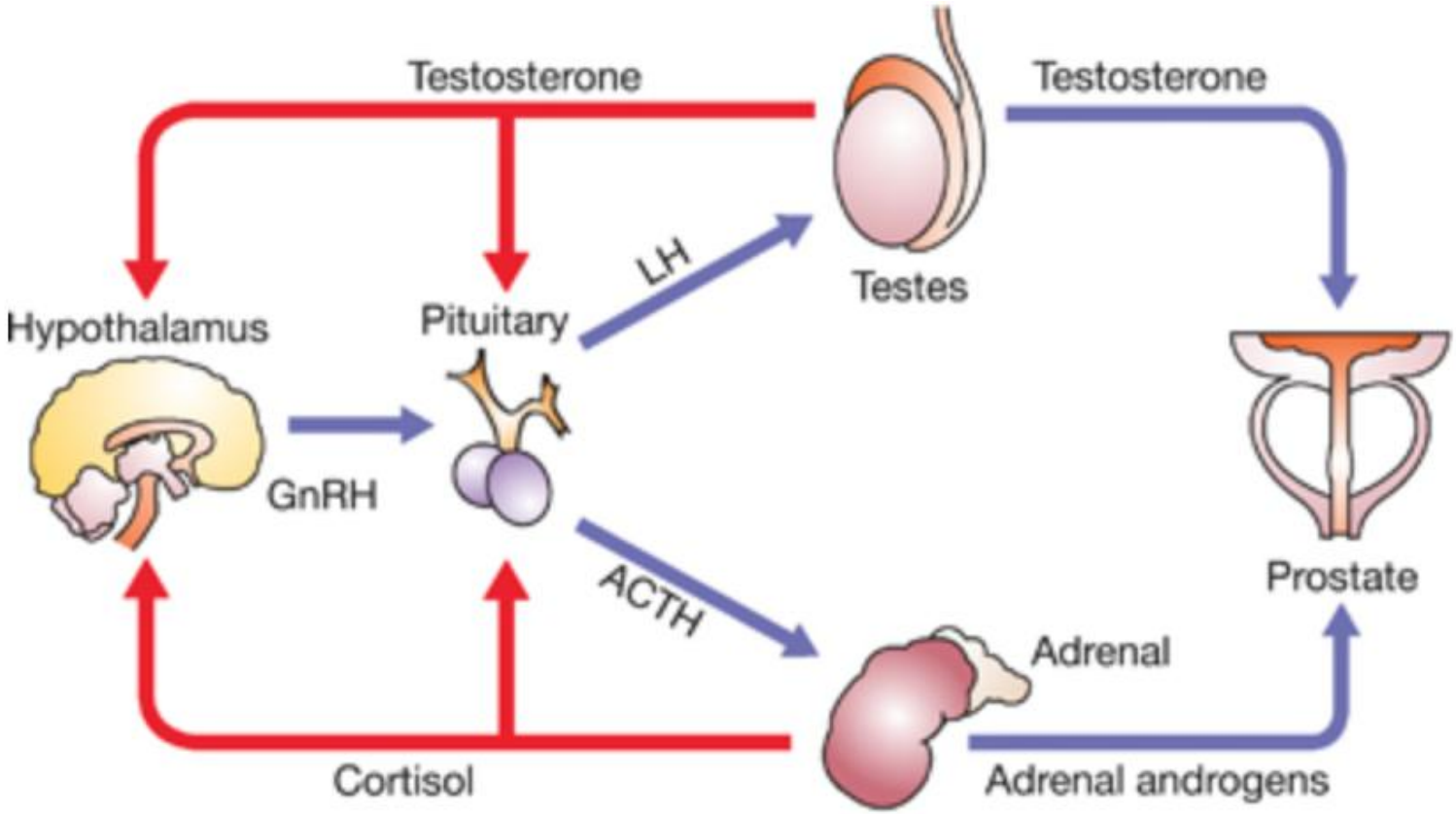
NHS

Learning objectives

1. Know which hormonal therapies are used in:
   - hormone-sensitive prostate cancer
   - castrate-resistant prostate cancer
2. Know how they work
3. Be aware of the side-effects of these agents
4. The future

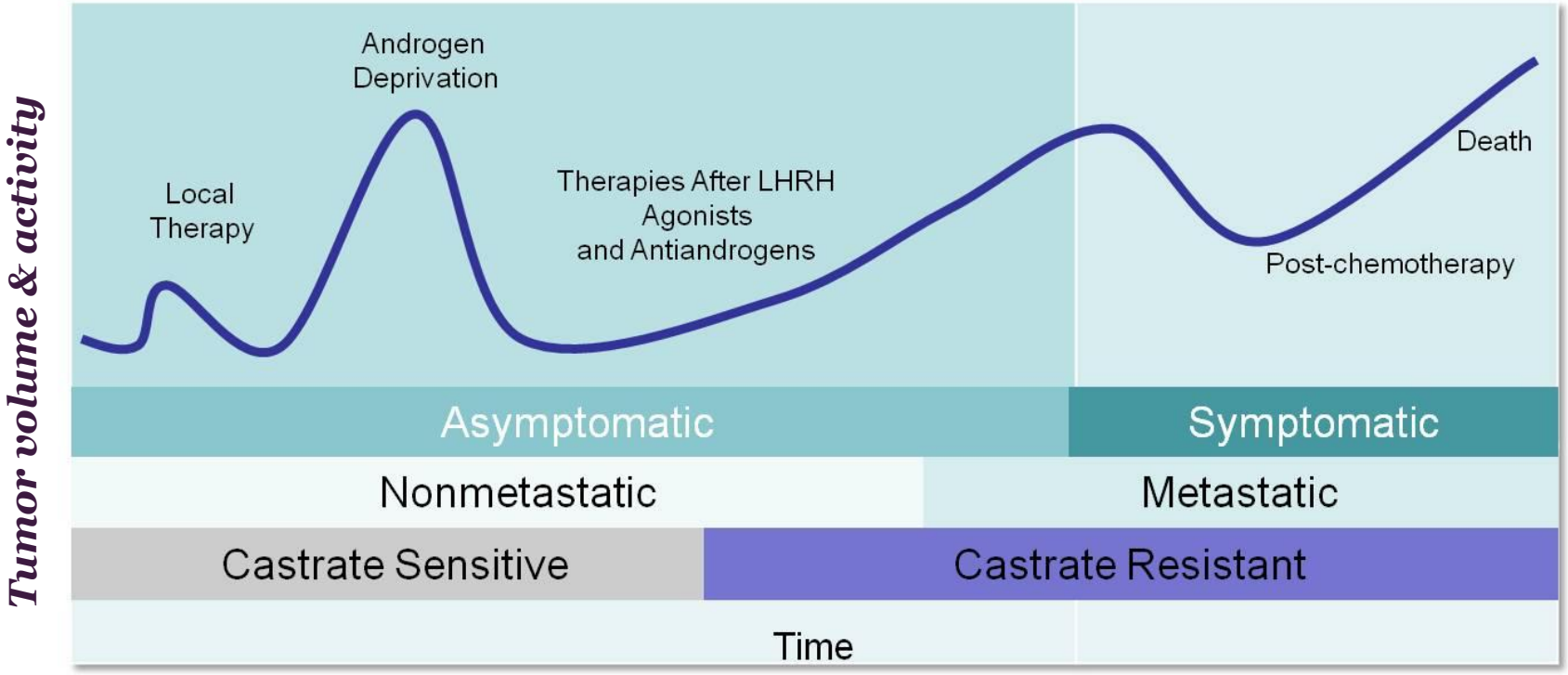
Endocrinology revision

Endocrine control of the prostate



Shore et al. 2013

Hormone sensitive & Castrate resistant prostate cancer

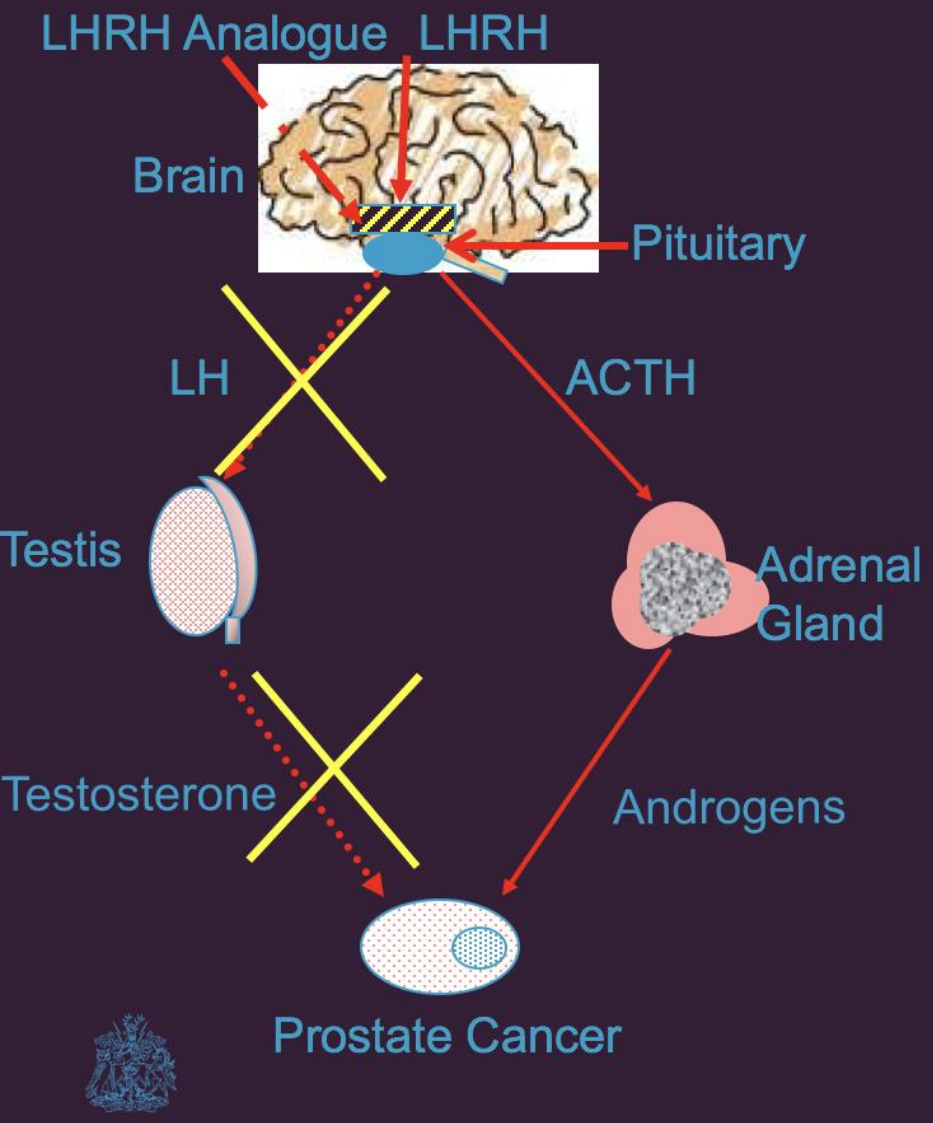


Castrate serum testosterone <50ng/dl or <1.7nmol/l +
Rise in PSA or radiological progression

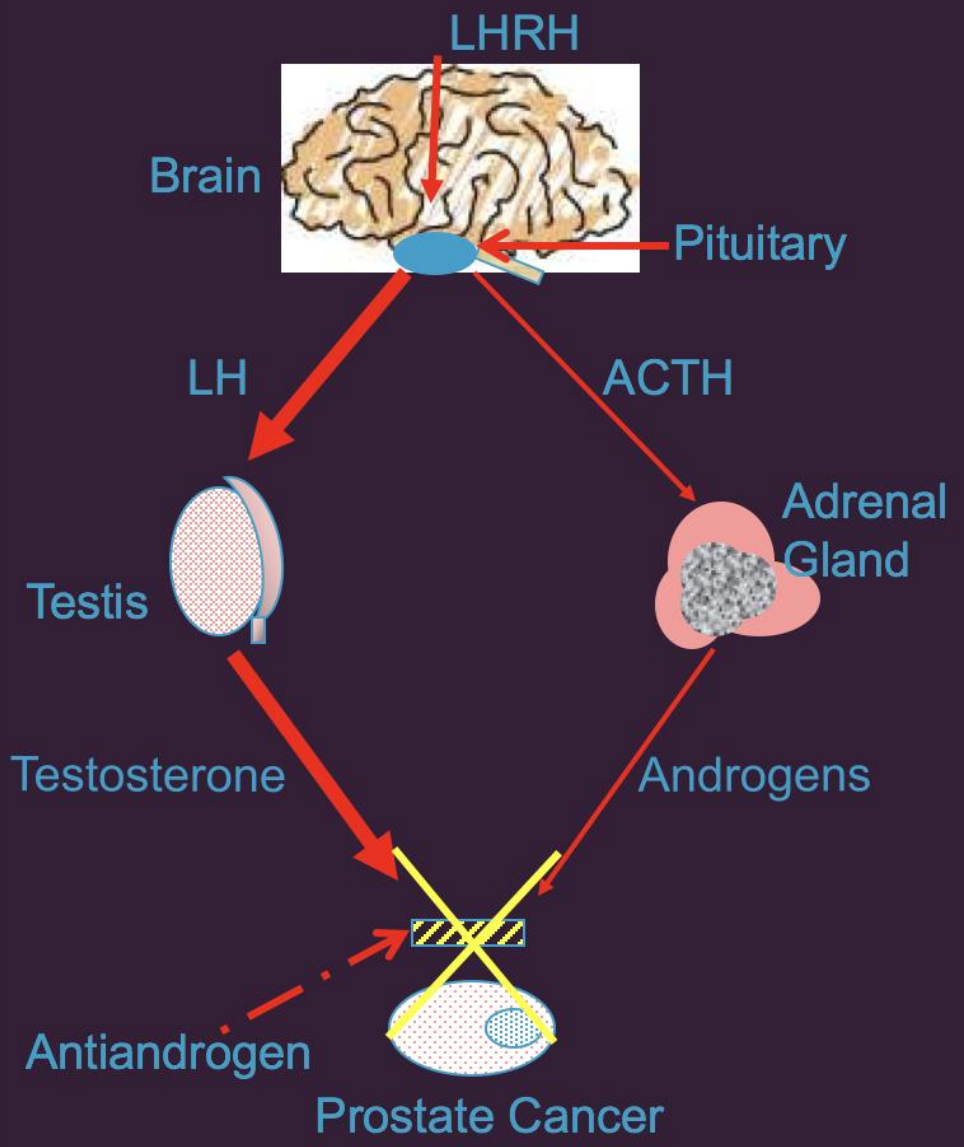
Castrate resistant prostate cancer

- Androgen deprivation therapy (ADT) = initial response rates of 80-90%
- Mean time of 2-3 years, disease progresses despite continuous hormonal manipulation
- ADT is continued indefinitely in these patients in conjunction with secondary therapies

LHRH Analogues



Antiandrogens



Courtesy of Dr A Tree

Antiandrogens

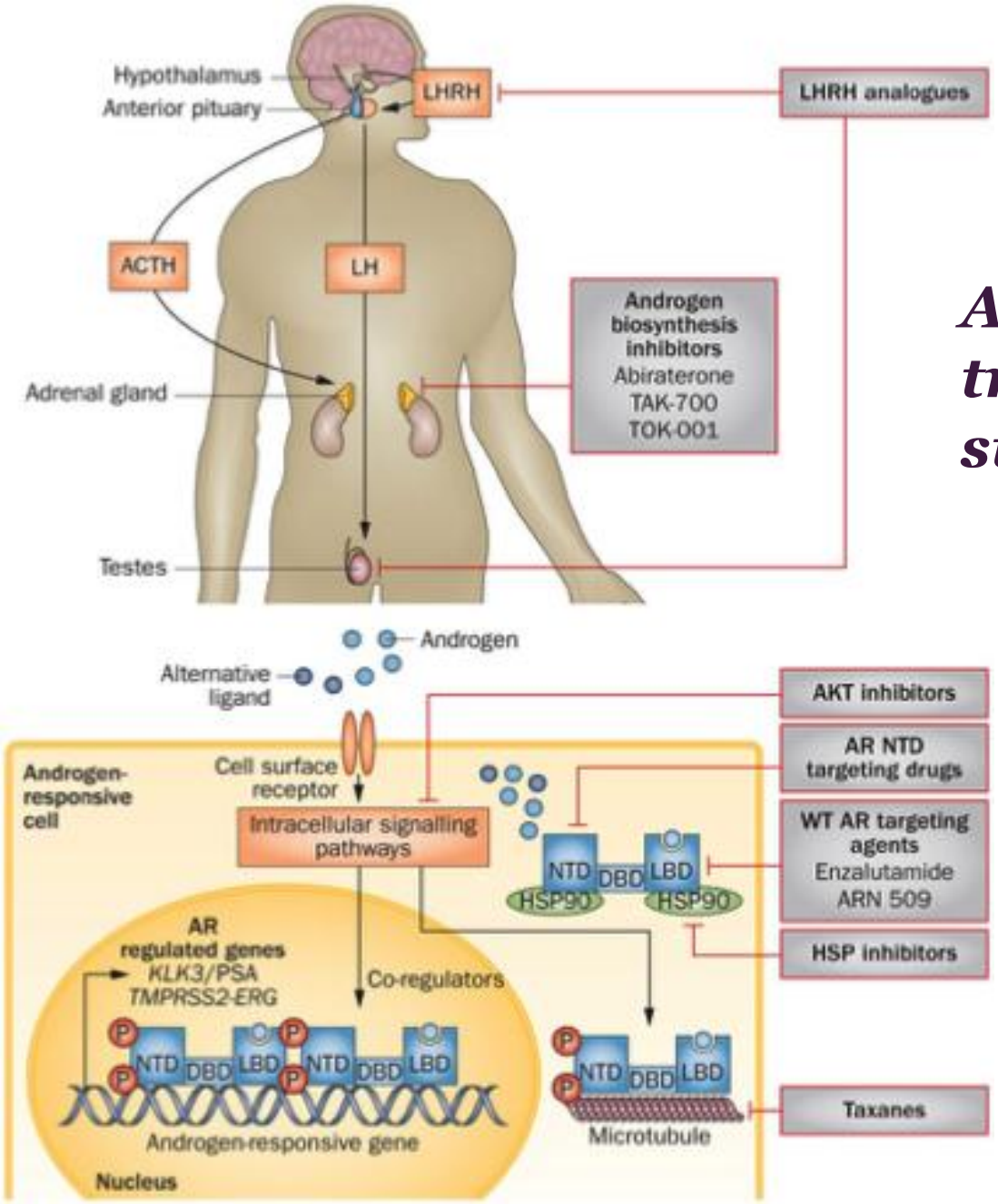
- Bicalutamide – preferred antiandrogen
  - tablet once daily (50mg)
  - less common S/E = LFTs abnormalities, diarrhoea
  - Significantly less active than newer antiandrogens

  - Bicalutamide vs. enzalutamide
    - TERRAIN trial = PFS: 5.8 vs. 15.7 months
    - STRIVE trial = PFS: 5.7 vs. 19.4 months

- Antiandrogen withdrawal
  - may result in clinical or biochemical response (>3-6wks)
  - mechanism unknown

Other hormonal therapies

AR targeting treatment strategies



Wong, Y. N. S. et al. (2014) Evolution of androgen receptor targeted therapy for advanced prostate cancer Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.72

Androgen Receptor targeting drugs

Abiraterone

CRPC

COU-AA-301 (post-docetaxel)
n=1195
COU-AA-302 (post-ADT)
n=1088

Hormone sensitive

STAMPEDE (n=1917)
LATTITUDE (n=1199)

Enzalutamide

CRPC

AFFIRM (post-docetaxel)
n=1199
PREVAIL (post-ADT)
n=1717

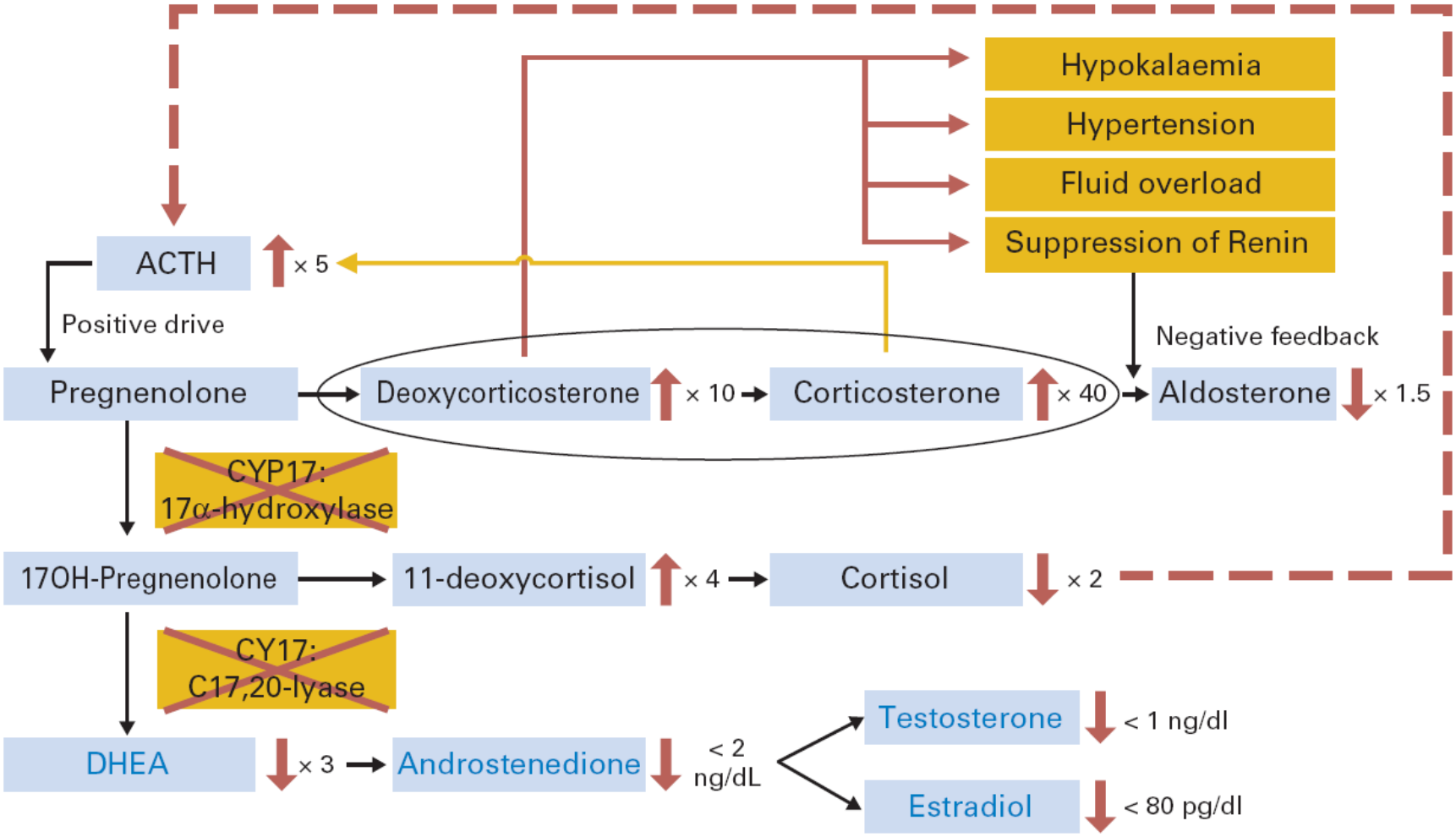
Androgen Receptor targeting drugs

Rationale for development

–Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels

–Androgen deprivation therapies, such as treatment with LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour

Abiraterone: Mechanism of action



Dosing

- The recommended dose is 1,000mg (two 500mg tablets) as a single daily dose that must not be taken with food
- Abiraterone is to be taken with low dose prednisone or prednisolone – the recommended dose is 10 mg daily
- Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated

Method of administration

- Administration with food significantly increases the absorption of abiraterone.
- The tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets.
- The tablets should be swallowed whole with water.
- In the event of a missed daily dose of either abiraterone, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

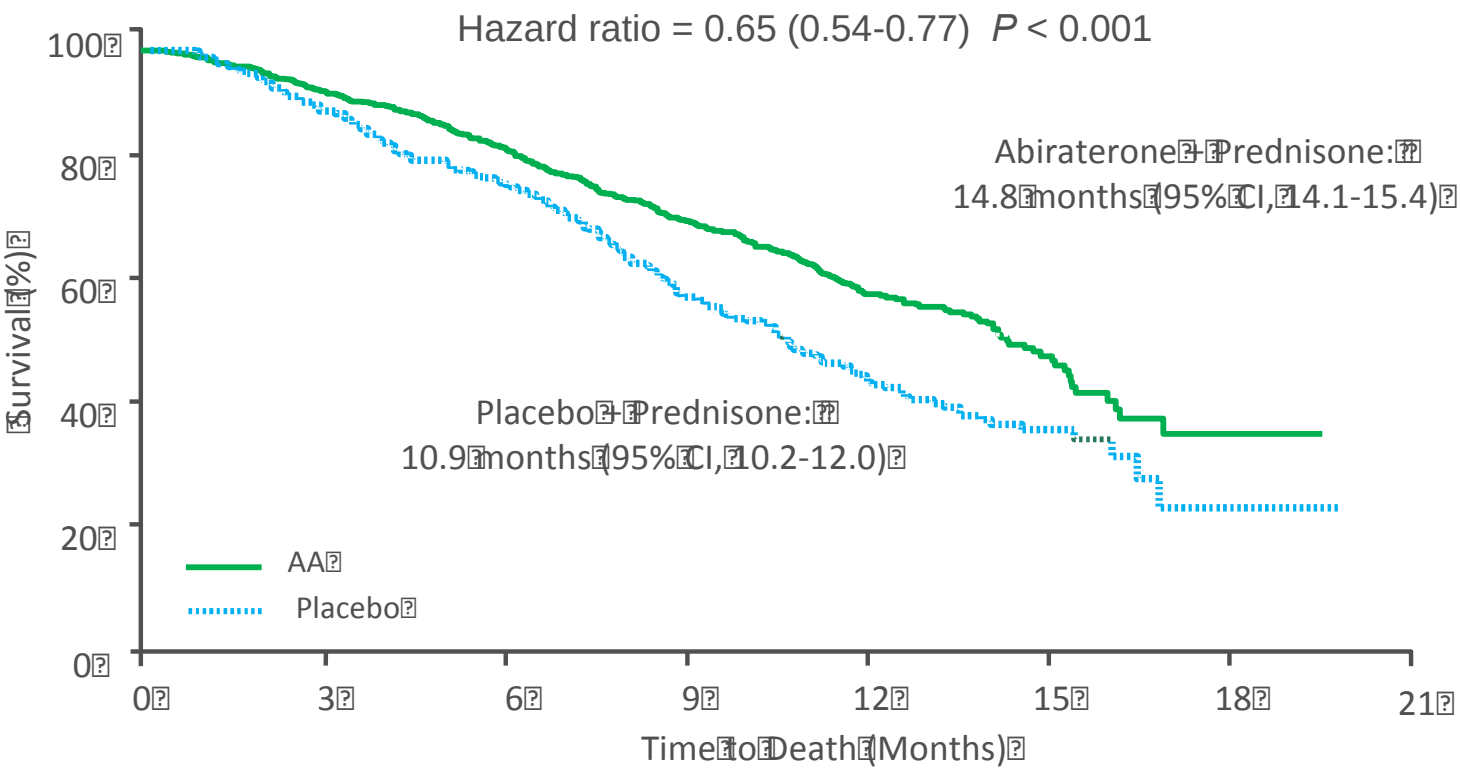
Monitoring

- Liver function tests should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter
- Blood pressure, serum potassium and fluid retention should be monitored monthly
- However, patients with a significant risk for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter
- In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with abiraterone, consider maintaining the patient's potassium level at ≥ 4.0mmol/L
- For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted.

Abiraterone Acetate (AA) trials - CRPC

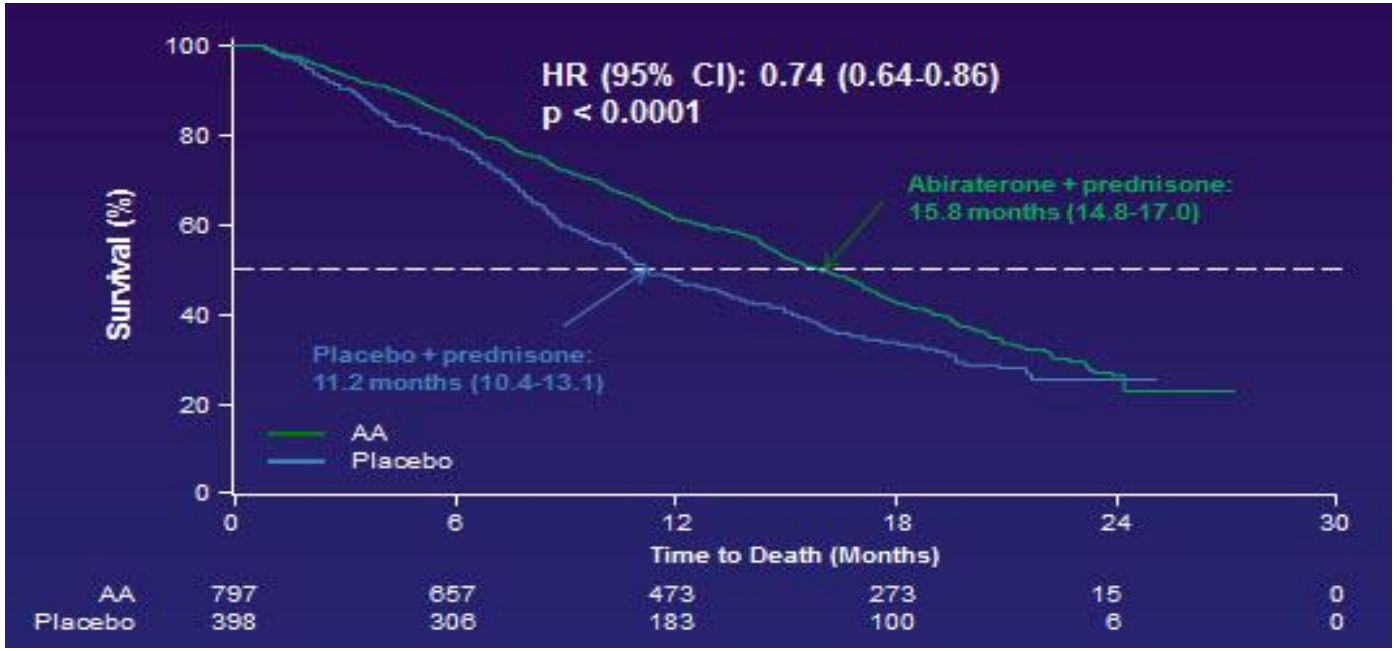
- Efficacy was established in two randomised placebo-controlled multicentre phase 3 clinical studies of patients with mCRPC
- COU-AA-302 = docetaxel naïve patients
- COU-AA-301 = patients who had received prior docetaxel
- Patients were using an LHRH analogue or were previously treated with orchiectomy
- Abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone 5 mg twice daily
- Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily

Overall Survival – Interim Analysis



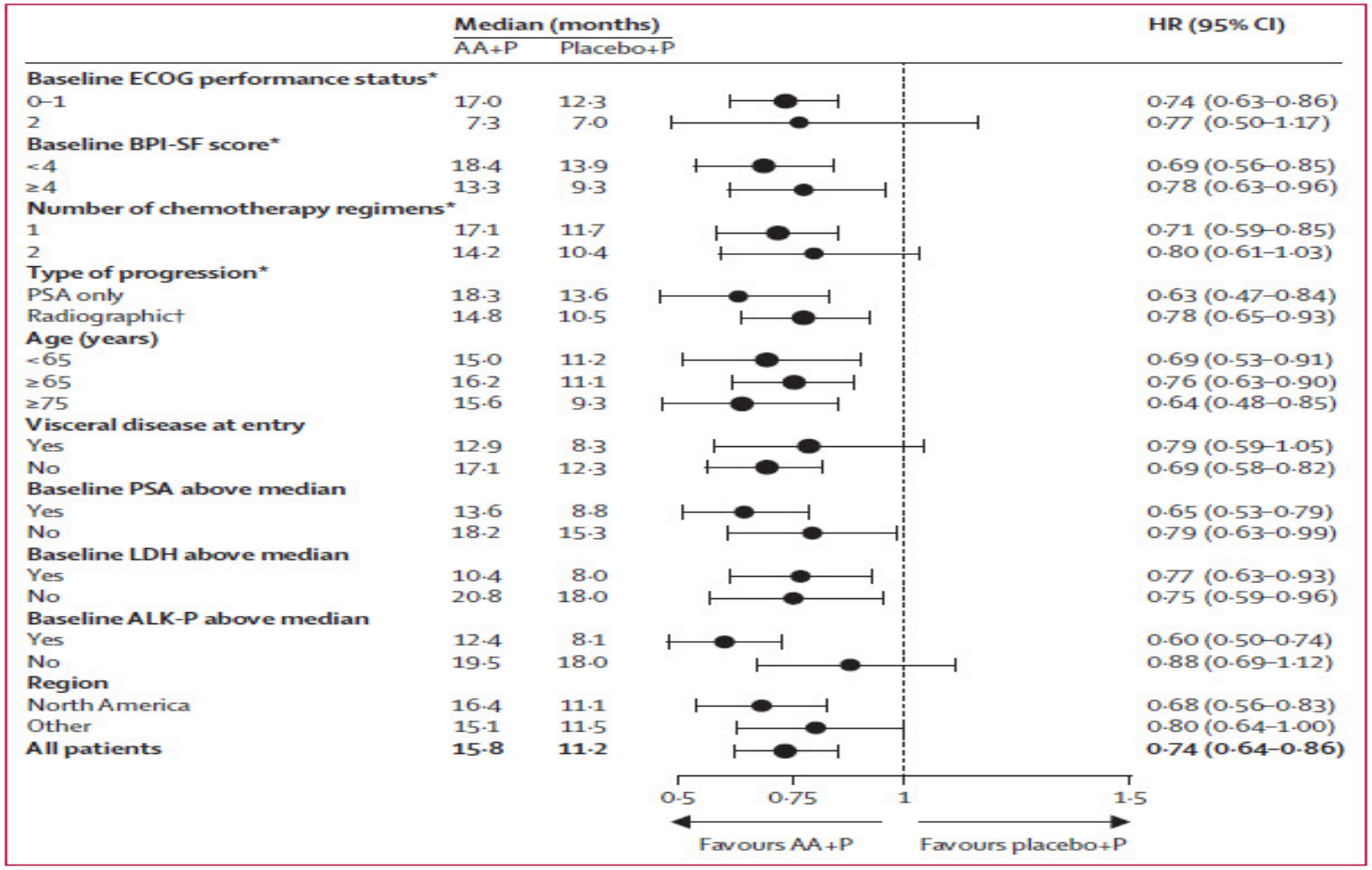
AA	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

Updated Analysis (775 Events): OS benefit of AA Increased From 3.9 to 4.6 Months

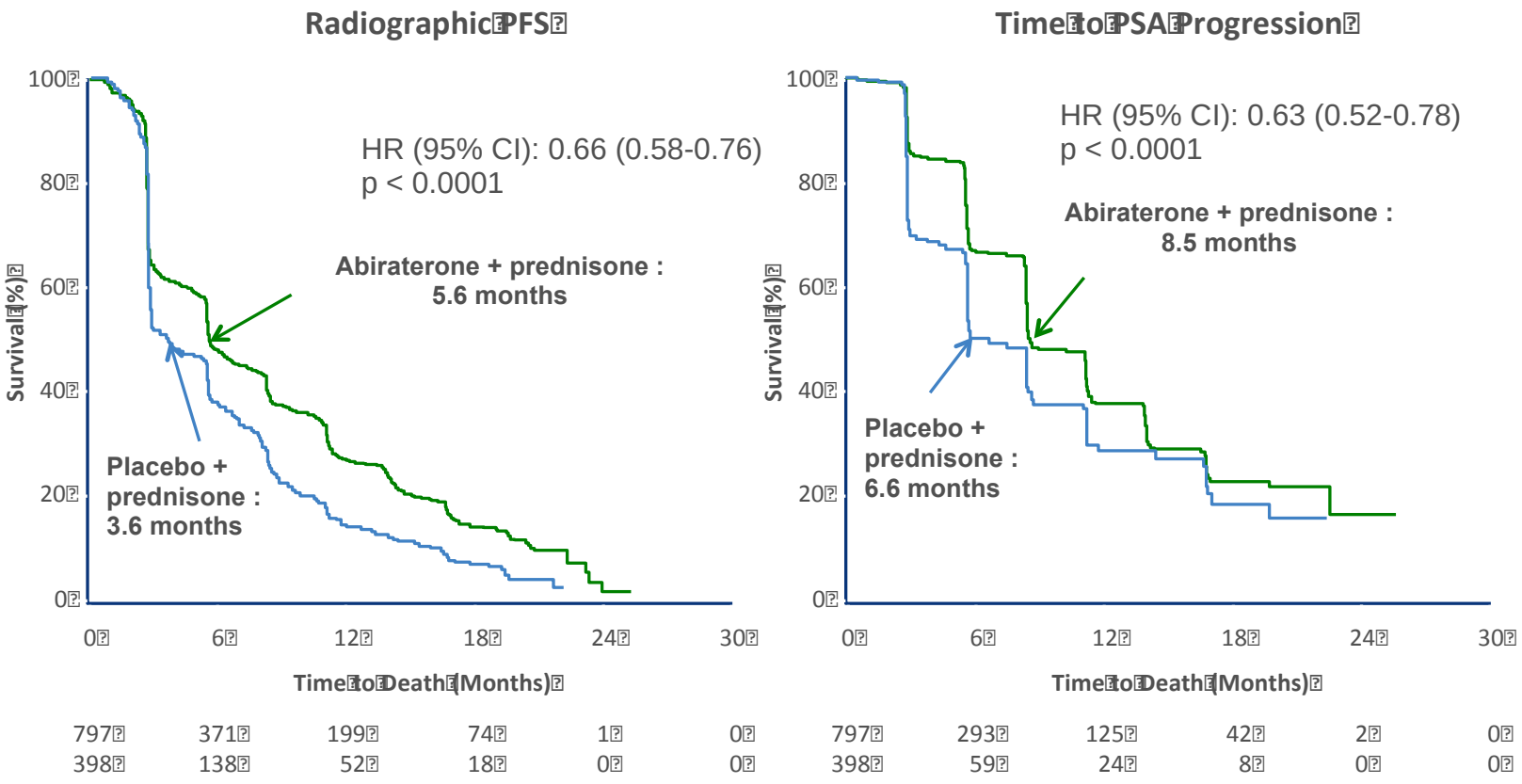


- Median duration of follow-up: 20.2 months
- Median duration of treatment: 8 months with abiraterone + prednisone vs. 4 months with placebo + prednisone

Survival Benefit Observed With AA Is Consistent for Majority of Subgroups



Secondary End Points: rPFS and TTPP significantly improved with AA



Adverse Events of Special Interest

	Abiraterone + Prednisone (n = 791)			Placebo + Prednisone (n = 394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Fluid retention or oedema	33%	2%	<1%	24%	1%	0
Hypokalaemia	18%	4%	<1%	9%	<1%	0
Cardiac disorders*	16%	4%	1%	12%	2%	<1%
Abnormalities in liver function tests	11%	4%	<1%	9%	3%	<1%
Hypertension	11%	1%	0	8%	<1%	0

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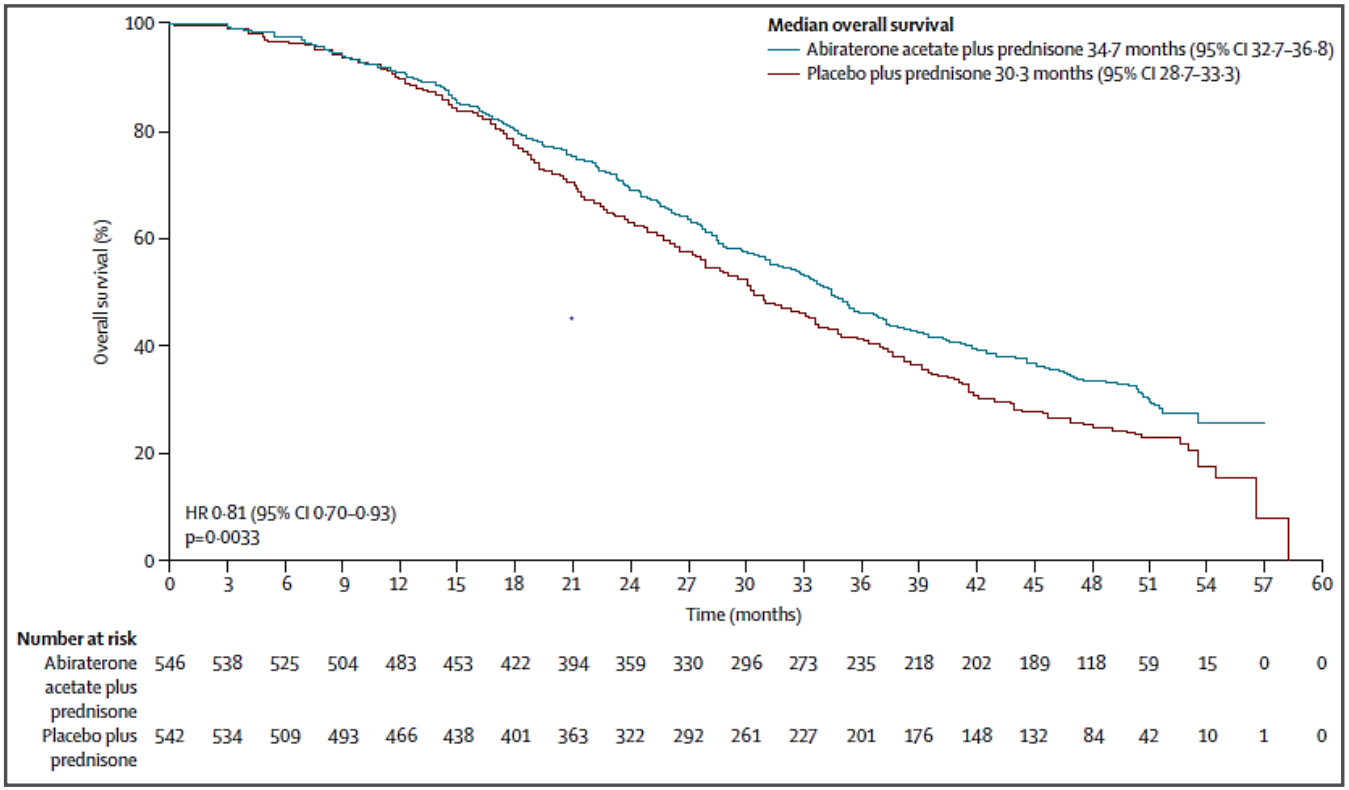
Conclusion: COU-AA-301

- Abiraterone prolongs OS in patients with mCRPC who have progressed after docetaxel chemotherapy
- Abiraterone + prednisone is well tolerated without the toxicity of chemotherapy
  - AEs more common with abiraterone + prednisone:
    - Fluid retention
    - Hypokalaemia
    - LFT abnormalities
    - Hypertension
- Inhibition of persistent androgen synthesis and AR mediated signalling with abiraterone + pred improves survival => a new treatment option for mCRPC

COU-AA-302: Results of the Final Overall Survival Analysis

Consistent Survival Benefit With Abiraterone Over Time



- Median follow-up of 49.2 months
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

Study discontinuation rate due to CA-AEs

- The investigator-reported study discontinuation rate due to CA-AEs was 0.6% (8/1333) for AA + P and 0.3% (3/934) for P alone
- Discontinuations in the AA + P group were attributed to hip fracture (n = 1), spinal fracture (n = 2), spinal compression fracture (n = 1), gastrointestinal hemorrhage (n = 2), melena (n = 1), and adrenal insufficiency (n = 1)
- In the P alone group, skin hemorrhage (n = 1), diabetes mellitus (n = 1), and upper gastrointestinal hemorrhage (n = 1) were cited by the investigator as reasons for discontinuation
- One patient in COU-AA-301 had a CA-AE that resulted in death; sponsor assessment of the cause of death was upper gastrointestinal hemorrhage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Abiraterone

- Post-chemotherapy
  - significantly prolongs survival of men with metastatic castration-resistant prostate cancer who have progressed after docetaxel chemotherapy.

- Pre-chemotherapy
  - significantly prolonged overall survival with a median follow up of more than 4 years compared with prednisolone alone by a margin that was both clinically and statistically significant


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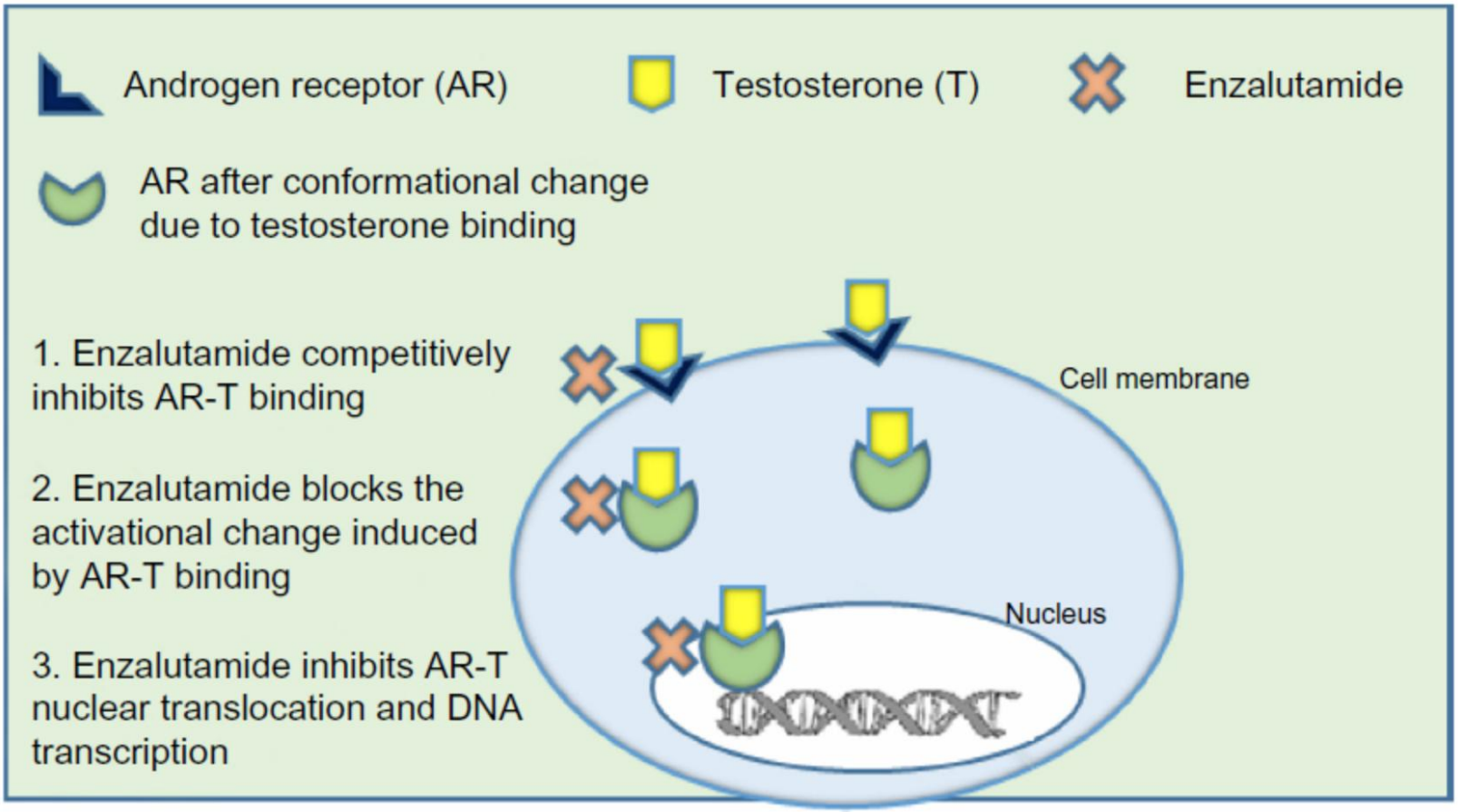
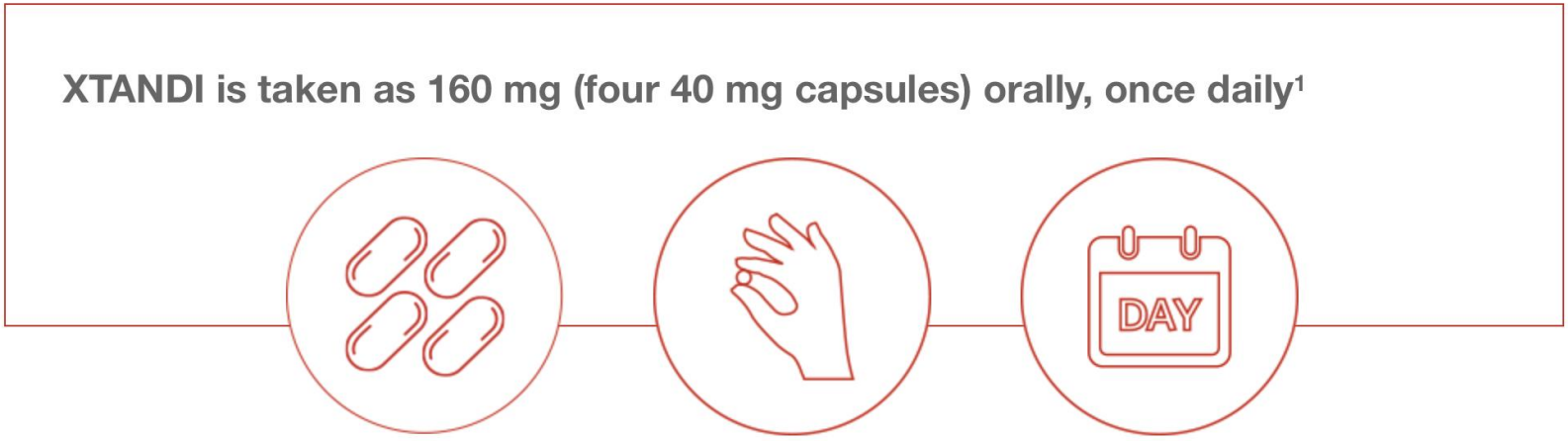
Enzalutamide: mechanism of action



Dosing



Concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If must be co-administered, reduce the Enzalutamide dose to 80mg daily.

Concomitant use of strong CYP3A4 inducers should be avoided if possible. If must be co-administered, increase the Enzalutamide dose to 240mg daily.

Method of administration

- Each capsule should be swallowed whole. Instruct patients not to chew, dissolve, or open the capsules.
- If a dose is missed, inform patients that they should take it as soon as they remember
- If patients forget to take their dose for the whole day, then they should take their normal dose the next day
- Can be taken at any time during the day, but should be taken at the same time each day

Monitoring

- No specific additional monitoring
- EXCEPT need to be aware of potential drug interactions
  - i.e. if co-administered with warfarin (CYP2C9 substrate), need additional INR monitoring
- Seizures

https://www.xtandihcp.com/dosing-administration

AFFIRM study: post chemotherapy

OS

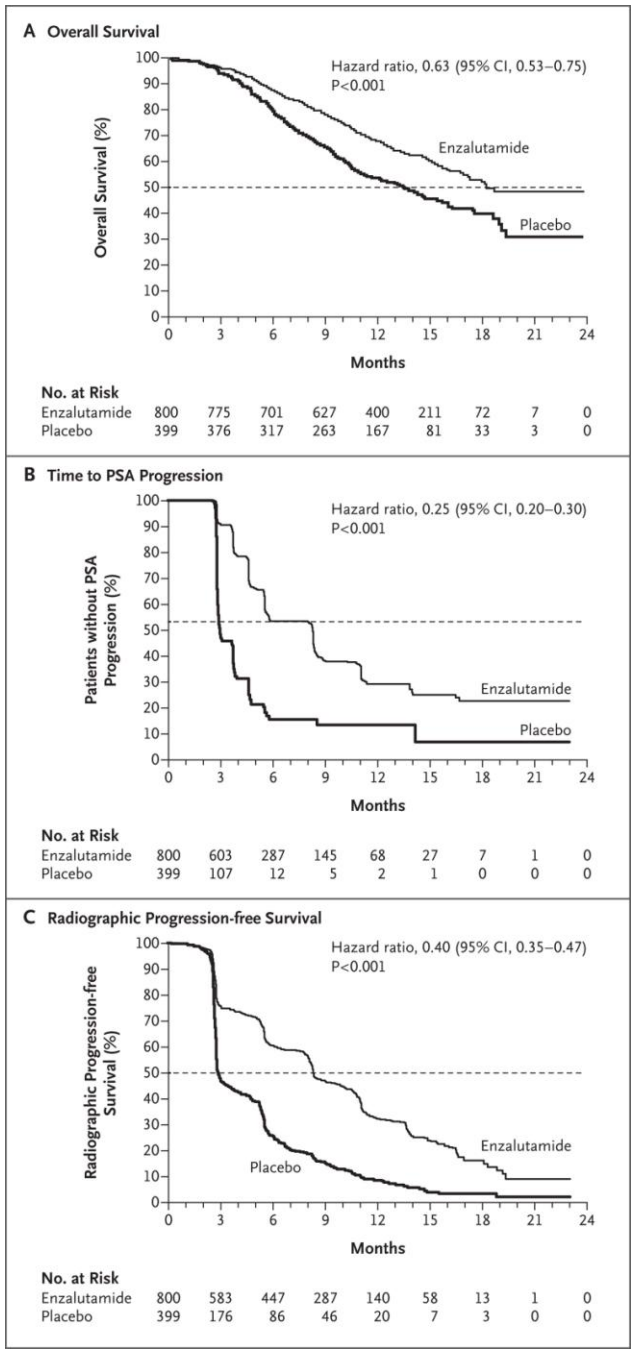
18.4 months vs. 13.6 months

Time to PSA progression

8.3 months vs. 3 months

Radiological PFS

8.3 months vs. 2.9 months



Scher HI et al. N Engl J Med 2012;367:1187-1197

Secondary End Points Related to Response and disease progression

Table 2. Secondary End Points Related to Response and Disease Progression.*

End Point	Enzalutamide (N=800)	Placebo (N=399)	Hazard Ratio (95% CI)	P Value
Confirmed PSA decline†				
Patients with ≥1 postbaseline PSA assessment — no. (%)	731 (91)	330 (83)		
PSA response — no./total no. (%)				
Decline ≥50% from baseline	395/731 (54)	5/330 (2)		<0.001
Decline ≥90% from baseline	181/731 (25)	3/330 (1)		<0.001
Soft-tissue objective response				
Patients with measurable disease — no. (%)	446 (56)	208 (52)		
Complete or partial objective response — no./total no. (%)	129/446 (29)	8/208 (4)		<0.001
FACT-P quality-of-life response†				
Patients with ≥1 postbaseline assessment — no. (%)	651 (81)	257 (64)		
Quality-of-life response — no./total no. (%)‡	281/651 (43)	47/257 (18)		<0.001
Progression indicators				
Time to PSA progression — mo			0.25 (0.20–0.30)	<0.001
Median	8.3	3.0		
95% CI	5.8–8.3	2.9–3.7		
Radiographic progression-free survival — mo			0.40 (0.35–0.47)	<0.001
Median	8.3	2.9		
95% CI	8.2–9.4	2.8–3.4		
Time to first skeletal-related event — mo			0.69 (0.57–0.84)	<0.001
Median	16.7	13.3		
95% CI	14.6–19.1	9.9–NYR		

* For a complete definition of end points, see Table 1S in the Supplementary Appendix. FACT-P denotes Functional Assessment of Cancer Therapy–Prostate, NYR not yet reached, and PSA prostate-specific antigen.
† Only patients with both baseline and postbaseline assessments are included.
‡ The quality-of-life response was defined as a 10-point improvement in the global score on the FACT-P questionnaire, as compared with baseline, on two consecutive measurements obtained at least 3 weeks apart.

Scher HI et al. N Engl J Med 2012;367:1187-1197

Adverse events, according to Grade

Table 3. Adverse Events, According to Grade.

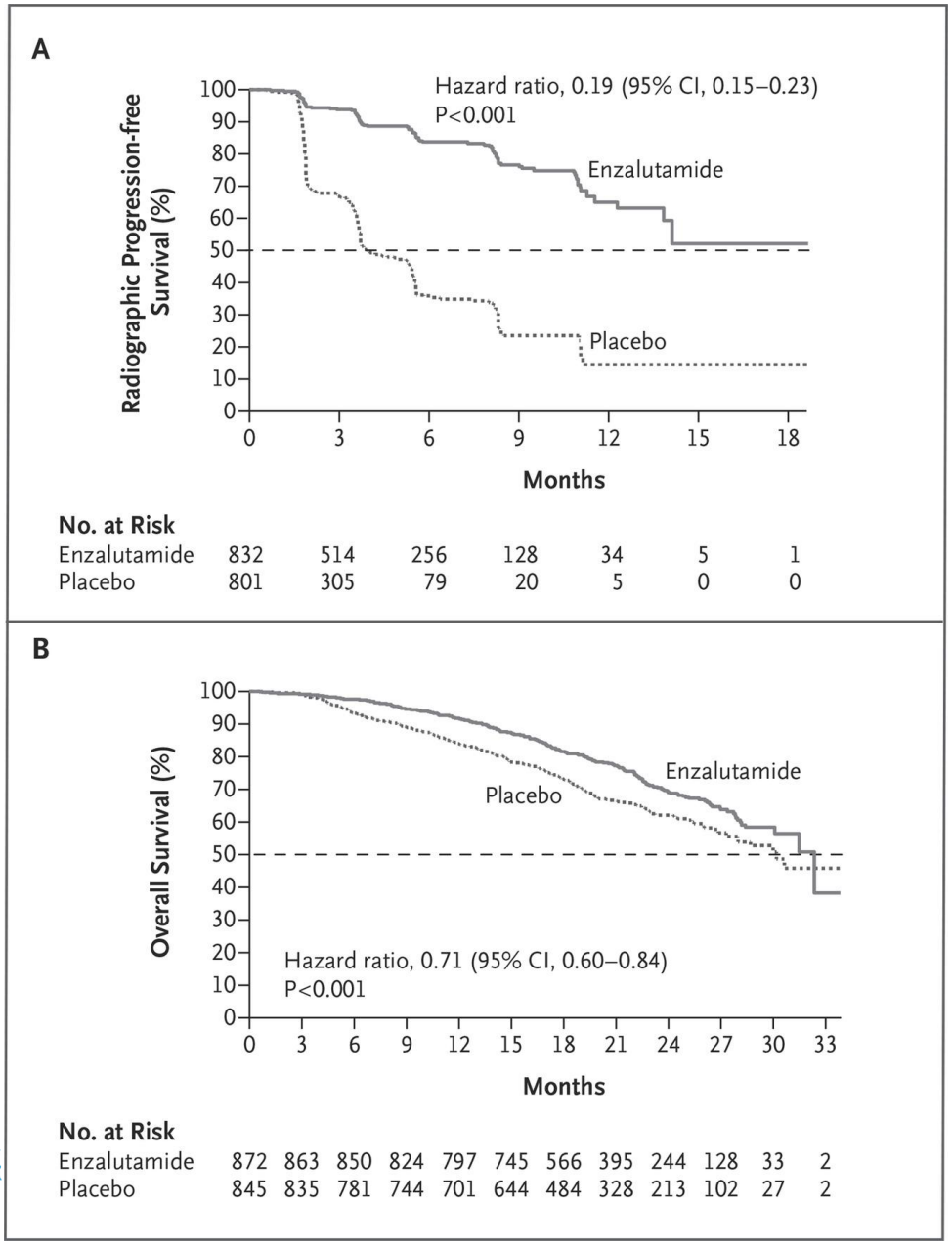
Adverse Event	Enzalutamide (N=800)		Placebo (N=399)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
≥1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
Any serious adverse event	268 (34)	227 (28)	154 (39)	134 (34)
Discontinuation owing to adverse event	61 (8)	37 (5)	39 (10)	28 (7)
Adverse event leading to death	23 (3)	23 (3)	14 (4)	14 (4)
Frequent adverse events more common with enzalutamide*				
Fatigue	269 (34)	50 (6)	116 (29)	29 (7)
Diarrhea	171 (21)	9 (1)	70 (18)	1 (<1)
Hot flash	162 (20)	0	41 (10)	0
Musculoskeletal pain	109 (14)	8 (1)	40 (10)	1 (<1)
Headache	93 (12)	6 (<1)	22 (6)	0
Clinically significant adverse events				
Cardiac disorder				
Any	49 (6)	7 (1)	30 (8)	8 (2)
Myocardial infarction	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Abnormality on liver-function testing†	8 (1)	3 (<1)	6 (2)	3 (<1)
Seizure	5 (<1)	5 (<1)	0	0

* Included in this category are adverse events that occurred in more than 10% of patients in the enzalutamide group and that occurred in the enzalutamide group at a rate that was at least 2 percentage points higher than that in the placebo group.

† Abnormalities on liver-function testing included hyperbilirubinemia and increased levels of aspartate aminotransferase or alanine aminotransferase.

Scher HI et al. N Engl J Med 2012;367:1187-1197

PREVAIL study: pre chemotherapy



Radiological PFS @ 12 months:
65% ENZ pts vs. 14% Placebo

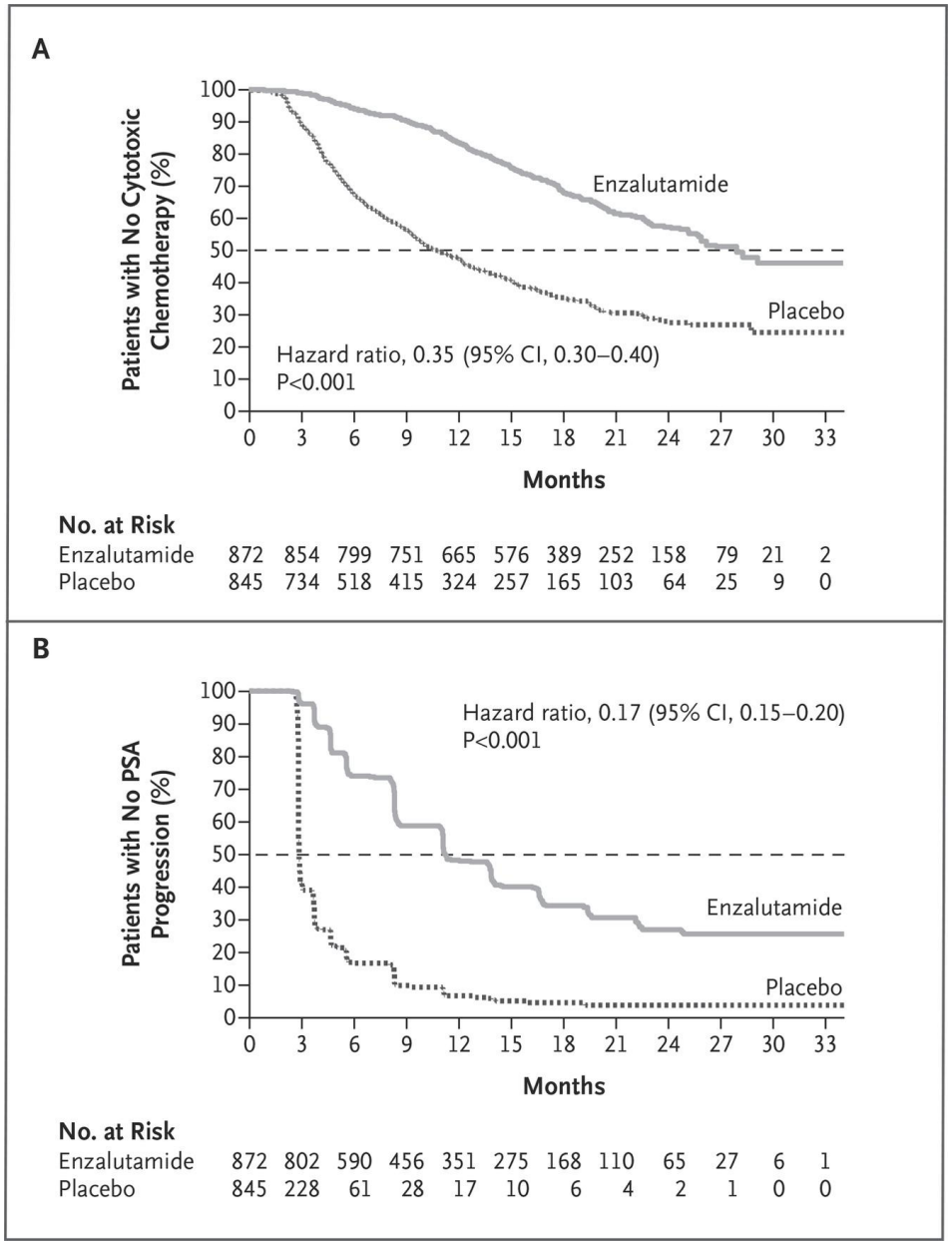
Overall survival:
72% ENZ pts vs. 63% Placebo alive at data-cut off date

Beer TM et al. N Engl J Med 2014;371:424-433

Time to chemo and increased PSA

Time to chemo:
28 months ENZ vs.
10.8 months Placebo

TTPP:
11.2 months ENZ vs.
2.8 months Placebo



Beer TM et al. N Engl J Med 2014;371:424-433

Secondary and exploratory endpoints

Table 1. Secondary and Prespecified Exploratory End Points.*

End Point	Enzalutamide (N=872)	Placebo (N=845)	Hazard Ratio (95% CI)	P Value
Median time until initiation of cytotoxic chemotherapy — mo	28.0	10.8	0.35 (0.30–0.40)	<0.001
Median time until decline in the FACT-P global score — mo†‡	11.3	5.6	0.63 (0.54–0.72)	<0.001
Median time until first skeletal-related event — mo§	31.1	31.3	0.72 (0.61–0.84)	<0.001
Median time until PSA progression — mo¶	11.2	2.8	0.17 (0.15–0.20)	<0.001
Confirmed change in PSA‖				
Patients with ≥1 post-baseline PSA assessment — no. (%)	854 (98)	777 (92)		
PSA decline of ≥50% from baseline — no./total no. (%)	666/854 (78)	27/777 (3)		<0.001
PSA decline of ≥90% from baseline — no./total no. (%)†	400/854 (47)	9/777 (1)		<0.001
Patients with measurable soft-tissue disease — no. (%)**	396 (45)	381 (45)		
Objective response	233 (59)	19 (5)		<0.001
Complete response	78 (20)	4 (1)		
Partial response	155 (39)	15 (4)		

* A complete definition of study end points is provided in Table S1 in the Supplementary Appendix. CI denotes confidence interval, and PSA prostate-specific antigen.
† This category was a prespecified exploratory end point.
‡ A decline on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) scale was defined as decrease of 10 points or more on the global score, which ranges from 0 to 156, with higher scores indicating a better quality of life.
§ The hazard ratio is a more accurate measure of treatment effect than are estimates of the median time until the event for late-occurring events in this study.
¶ PSA progression was based on criteria of the Prostate Cancer Clinical Trials Working Group 2.
‖ Only patients with baseline and post-baseline assessments are included.
** Only patients with measurable soft-tissue disease at baseline, as assessed on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1, are included.

Beer TM et al. N Engl J Med 2014;371:424-433

Most common adverse events & events of special interest

Table 3. Most Common Adverse Events and Events of Special Interest.

Adverse Events	Enzalutamide (N=871)		Placebo (N=844)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Most common adverse events*				
Fatigue	310 (36)	16 (2)	218 (26)	16 (2)
Back pain	235 (27)	22 (3)	187 (22)	25 (3)
Constipation	193 (22)	4 (<1)	145 (17)	3 (<1)
Arthralgia	177 (20)	12 (1)	135 (16)	9 (1)
Decreased appetite	158 (18)	2 (<1)	136 (16)	6 (1)
Hot flush	157 (18)	1 (<1)	65 (8)	0
Diarrhea	142 (16)	2 (<1)	119 (14)	3 (<1)
Hypertension	117 (13)	59 (7)	35 (4)	19 (2)
Asthenia	113 (13)	11 (1)	67 (8)	8 (1)
Fall	101 (12)	12 (1)	45 (5)	6 (1)
Weight loss	100 (11)	5 (1)	71 (8)	2 (<1)
Edema peripheral	92 (11)	2 (<1)	69 (8)	3 (<1)
Headache	91 (10)	2 (<1)	59 (7)	3 (<1)
Specific adverse events				
Any cardiac adverse event	88 (10)	24 (3)	66 (8)	18 (2)
Atrial fibrillation	16 (2)	3 (<1)	12 (1)	5 (1)
Acute coronary syndromes	7 (1)	7 (1)	4 (<1)	2 (<1)
Acute renal failure	32 (4)	12 (1)	38 (5)	12 (1)
Ischemic or hemorrhagic cerebrovascular event	12 (1)	6 (1)	9 (1)	3 (<1)
Elevation in alanine aminotransferase level	8 (1)	2 (<1)	5 (1)	1 (<1)
Seizure	1 (<1)†	1 (<1)†	1 (<1)	0

* Included in this category are adverse events that were reported in at least 10% of patients in the enzalutamide group at a rate that was at least 2 percentage points higher than that in the placebo group.
† This seizure occurred after the data-cutoff date.

Beer TM et al. N Engl J Med 2014;371:424-433

Enzalutamide

- Post-chemotherapy
  - significantly prolonged the survival of men with metastatic castration-resistant prostate cancer after chemotherapy.

- Pre-chemotherapy
  - significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer

Rationale for abiraterone in hormone sensitive prostate cancer

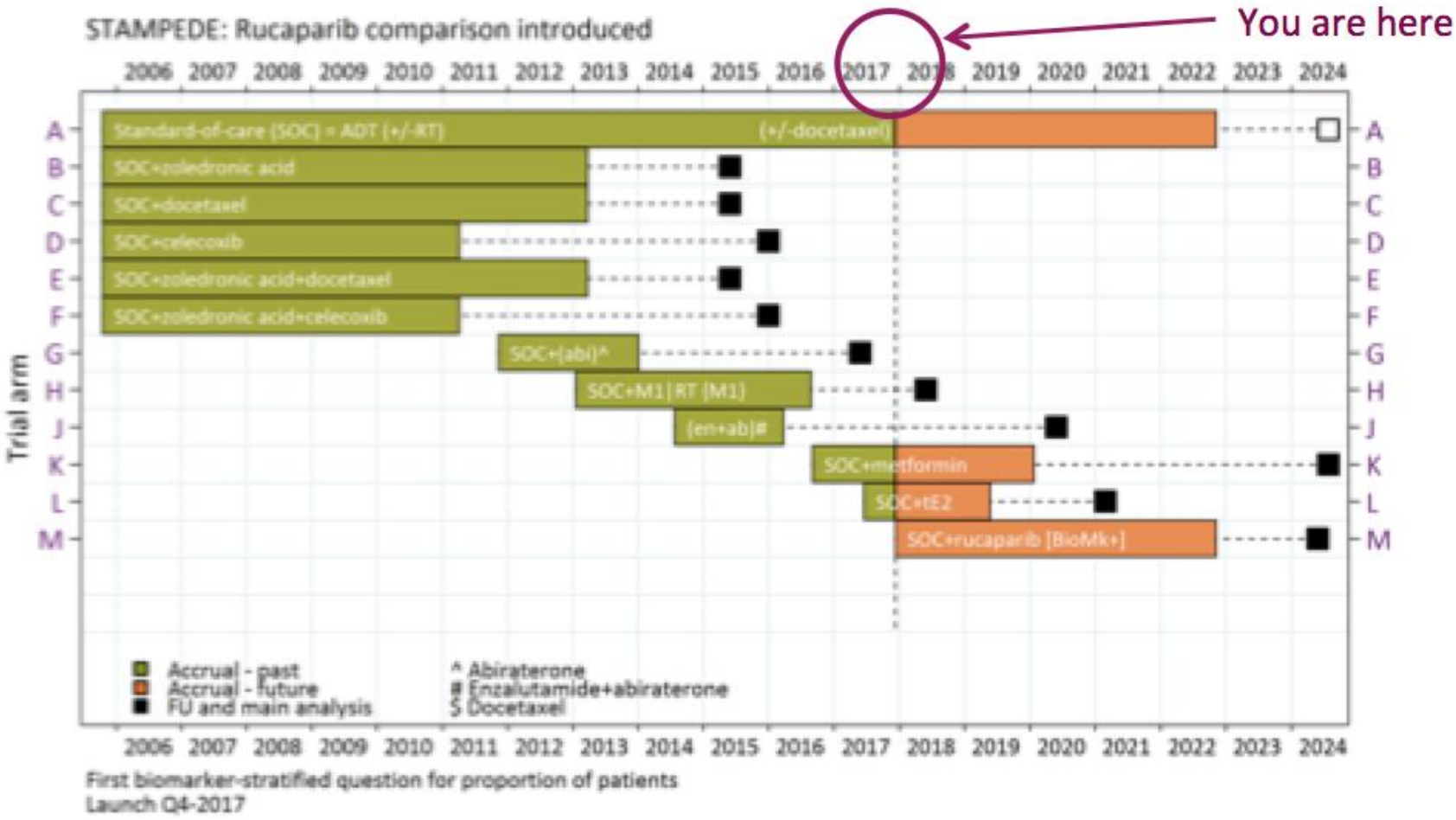
- Mechanisms of resistance to ADT may develop early[1-3]
- ADT alone does not inhibit androgen synthesis by:
  - adrenal
  - prostatic cancer cells
- AA + P:
  - improves OS in mCRPC[4,5]
  - reduces tumor burden in high-risk, localized PC[6,7]

- These data suggest a potential role for inhibiting extragonadal androgen biosynthesis ***prior to the emergence of castration resistance***

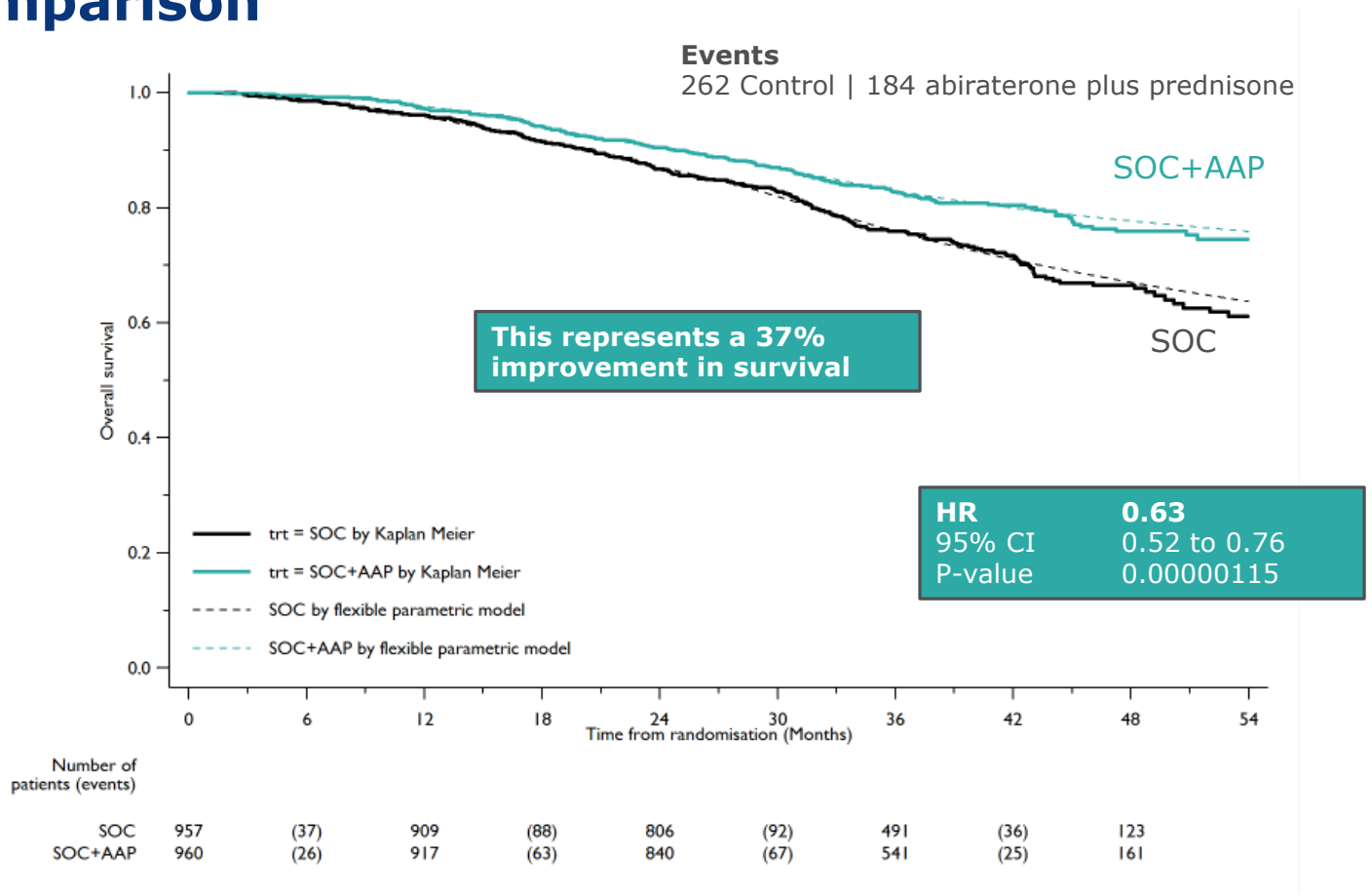
1. Gravis G, et al. Eur Urol. 2016:70:256-262. 2. Sweeney C, et al. N Engl J Med. 2015;373:737-746. 3. James N, et al. Lancet. 2016;387:1163-1177. 4. de Bono JS, et al. N Engl J Med. 2011;364:1995-2005. 5. Ryan CJ, et al. Lancet Oncol. 2015;16:152-160. 6. Taplin ME, et al. J Clin Oncol. 2014;32:3705-3715. 7. Efstathiou E, et al. J Clin Oncol. 2015;33(suppl):15s. Abstract 5061.

STAMPEDE trial

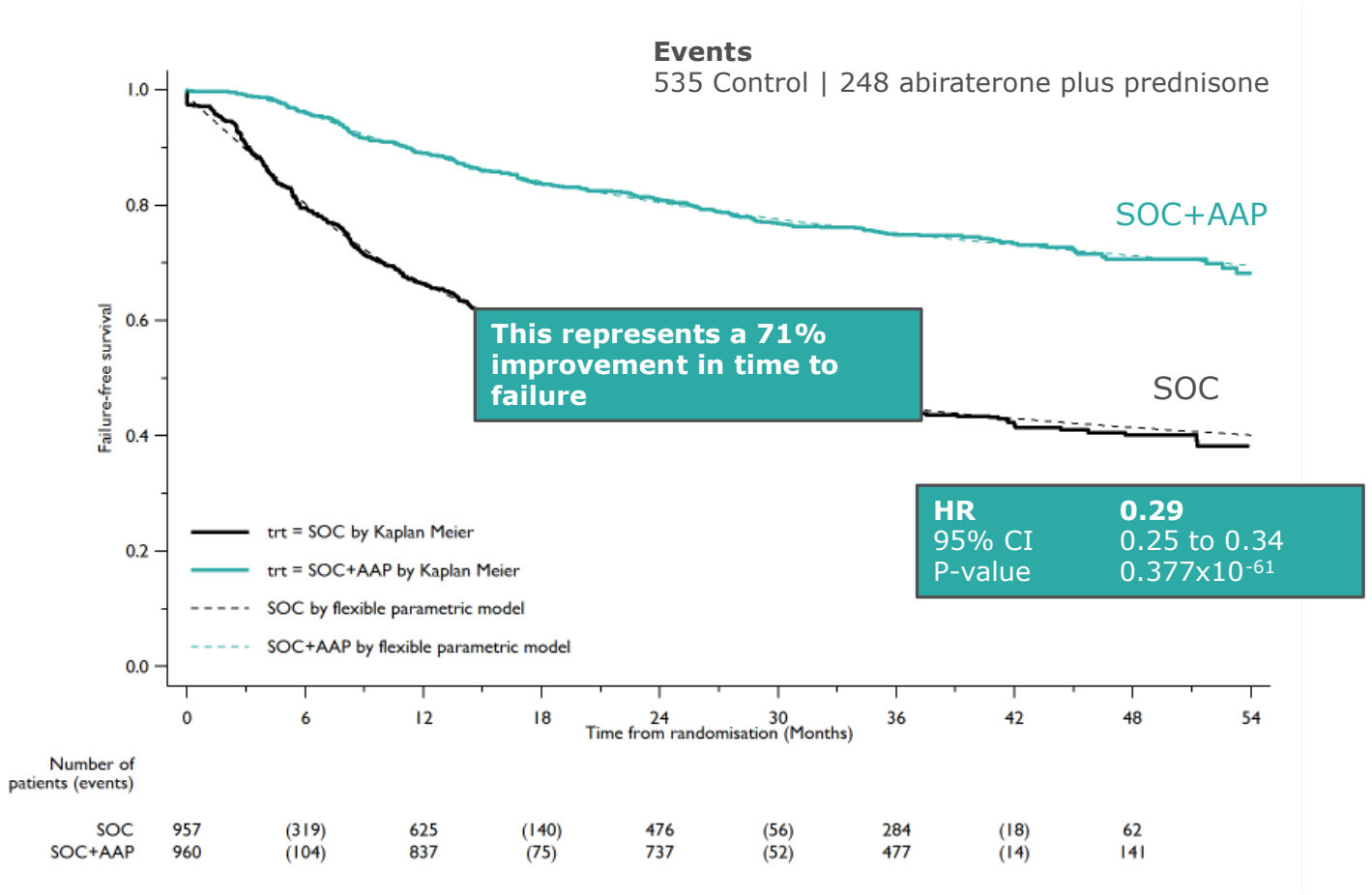
Inclusion criteria



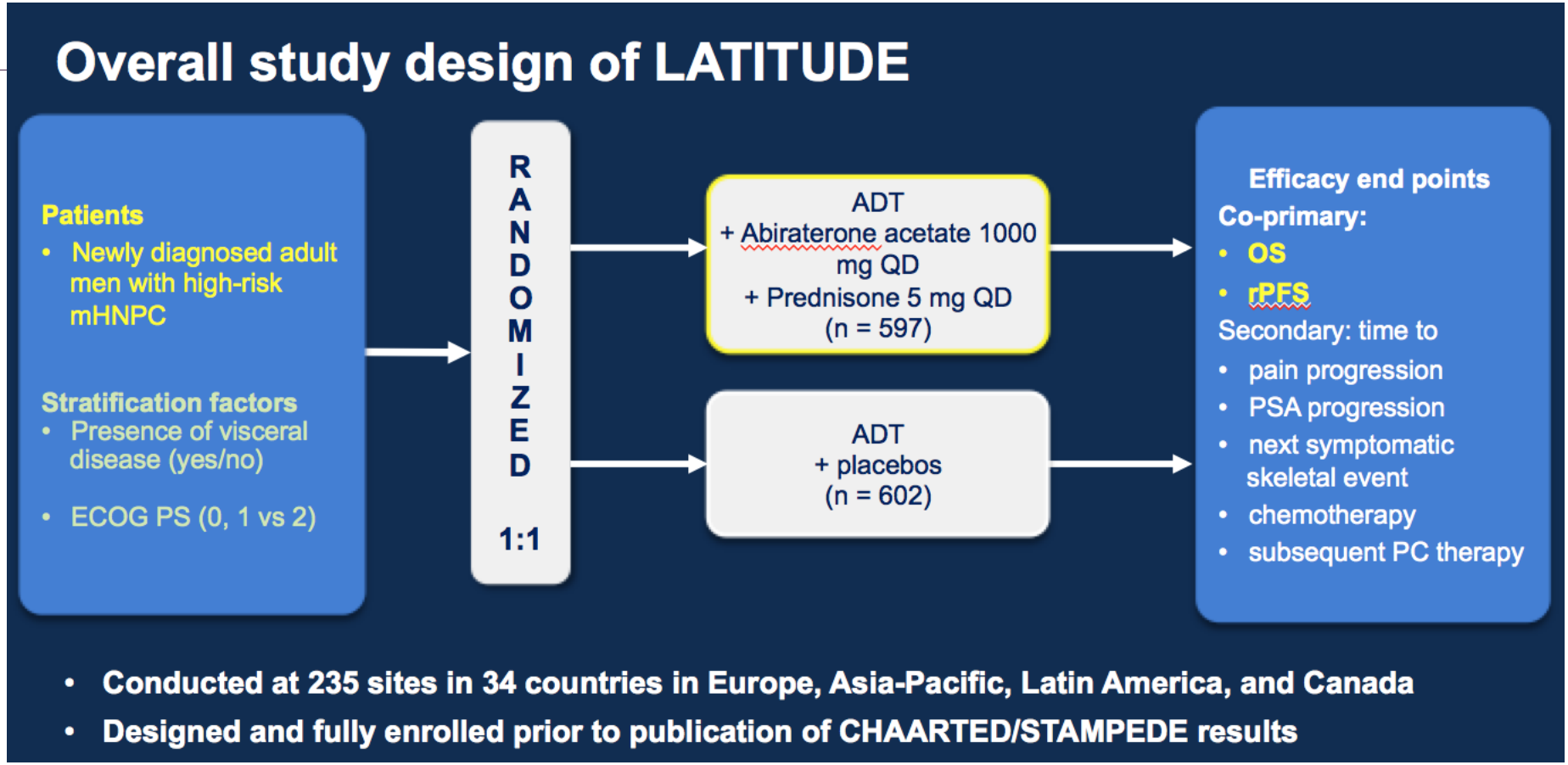
OS – STAMPEDE "abiraterone plus prednisone comparison"



FFS – STAMPEDE "AA comparison"

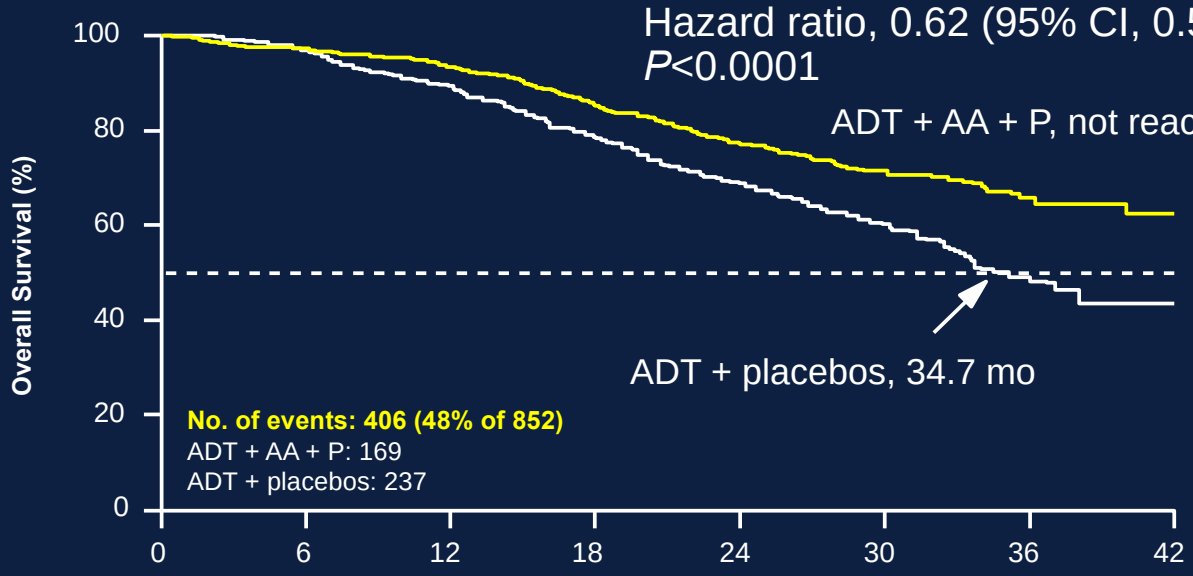


LATITUDE trial



High risk = at least 2 of 3 below criteria
Gleason score ≥8
Presence of >3 lesions on bone scan
Presence of measurable visceral lesion

Statistically significant 38% risk reduction of death

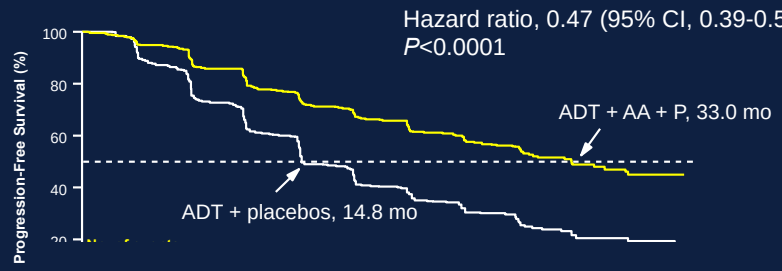


OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

Median follow-up: 30.4 months

Statistically significant 53% risk reduction of radiographic progression or death



Statistically significant improvement in all secondary end points

Secondary End Points	ADT + AA + P (n = 597) Median (months)	ADT + placebos (n = 602) Median (months)	HR (95% CI)	*P* Value
Time to PSA progression	33.2	7.4	0.30 (0.26-0.35)	<0.0001
Time to pain progression	NR	16.6	0.70 (0.58-0.83)	<0.0001
Time to next symptomatic skeletal event	NR	NR	0.70 (0.54-0.92)	0.0086
Time to chemotherapy	NR	38.9	0.44 (0.35-0.56)	<0.0001
Time to subsequent prostate cancer therapy	NR	21.6	0.42 (0.35-0.50)	<0.0001

NR = not reached.

Enzalutamide in hormone sensitive prostate cancer

- No randomised mature data
- Trials recruiting
  - ENZARAD study
    - Randomised phase III of enzalutamide with ADT with RT for high risk, localised prostate cancer
- STAMPEDE trial – Arm J
  - Abiraterone and enzalutamide
  - Survival data expected 2019

Androgen Receptor targeting drugs = improved overall survival

Abiraterone

CRPC

COU-AA-301 (post-docetaxel)

15.8 months vs. 11.2 months

COU-AA-302 (post-ADT)

34.7 months vs. 30.3 months

Hormone sensitive

STAMPEDE –

3 year survival: 83% vs. 76%

LATITUDE –

OS significantly increased:

NR vs. 34.7 months

Enzalutamide

CRPC

AFFIRM (post-docetaxel)

18.4 months vs. 13.6 months

PREVAIL (post-ADT)

32.4 months vs. 30.2 months

Abiraterone versus Enzalutamide

- Toxicity profile & Patient specific factors

- AQUARIUS study:

Prospective, observational, multi centre phase 4 study assessing PROs in metastatic CRPC patients treated with Abi or Enz

- 3 month F/U data (n= 105)= favourable outcomes for perceived cognitive impairments, cognitive functioning, fatigue for Abi vs. Enz

- Canadian group:

Randomised phase II = n:202

- Median FACT-P QIL score was stat significantly higher at 12 and 24 weeks in Abi arm
- Higher proportion of patients had moderate or worse depression score at 12 and 24 weeks
- Decline in cognition in Enzalutamide arm (p=0.06)

As per circulation list

NHS England

Specialised Commissioning
NHS England
Skipton House, 5th Floor
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13 October 2017

Dear Colleague

Abiraterone for hormone-sensitive metastatic prostate cancer

I am writing to advise you regarding NHS England's position on the use of abiraterone for hormone-sensitive metastatic prostate cancer following the recent publication of the results of two large trials.

Using conservative assumptions of an eligible population of 7000 patients and a treatment duration of 3 years, the drug budget impact at full year effect is estimated to be at £745m at list price (inc VAT)

NICE: appraisal beginning mid Nov 2017, final guidance expected to publish in Sept 2018
Not know whether the use of abiraterone in this indication is a cost effective use of NHS resources of not

NHS England will not commission the use of abiraterone in hormone-sensitive prostate cancer – will be reviewed after NICE assessment

Conclusions

Overall survival benefit in CRPC patients with abiraterone and enzalutamide seen (pre and post chemotherapy)

HOWEVER

No RCT comparing abiraterone and enzalutamide

Optimal sequencing within available treatment options uncertain

Abiraterone – shown to have a survival benefit in hormone sensitive high-risk prostate cancer patients

HOWEVER

Not NICE approved

Docetaxel chemotherapy shown similar benefit

The ROYAL MARSDEN
NHS Foundation Trust

Thank you

Any questions?

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NHS