Advanced Prostate Cancer

Professor Heather Payne
Consultant Clinical Oncologist, UCLH

Historical Treatment for Advanced Prostate Cancer

- 1st Line –LHRH agonist or orchidectomy
- 2nd Line – addition and withdrawal of antiandrogen/switch of antiandrogen
- 3rd Line stilboestrol/steroids/chemotherapy (mitoxantrone)
- AIM OF THERAPY – symptom control only

Symptoms and Treatment of HRPC have a Profound Effect on Quality of Life (QoL)

- Hormone refractory prostate cancer (HRPC) ?CRPC is associated with significant symptoms from treatment and the disease itself
  - HRPC: fatigue, anorexia, lymphoedema, urinary obstruction, haematuria, incontinence, rectal obstruction
  - Androgen deprivation therapy (ADT): hot flushes, loss of sexual desire, erectile dysfunction, osteoporosis, anaemia, fatigue, metabolic changes
  - Skeletal metastases (common in this patient group): pain, pathological fractures, spinal cord compression, anaemia, thrombocytopenia

- This burden is thought to profoundly affect patient QoL

- With patients diagnosed at increasingly younger ages, maintenance of QoL is paramount

The Last Decade has Changed our Management of HRPC

- …for the better!
- …we have even changed the name!

New Hormone Agents and the Concept of Castration-Resistant Prostate Cancer

- Advancing prostate cancer is not uniformly refractory to further hormonal manipulation and androgens and disease progression are frequently dependent on and androgen synthesis and androgen receptor interactions.

- Castration-resistant prostate cancer, which is still hormone sensitive, has been clearly characterised, with new drugs such as abiraterone acetate and enzalutamide

What are the Therapy Options for Metastatic CRPC?

- Docetaxel
- Abiraterone Acetate
- Enzalutamide
- Steroids
- Cabazitaxel
- (Oestrogens)
- Radium 223

- FUTURE – First line therapy
-
- FUTURE – Drugs in late stage clinical trials

TAX327 Study Design

Stratification:

Pain level
PPI ≥ 2 or AS ≥ 10
vs.
PPI < 2 or AS < 10

KPS
≤70 vs. ≥ 80

RANDOMIZE

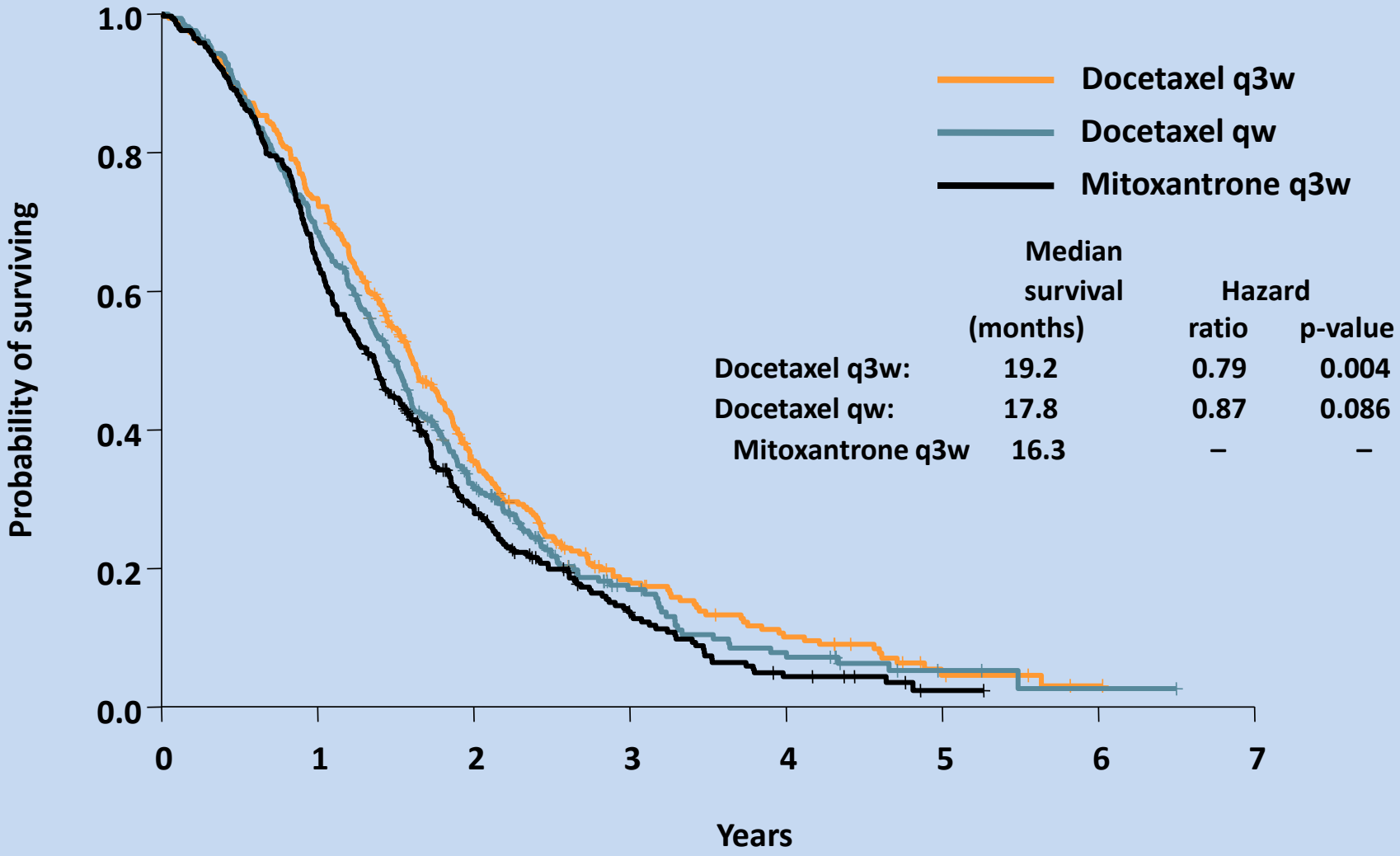
Docetaxel 75 mg/m^2 q3 wks +
Prednisone 5 mg bid

Docetaxel 30 mg/m^2 wkly
5 of 6 wks +
Prednisone 5 mg bid

Mitoxantrone 12 mg/m^2
q3 wks +
Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

TAX 327: Updated Survival Analysis



	Median survival (months)	Hazard ratio	p-value
Docetaxel q3w:	19.2	0.79	0.004
Docetaxel qw:	17.8	0.87	0.086
Mitoxantrone q3w	16.3	–	–

Berthold DR, et al. J Clin Oncol 2008;26:242–245

TAX 327 – Other End Points

- A total of 45% of those in the docetaxel arm had a PSA reduction ≥50% compared to 32% of those having mitoxantrone (p=0.0005)

- Increased benefits in pain response (35% versus 22%, p=0.01) were demonstrated in favour of docetaxel

- Quality of life was improved in 13% of patients receiving mitoxantrone, 22% of patients receiving 3-weekly docetaxel (p=0.009) and 23% of patients receiving weekly docetaxel (p=0.005)

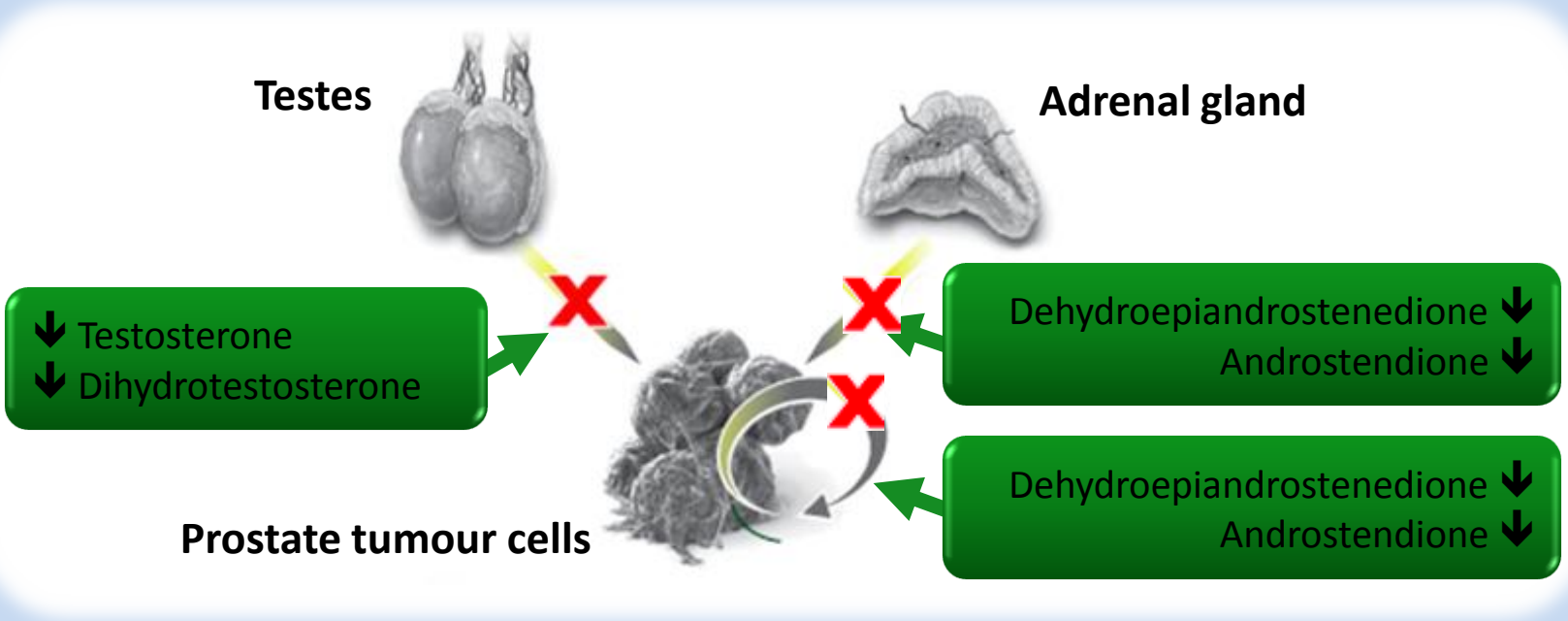
TAX 327 – Toxicity

- Toxicity included Grade 3 or 4 neutropenia and were higher in the every-3-week docetaxel arm (3%), with rates of febrile neutropenia at 2.7%.
- In comparison, Grade 3 or 4 neutropenia was noted in 0.0% and 0.9% with weekly docetaxel or mitoxantrone.

- **Toxicities of Docetaxel**
  - Haematological: neutropenia (95.5%); anaemia (90.4%); febrile neutropenia (11.0%); thrombocytopenia (8.0%)
  - Nausea and Vomiting
  - Fatigue
  - Peripheral neuropathy
  - Alopecia
  - Abnormalities of LFT's
  - Sore mouth
  - Diarrhoea
  - Palmar- plantar syndrome, itchy rash, discoloured fingernails

Management of metastatic CRPC
Pre-docetaxel

Abiraterone Inhibits Androgen Production at all Three Sources

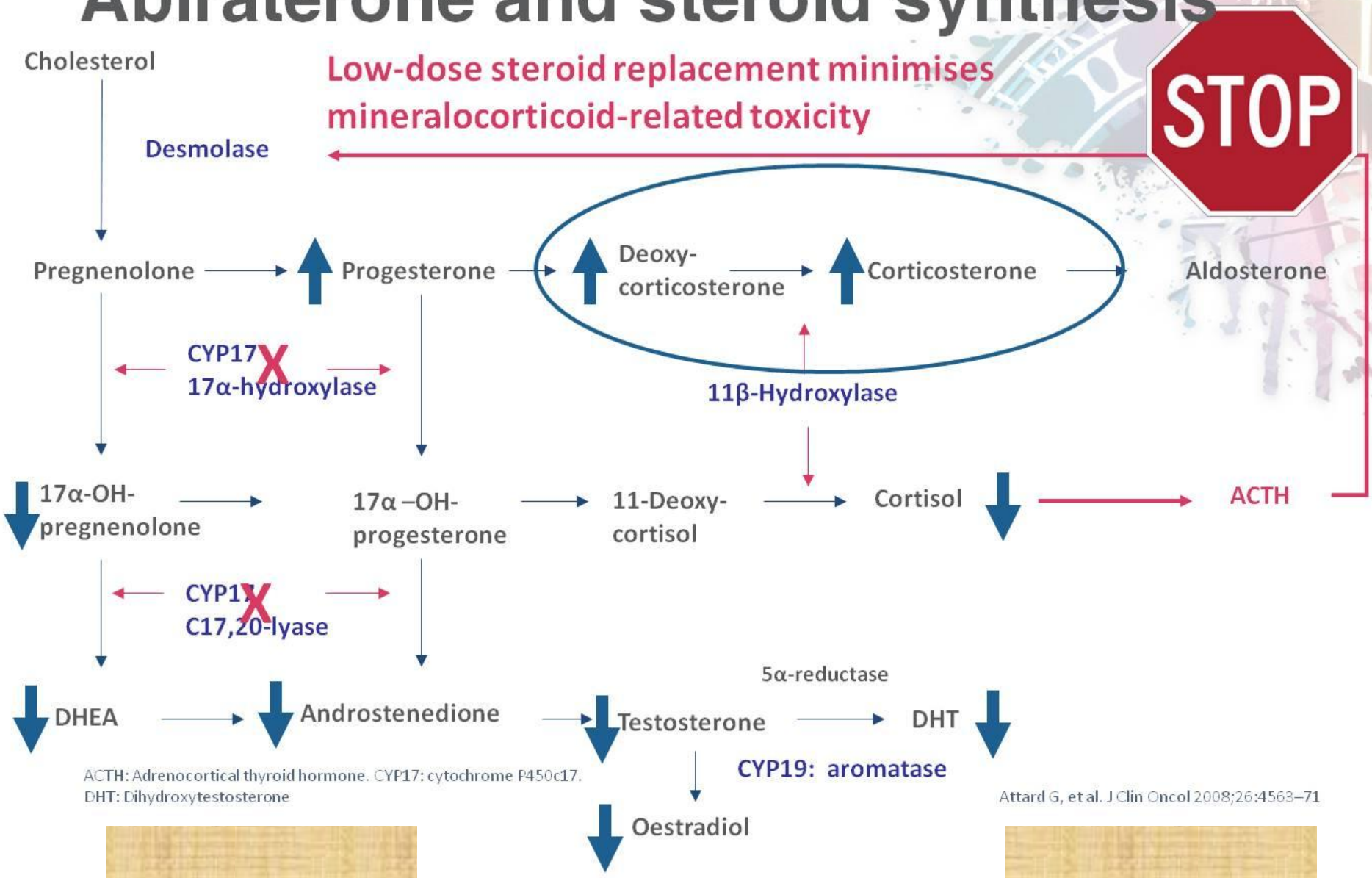


- **Conventional androgen deprivation therapies decrease androgen production by the testes but do not affect androgen biosynthesis by adrenal glands or in the tumors itself[1]**

- **Abiraterone acetate (Zytiga®) targets all three sources of androgen production[1]**

1. ZYTIGA® SmPC August 2013
2. Chen et al. *Lancet Oncol* 2009;10:981-991

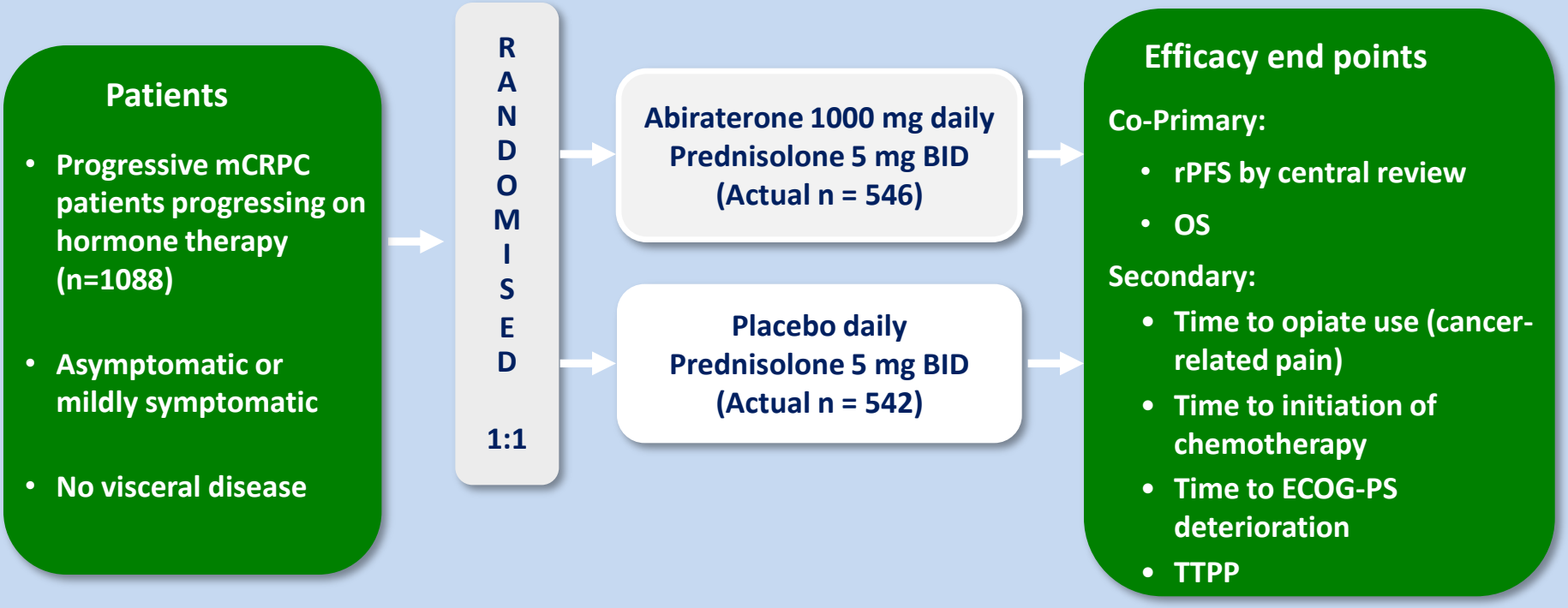
Abiraterone and steroid synthesis



ACTH: Adrenocortical thyroid hormone. CYP17: cytochrome P450c17.
DHT: Dihydroxytestosterone

Attard G, et al. J Clin Oncol 2008;26:4563–71

Randomised Phase III Study of Abiraterone Acetate in Patients who have mCRPC who have Progressed Following Hormone Therapy



- **Conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada**
- **Stratification by ECOG performance status 0 vs. 1**
- **Patients treated until radiographic progression or unequivocal clinical progression**

- **First use of rPFS adapted from PCWG2 criteria** including **independent review**

1. Ryan et al. ESMO 2012; Abstract 8940 (Oral Presentation)
2. Ryan et al. NEJM 2013; 368:138-148

Treatment Arms Were Evenly Matched

	Abiraterone (n = 546)	Prednisone (n = 542)
Median age, years (range)	71 (44-95)	70 (44-90)
Median time from initial diagnosis to first dose (years)	5.5	5.1
Median PSA (ng/mL)	42.0	37.7
Gleason score (≥ 8) at initial diagnosis	54%	50%
Extent of disease		
Bone metastases	83%	80%
> 10 bone metastases	48%	47%
Soft tissue[a]	49%	50%
Pain (BPI-SF)		
0-1	66%	64%
2-3	32%	33%

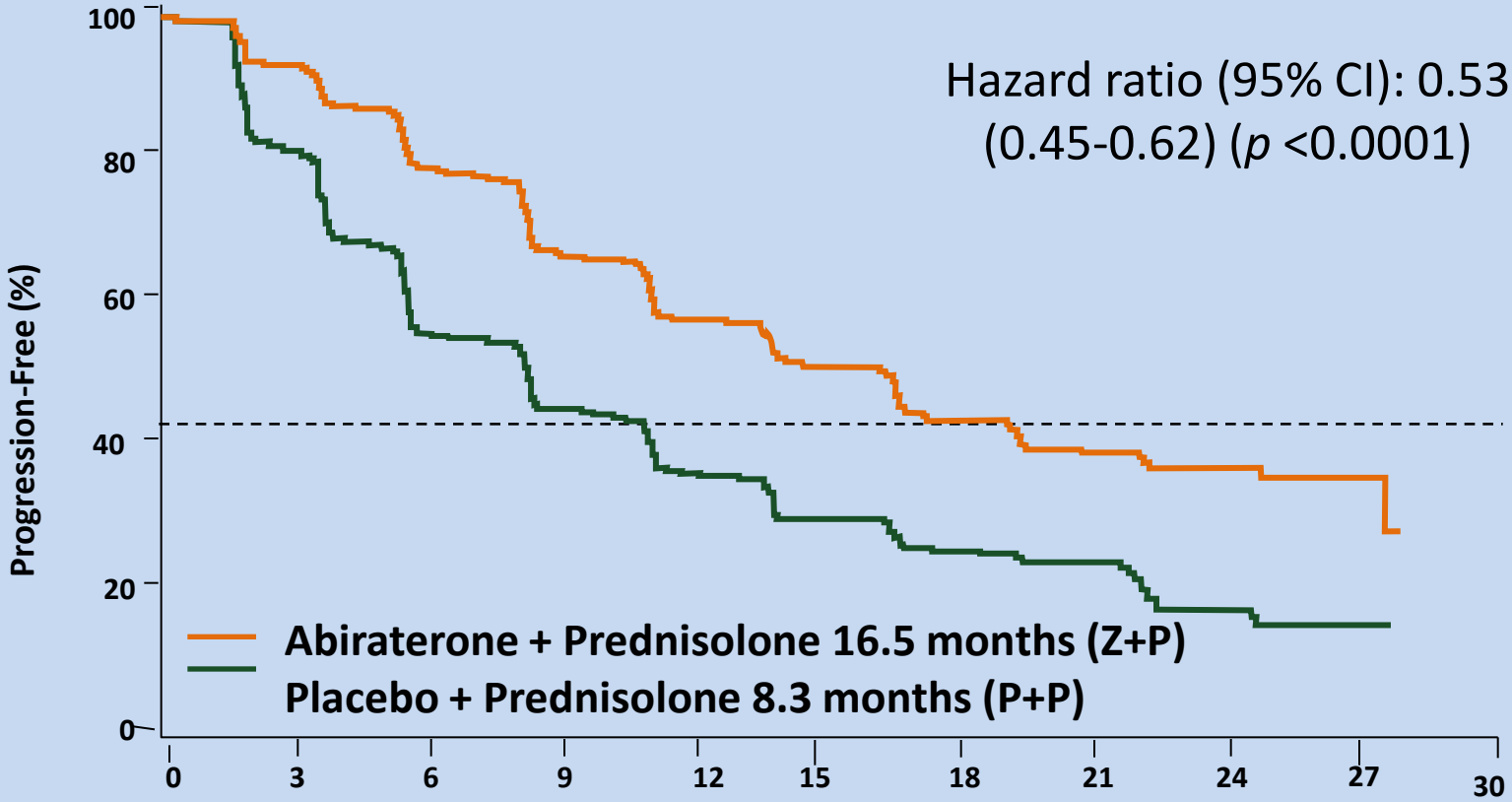
Rathkopf et al. ASCO GU 2013; Abstract 5 (Oral Presentation)

COU-AA-302: rPFS Definition

- Progressive disease (PD) by bone scan: Adapted Prostate Cancer Working Group 2 Consensus Criteria
  - Blinded central radiologist review
  - < 12 weeks after randomization
    - ≥ 2 new bone lesions plus 2 additional at confirmation ("2+2")
  - ≥ 12 weeks after randomization
    - ≥ 2 new bone lesions with subsequent confirmation
- PD (soft tissue lesions) by CT or MRI by modified RECIST criteria
- Death from any cause

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

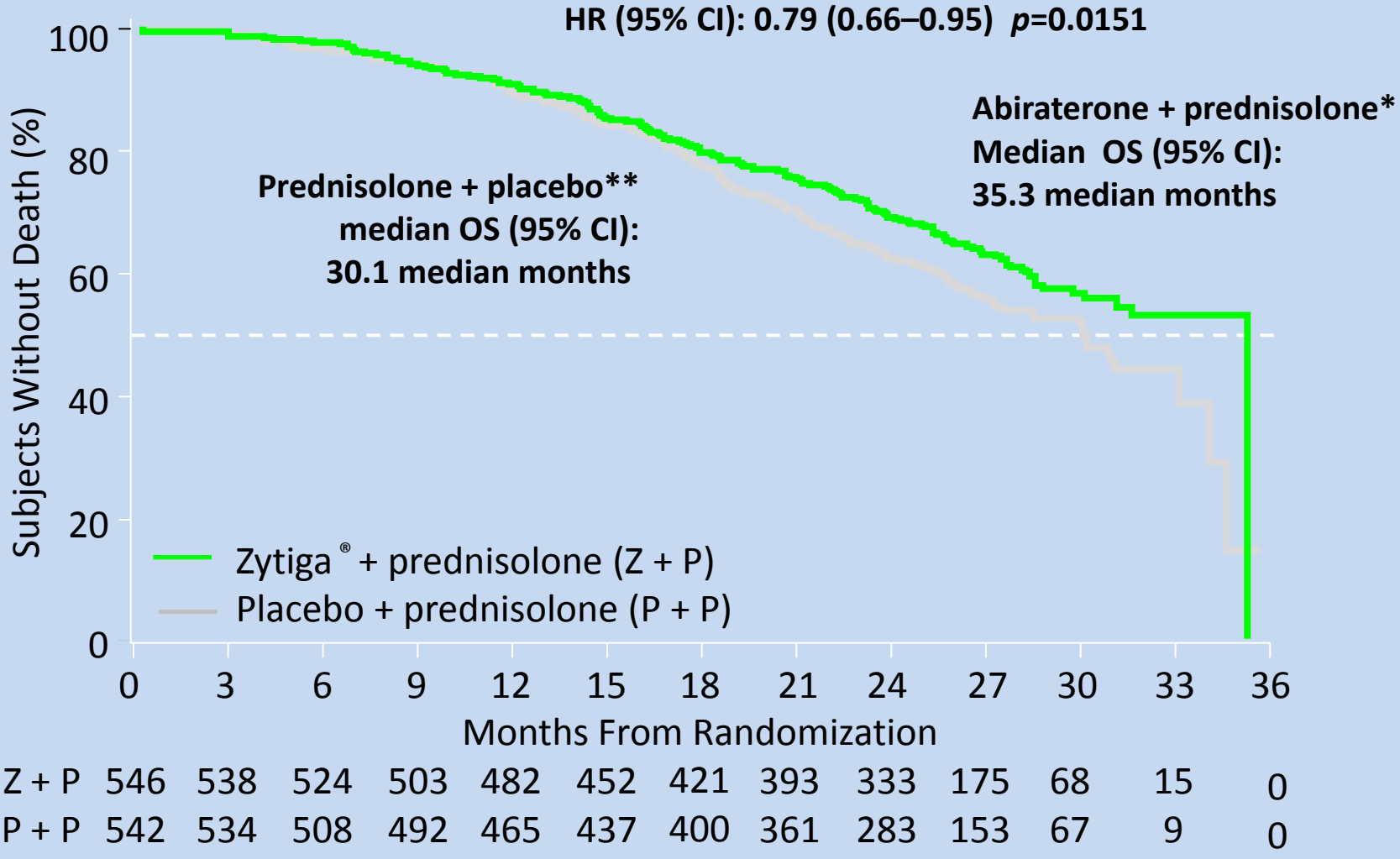
Statistically Significant Improvement in rPFS Primary End Point



No. at risk											
Z+ P	546	485	389	311	240	195	155	85	38	9	0
P + P	542	406	244	177	133	100	80	37	14	1	0

1.. Ryan et al. NEJM 2013; 368:138-148
2. Zytiga® SmPC December 2012

Improved Trend in OS Primary End Point



IA3 data. *Prespecified significance level by O'Brien-Fleming Boundary = 0.0035.

1. Rathkopf D. J Clin Oncol 31, 2013 (suppl; abstr 5009)

Statistically Significant Improvement in all Secondary End Points

	Abiraterone + P	Placebo + P		
	Median (months)	Median (months)	HR (95% CI)	P Value
Time to opiate use (cancer related pain)	NR	23.7	0.71 (0.59, 0.85)	<0.001
Time to chemotherapy initiation	26.5	16.8	0.61 (0.51, 0.72)	<0.001
Time to ECOG PS deterioration	12.3	10.9	0.83 (0.72, 0.94)	0.0052
Time to PSA progression	11.1	5.6	0.50 (0.43, 0.58)	<0.001

Note: All secondary end points remain significant after adjusting for multiplicity testing

1. Rathkopf et al. ASCO GU 2013; Abstract 5 (Oral Presentation)

Median Times to Functional Status Degradation[1]

	Abiraterone + prednisolone (months)	Placebo + Prednisolone (months)	P Value	Hazard Ratio (95% CI)
FACT-G	16.6	11.1	0.002	0.76 (0.63-0.91)
PCS	11.1	5.8	< 0.001	0.70 (0.60-0.83)
Physical well-being	14.8	11.1	0.002	0.76 (0.64-0.90)
Functional well-being	13.3	8.4	0.001	0.76 (0.64-0.90)
Emotional well-being	22.1	14.2	0.001	0.71 (0.59-0.87)
Social/Family well-being	18.4	16.6	0.528	0.94 (0.78-1.14)

1. Basch et al. ESMO 2012; Abstract 8950 (Oral Presentation)

Adverse Events of Special Interest

	Abiraterone + P (n = 542) %		Placebo + P (n = 540) %	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention / oedema	28	<1	24	2
Hypokalemia	17	2	13	2
Hypertension	22	4	13	3
Cardiac disorders	19	6	16	3
Atrial fibrillation	4	1	5	<1
ALT increased	12	5	5	<1
AST increased	11	3	5	<1

Selected on the basis of the safety profile of Phase ll and Phase lll studies of abiraterone

1. Ryan et al. NEJM 2013; 368:138-148

Final Overall Survival Analysis of COU-AA-302, a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy

CJ Ryan,[1] MR Smith,[2] K Fizazi,[3] K Miller,[4] PFA Mulders,[5] CN Sternberg,[6] F Saad,[7] T Griffin,[8] EJ Small[1], P De Porre,[9] YC Park,[10] J Li,[10] T Kheoh,[8] V Naini,[8] A Molina,[11] and DE Rathkopf[12]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [2]Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA; [3]Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [4]Department of Urology, Charité Berlin, Berlin, Germany; [5]Radboud University Medical Centre, Nijmegen, The Netherlands; [6]San Camillo and Forlanini Hospitals, Rome, Italy; [7]University of Montréal, Montréal, QC, Canada; [8]Janssen Research & Development, Los Angeles, CA, USA; [9]Janssen Research & Development, Beerse, Belgium; [10]Janssen Research & Development, Raritan, NJ, USA; [11]Janssen Research & Development, Menlo Park, CA, USA; [12]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

Challenges in Demonstrating OS Benefit in mCRPC Trials

- Multiple new treatments available with proven OS benefit
- Sequential use of 2 or more of these treatments common
- Chronicity and heterogeneity of mCRPC treatment sequencing may confound ability to measure OS benefit
- Requires larger and longer clinical studies

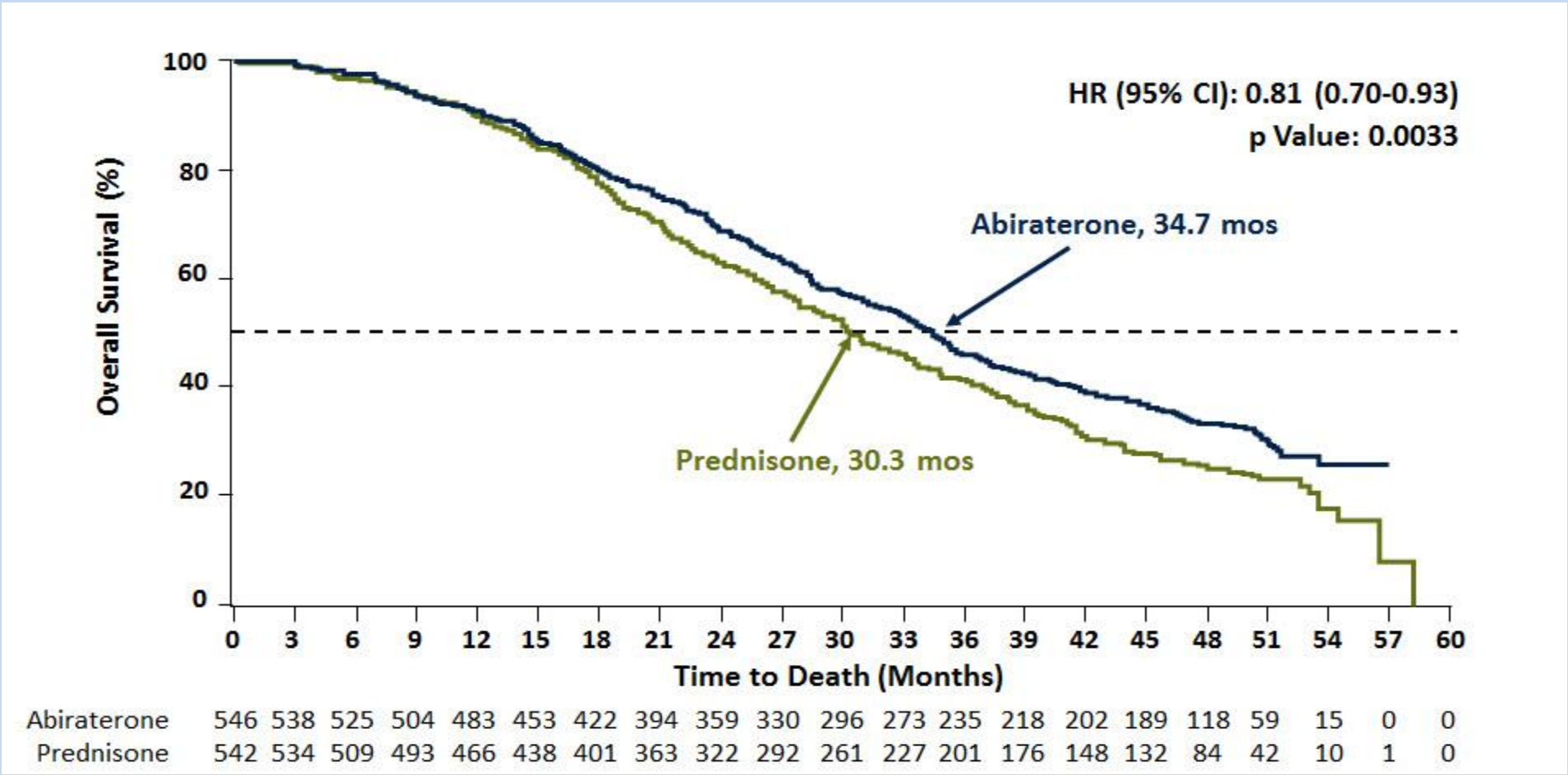
Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

Most Patients Discontinued Due to Progression

	Abiraterone (n = 542)	Prednisone (n = 540)
Median duration of follow-up	49.2 months	
Median no. of cycles of therapy, range	15.0 (1-62)	9.0 (1-54)
Treatment discontinued	92.3%	100%
Reasons for discontinuation		
Progression	68%	69%
Radiographic only	30%	32%
Unequivocal clinical progression only[a]	26%	26%
Radiographic and clinical	13%	10%
Adverse event	9%	6%
Withdrew consent	8%	10%
Other	8%	6%

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

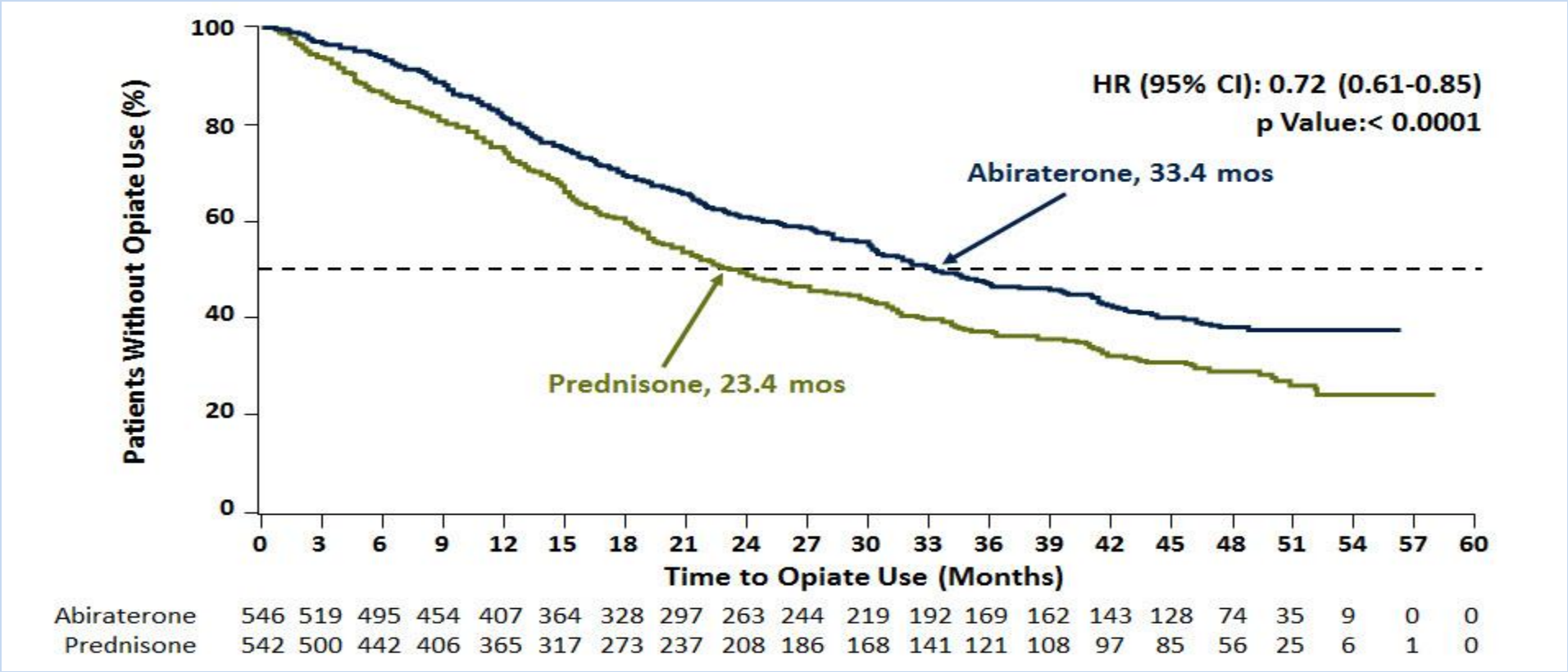
Final OS Analysis



- 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)

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

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



- 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

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

Subsequent Therapy Was Common in Both Groups

	Abiraterone n (%)	Prednisone n (%)
No. with selected subsequent therapy for mCRPC	365 (67)	435 (80)
Abiraterone	69 (13)	238 (44)[a]
Cabazitaxel	100 (18)	105 (19)
Docetaxel	311 (57)	331 (61)
Enzalutamide	87 (16)	54 (10)
Ketoconazole	42 (8)	68 (13)
Radium-223	20 (4)	7 (1)
Sipuleucel-T	45 (8)	32 (6)

[a]Includes 93 patients who received abiraterone per protocol amendments.

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

Practical Management – Abiraterone Acetate

- Oral, Not confined to cancer centre (accessible to all patients), Well tolerated.

- The tablets should be swallowed whole with water. No food should be consumed for at least two hours before, and at least one hour after taking abiraterone.

- Abiraterone is prescribed in combination with prednisolone. The recommended dosage of prednisolone is 5 mg bd.

- Serum transaminases and bilirubin should be measured prior to starting treatment with abiraterone every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly.

Assessment of Corticosteroid-Associated AE's With Long-Term Exposure to Low-Dose Prednisone Given With AA to mCRPC

Fizazi et al – GU ASCO 2015

Corticosteroid-related AEs tend to occur at higher doses and/or treatment durations than those approved for administration in combination with abiraterone for mCRPC.

Investigation of whether long-term use of low-dose prednisone with or without abiraterone leads to corticosteroid-associated AEs.

The overall incidence of all-grade corticosteroid-associated AEs for any prednisone exposure was All=24.6%, A+P=25.5%, and P=23.3%

The incidence of grade ≥ 3 corticosteroid-associated AEs for any prednisone exposure was All =4.5%, A+P=5.1%, and P=3.7%

The frequency of corticosteroid-associated AEs remained low, even with increased duration of exposure to prednisone and long-term treatment with abiraterone + prednisone is well tolerated

Assessment of Corticosteroid-Associated AE's With Long-Term Exposure to Low-Dose Prednisone Given With AA to mCRPC

Fizazi et al

	A + P -1333	P = 934	Total = 226
Hyperglycaemia	7.8% /2.1%	6.9%	7.4%
Weight Increase	3.9%	4.8%	4.3%
Ecchymoses	2.9%	3.0%	2,9%
Cushingoid State	1.4%	1.6%	1.5%
Diabetes Mellitus	1.1%	1.3%	1.1%
Cataract	1.3%	1.4%	1.3%
Skin atrophy	0.9%	1.2%	1.9%

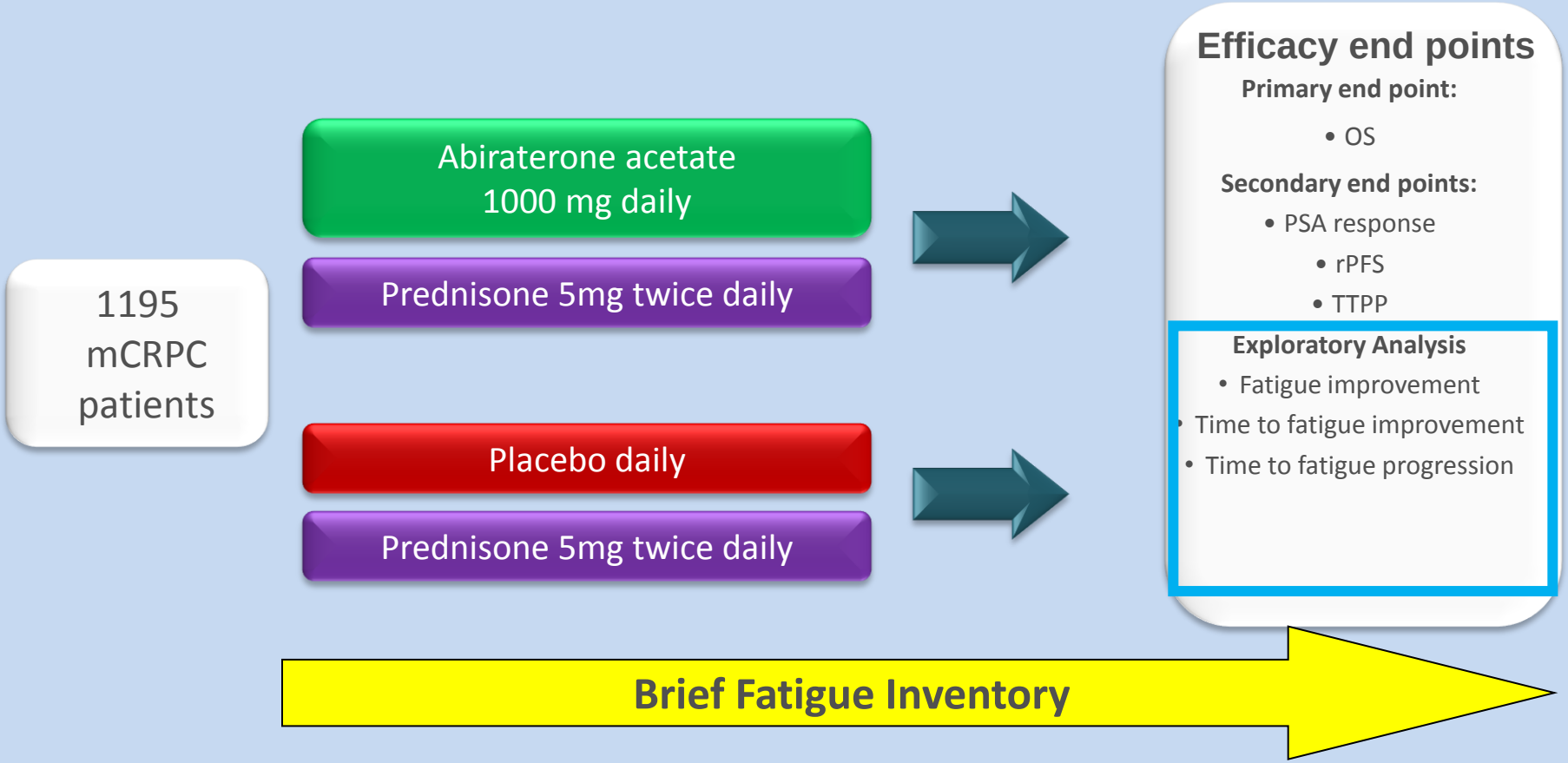
Conclusions - Abiraterone

- Median follow-up of more than 4 years, abiraterone improvement in overall survival was statistically significant
  - 44% in the prednisone arm received abiraterone
- Abiraterone delayed the need for opiate analgesics
- No new safety signals were observed
- Despite early unblinding, final survival data support continued data collection vs. early trial termination in clinical trial conduct

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

Study Design

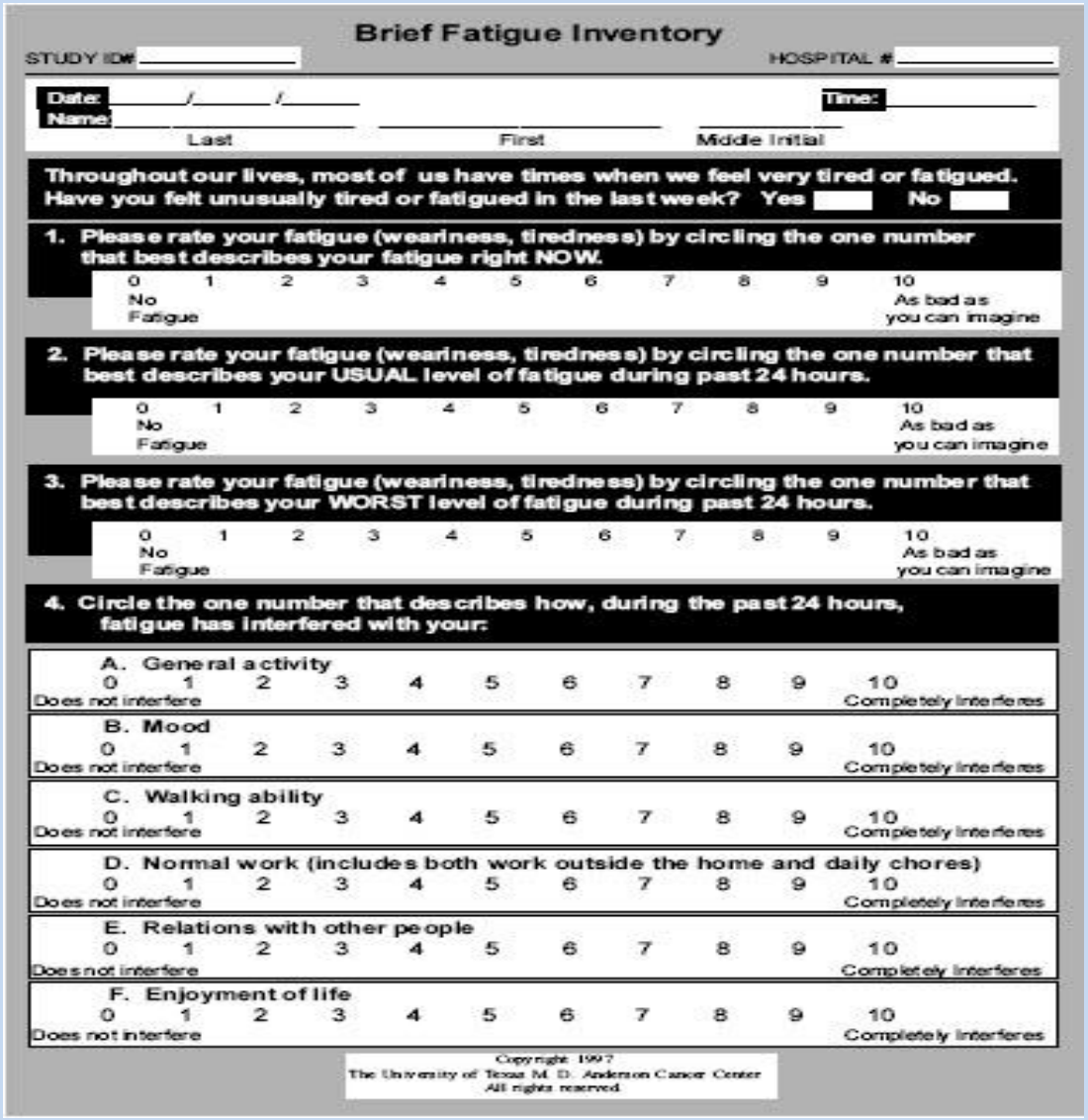
Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study
(147 sites in 13 countries; USA, Europe, Australia, Canada)



Patient-reported fatigue was assessed at baseline (within 14 days prior to the first dose of study treatment) and 1st day of each treatment cycle until discontinuation

Sternberg et al. Ann Oncol 2013; 24: 1017-1025

Brief Fatigue Inventory (BFI)



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely interferes

Sternberg et al. Ann Oncol 2013; 24: 1017-1025

Conclusions - Abiraterone

- Abiraterone +prednisone was associated with:
  - delayed fatigue progression and improvements in patient-reported fatigue outcomes compared with prednisone alone in patients with mCRPC after docetaxel chemotherapy
  - more rapid fatigue improvement

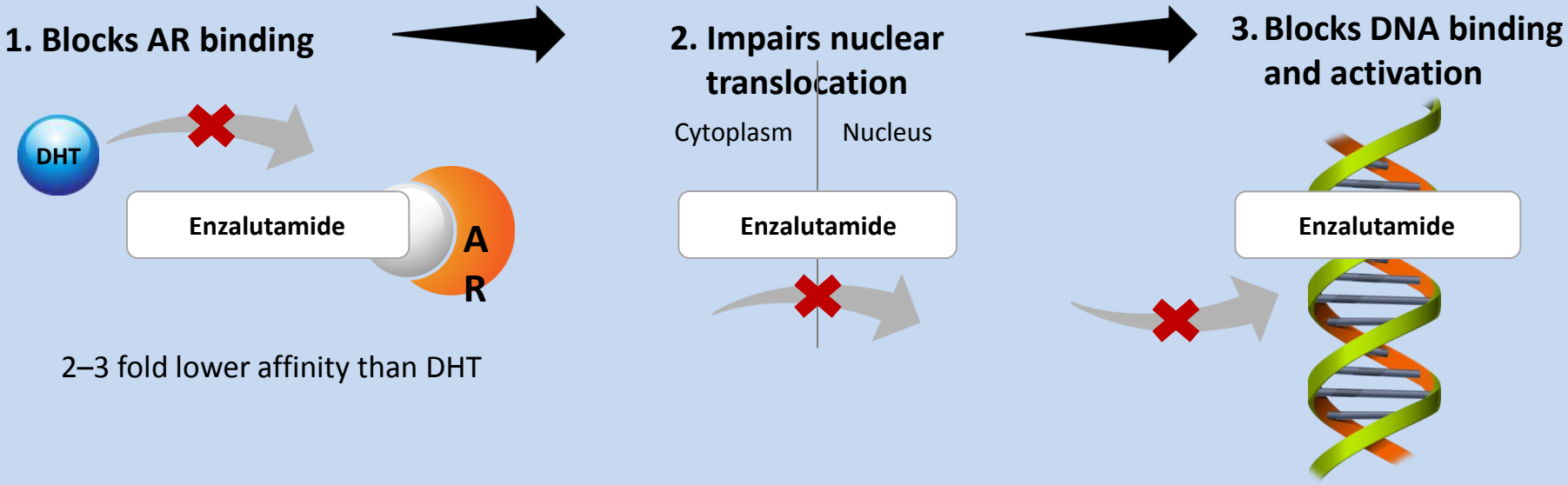
- The effect size of these benefits is very likely perceivable by and meaningful to patients

- This clinically meaningful relief of a debilitating symptom of advanced prostate cancer further supports abiraterone as a valuable option for the treatment of mCRPC after docetaxel chemotherapy
  - in particular when considering the previously reported OS and PFS benefit, as well as the multidimensional improvements across various other QoL domains

Sternberg et al. Ann Oncol 2013; 24: 1017-1025

Enzalutamide

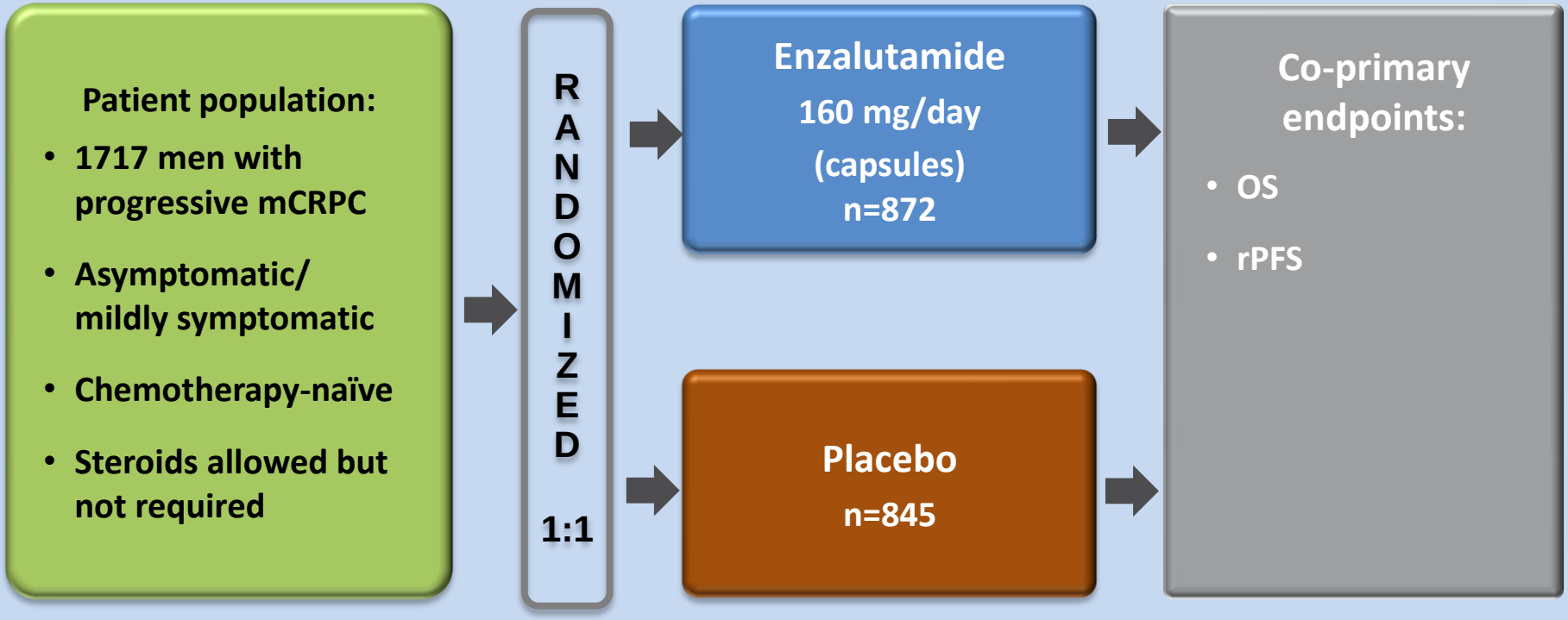
- Enzalutamide is an AR signalling inhibitor that inhibits AR signalling in three distinct ways:



Tran *et al. Science* 2009;324:787–90; Watson *et al. Proc Natl Acad Sci* USA 2010;107:16759–65.

AR, androgen receptor;
DHT, dihydrotestosterone

PREVAIL: A Phase III trial of Enzalutamide after Progression on ADT in Men with mCRPC



ADT=androgen-deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; rPFS=radiographic progression-free survival.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation; ClinicalTrials.gov identifier: NCT01212991.

Treatment Groups were Well Balanced for Baseline Disease Burden

Disease measure	Enzalutamide (n=872)	Placebo (n=845)
PSA, median, ng/mL	54.1	44.2
LDH, median, IU/L	185.0	185.0
Bone disease	85.0%	81.7%
Soft tissue disease	59.3%	59.6%
Visceral disease (liver and/or lung)	11.2%	12.5%

LDH=lactate dehydrogenase; PSA=prostate-specific antigen

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

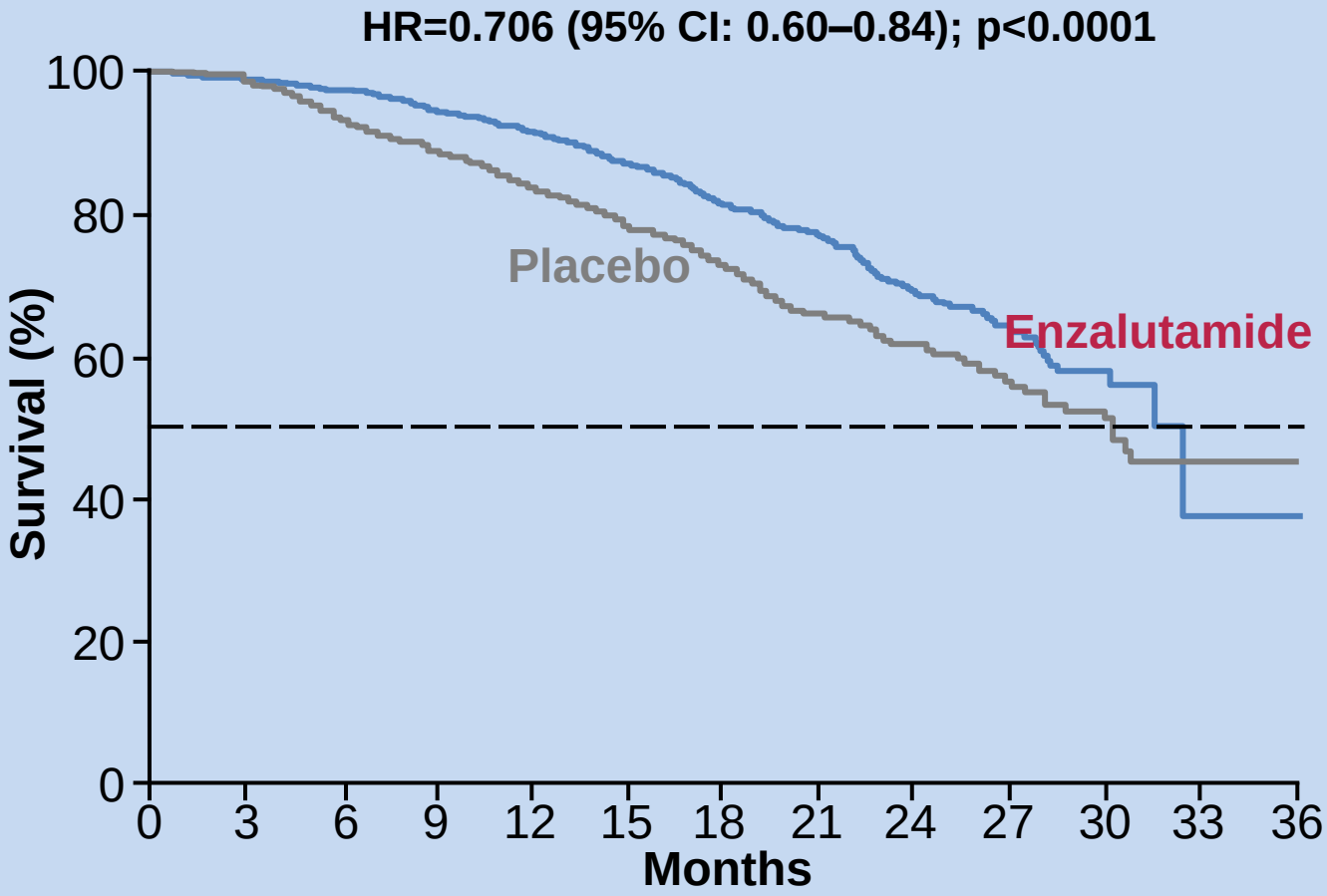
Median Duration of Enzalutamide Treatment was More than 3-times Longer than for Placebo

	Enzalutamide (n=872)	Placebo (n=845)
Duration of treatment, median, months	16.6	4.6
Patients with ≥ 12-months duration	67.9%	18.0%
Treatment ongoing at data cutoff date	42.1%	7.2%
Median OS follow-up, months	22.2	22.4

OS=overall survival.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Enzalutamide Reduced the Risk of Death by 29%



Enzalutamide, n	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo, n	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)

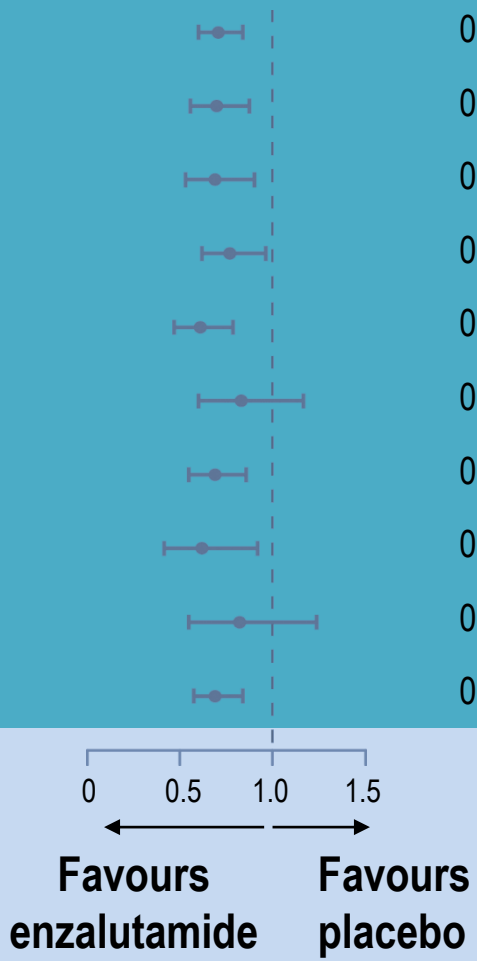
NYR = Not Yet Reached

CI=confidence interval; HR=hazard ratio.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Survival Benefit was Observed Across Subgroups

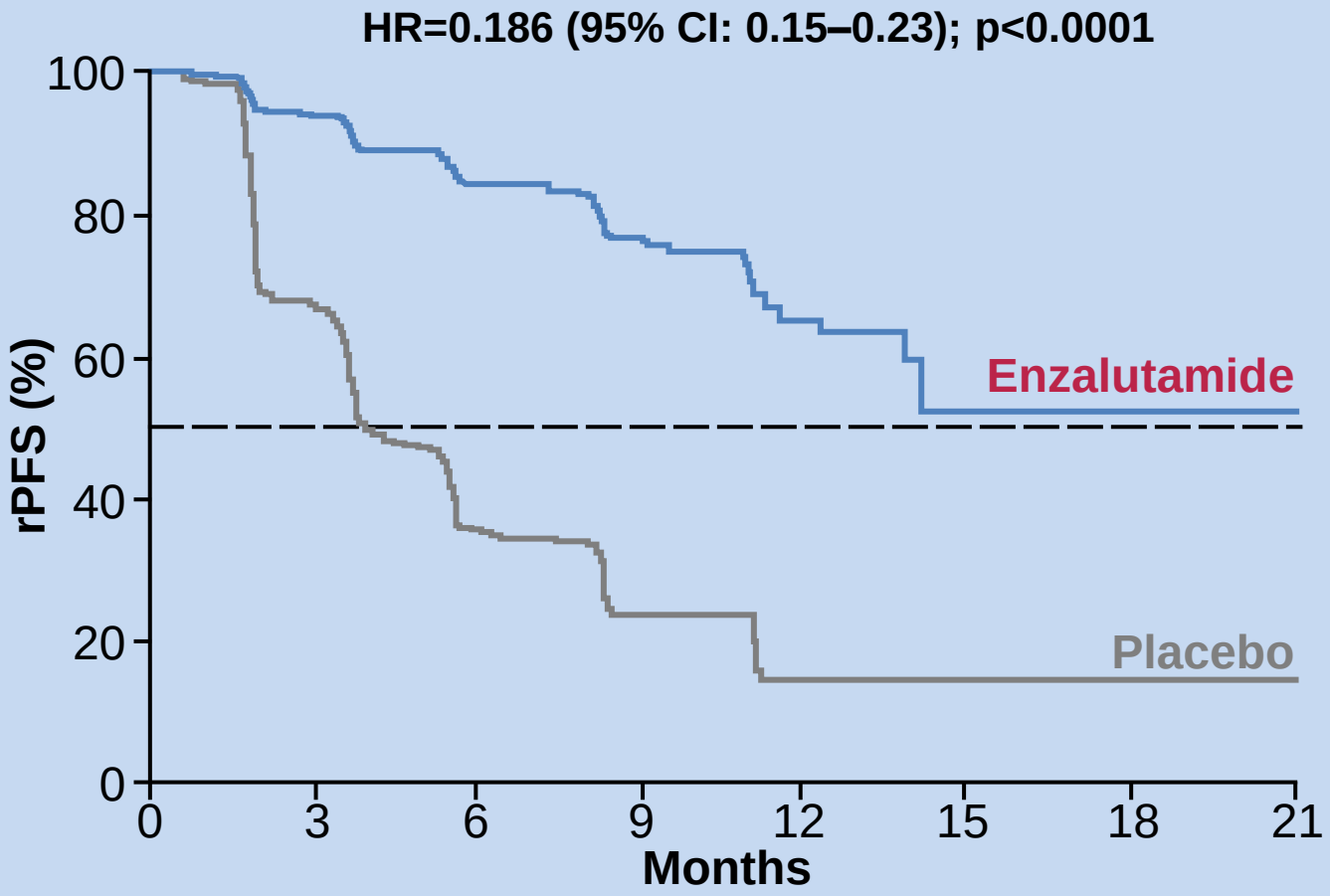
Subgroup	Number of patients enzalutamide / placebo	Hazard ratio for death (95% CI)
All patients	872 / 845	0.71 (0.60–0.84)
ECOG performance status = 0	584 / 585	0.70 (0.56–0.87)
ECOG performance status = 1	288 / 260	0.69 (0.53–0.90)
Age <75	555 / 553	0.77 (0.62–0.96)
Age ≥75	317 / 292	0.60 (0.47–0.79)
Geographic region – North America	218 / 208	0.83 (0.60–1.16)
Geographic region – Europe	465 / 446	0.68 (0.54–0.86)
Geographic region – Rest of world	189 / 191	0.62 (0.42–0.92)
Visceral disease (lung and/or liver) – Yes	98 / 106	0.82 (0.55–1.23)
Visceral disease (lung and/or liver) – No	774 / 739	0.69 (0.57–0.83)



ECOG=European Co-operative Group.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Enzalutamide Prolonged Radiographic Progression Free Survival



Enzalutamide, n	832	514	256	128	34	5	1	0
Placebo, n	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

CI=confidence interval; HR=hazard ratio; rPFS=radiographic progression-free survival.

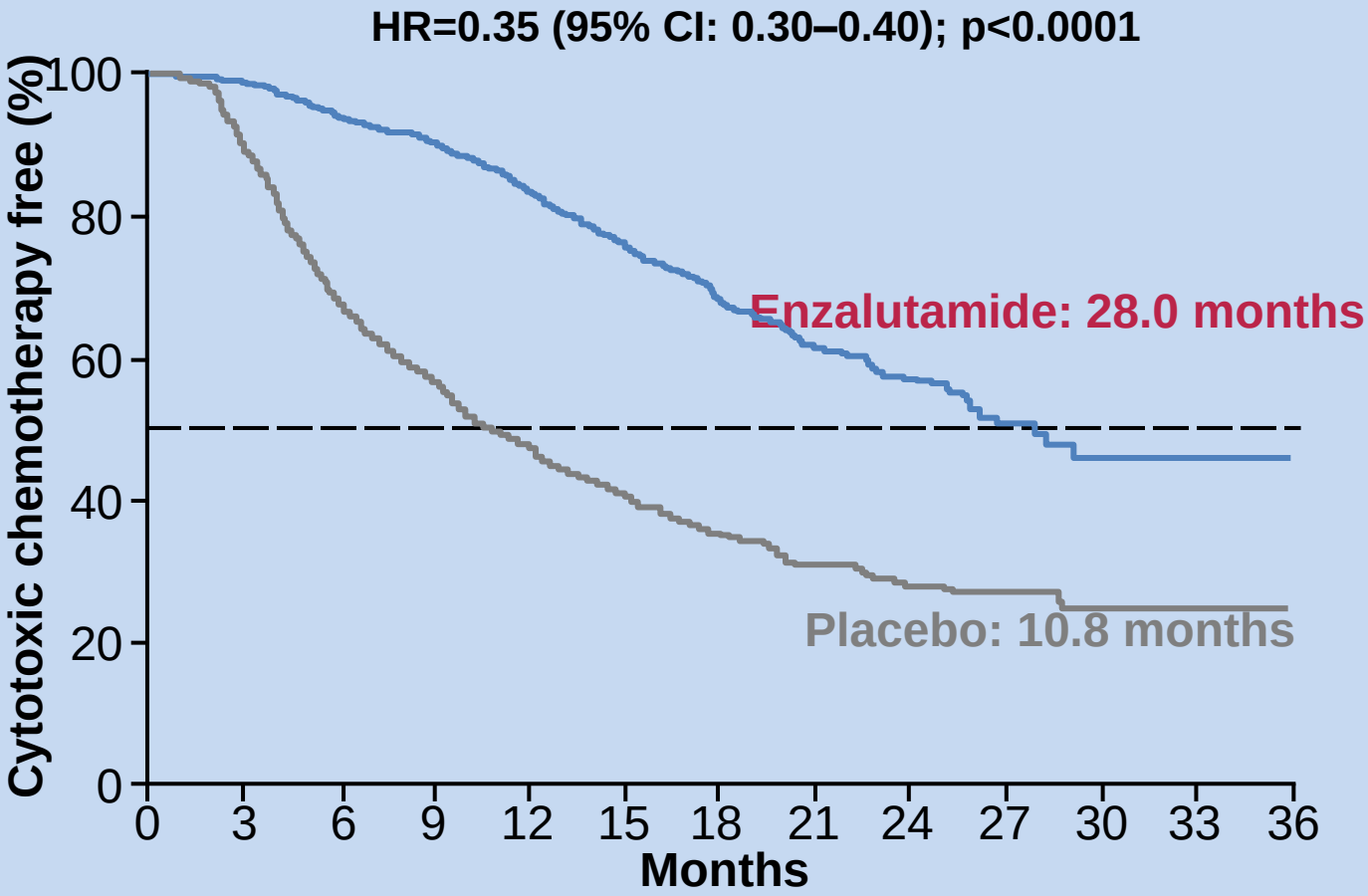
Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Subsequent Therapies were Used More Commonly in the Placebo Group

	Enzalutamide (n=872)	Placebo (n=845)
Patients with at least one subsequent life-extending therapy	40.3%	70.3%
Percentage of patients receiving subsequent therapies		
Docetaxel	32.8%	56.7%
Abiraterone	20.5%	45.6%
Cabazitaxel	5.8%	13.0%
Enzalutamide	1.0%	4.4%
Sipuleucel-T	1.4%	1.2%

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Enzalutamide Delayed Median Time to Chemotherapy by 17 Months



Enzalutamide, n	872	854	799	751	665	575	388	252	158	78	21	2	0
Placebo, n	845	734	518	415	324	257	165	103	64	25	9	0	0

CI=confidence interval; HR=hazard ratio.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Most Common Adverse Events* and Adverse Events of Interest

	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 adverse events	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

*At least 20% on enzalutamide and ≥2% more than placebo; †one seizure occurred after the data cutoff date.

ALT=alanine aminotransferase.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

Conclusions - Enzalutamide

- Treatment with enzalutamide:
  - Significantly reduced the risk of death
  - Significantly delayed the progression of metastatic disease and achieved meaningful responses in soft tissue disease
  - Significantly delayed the time to initiation of cytotoxic chemotherapy
  - Significantly delayed deterioration in quality of life
- Enzalutamide, an oral once-daily medicine, was well tolerated over a prolonged treatment period
- Enzalutamide added to ADT at progression provides meaningful clinical benefit to men with metastatic prostate cancer

ADT=adrogen-deprivation therapy.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

TERRAIN Study

- Phase 2 efficacy and safety trial of enzalutamide versus bicalutamide in men with mCRPC
- 375 men with asymptomatic/mildly symptomatic, chemotherapy naïve progressive mCRPC
- Progressed on LHRHa/orchidectomy
- Steroids allowed but not required
- Randomised 1:1 - Bicalutamide 50mg (191) vs Enzalutamide 160mg (184)

- Primary Endpoint – PFS (radiographic progression, change in new neoplastic therapy or death)

- Secondary Endpoints
- PSA response
- Time to PSA progression

TERRAIN Study

- Treatment groups were well matched for baseline patient characteristics and disease burden

	Enzalutamide (184)	Bicalutamide(191)
Median Age	72	71
ECOG PS=0	70.7%	76.4%
GS >/= 8 at diagnosis	55.4%	57.6%
PSA Median ng/ml	20.6	21.4
Bone Disease only	45.1%	48.2%
Soft Tissue Disease Only	19.6%	15.2%
Bone and Soft Tissue Disease	34.8%	36.1%

TERRAIN Study

- Median duration of treatment: enzalutamide 11.7 months; bicalutamide 5.8 months

- Estimated median PFS, months (95% CI)
- Enzalutamide: 15.7 (11.5,19.4);
- Bicalutamide: 5.8 (4.8, 8.1)
- HR (95% CI): 0.44 (0.34, 0.57); p<0.0001

- Estimated median Time to PSA progression, months (95% CI)
-
- Enzalutamide: 19.4 (16.6, NYR)
- Bicalutamide: 5.8 (5.6, 8.3)

TERRAIN Study - Conclusions

- Treatment with enzalutamide compared to bicalutamide:
- Delayed the progression of metastatic disease by 56%, $p<0.0001$
- The treatment effect was robust and consistent across all pre-specified subgroups
- Significantly delayed the time to PSA progression
- PSA response was 82% in the enzalutamide arm compared to 21% in the bicalutamide arm
- Enzalutamide demonstrated safety broadly consistent with its known safety profile in patients with mCRPC
- Enzalutamide given to castrate men with metastatic prostate cancer who have progressed while on LHRHa or after receiving a bilateral orchiectomy provides meaningful clinical benefit

Conclusions

- Improvements in progression free survival and overall survival rates observed with novel agents in advanced prostate cancer have led to a shift in treatment paradigm
- Emerging therapies mean that the future is bright
- Clinical practice is likely to continue changing over the next few years
- Need for clear guidelines to ensure optimum use and sequencing of treatments

1. Payne, H et al, Optimizing the care of patients with advanced prostate cancer in the UK: current challenges and future opportunities, BJU 2012, 10(5):658-67
2. Osanto S, Van Poppel H, Emerging novel therapies for advanced prostate cancer, Ther Adv Urol. 2012 Feb;4(1):3-12