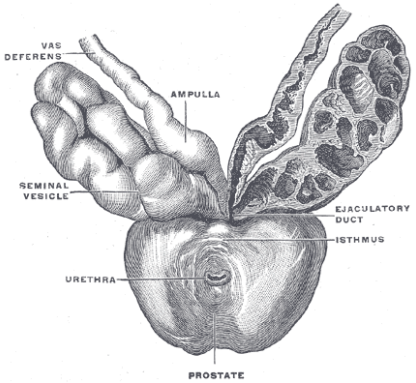
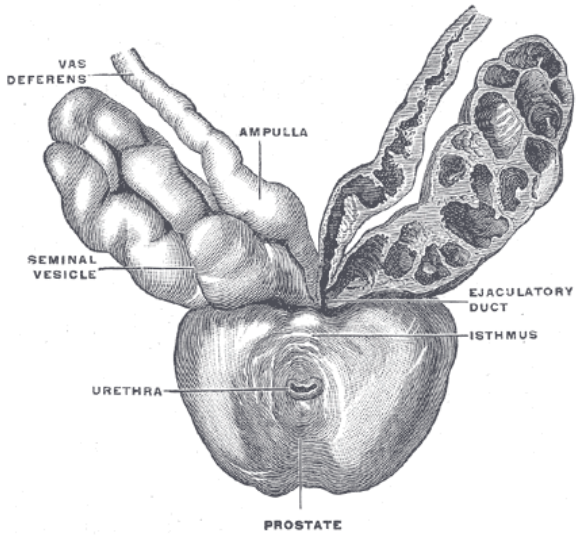


Management of castration resistant prostate cancer after first line hormonal therapy fails

Simon Crabb

Senior Lecturer in Medical Oncology

University of Southampton



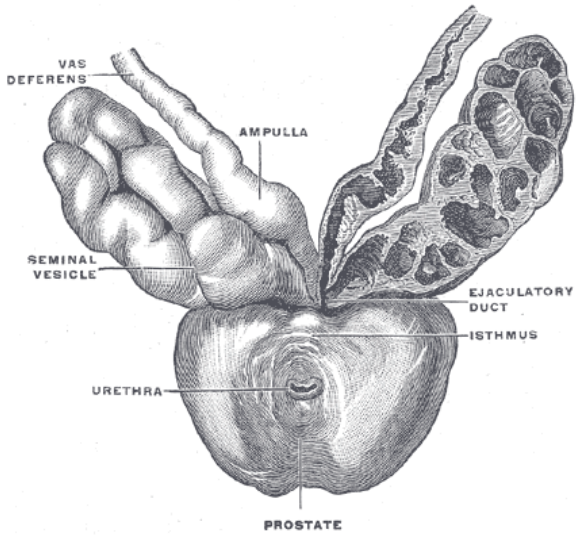
WHAT ARE THE AIMS OF TREATMENT?

Cure?

Nothing I will discuss today will cure anyone.
We need to remember to mention this to our patients.

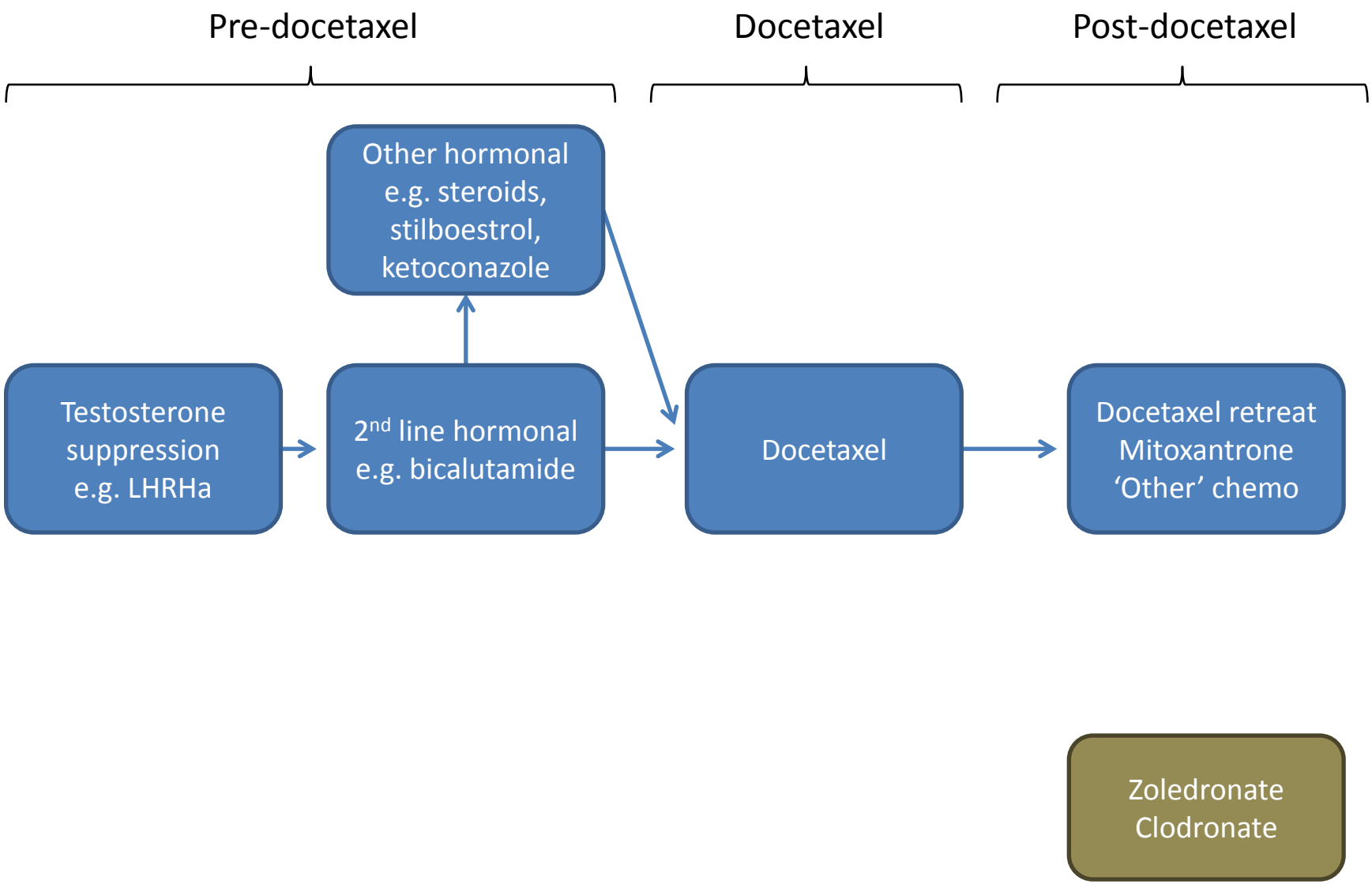
Other aims that matter to our patients

- Prolonged survival
- Improved quality of life
- Reduction in pain
- Reduction in skeletal related events
- Time to do things
- Improved progression free survival
- Reduction in PSA

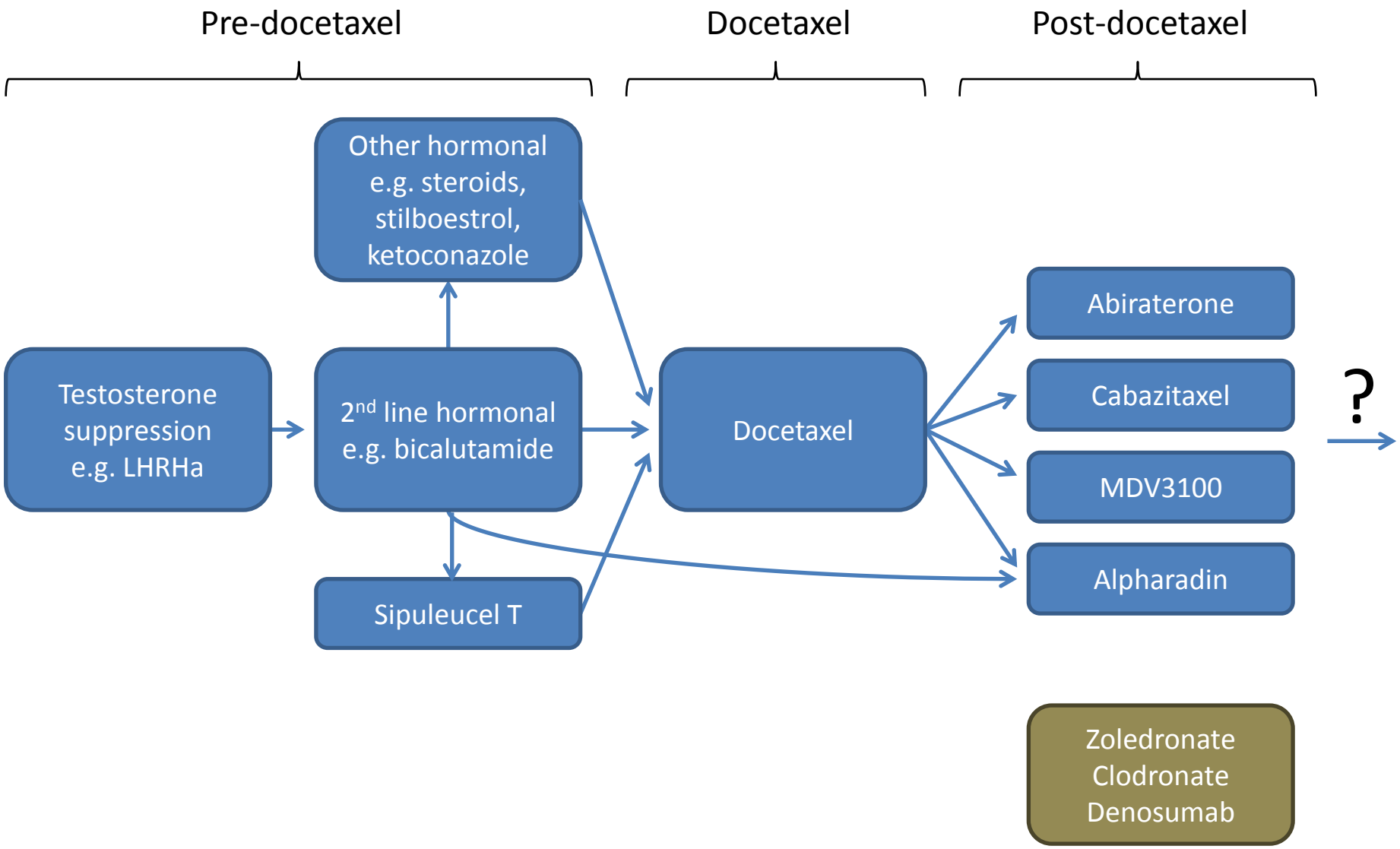


GENERAL OPTIONS FOR TREATMENT

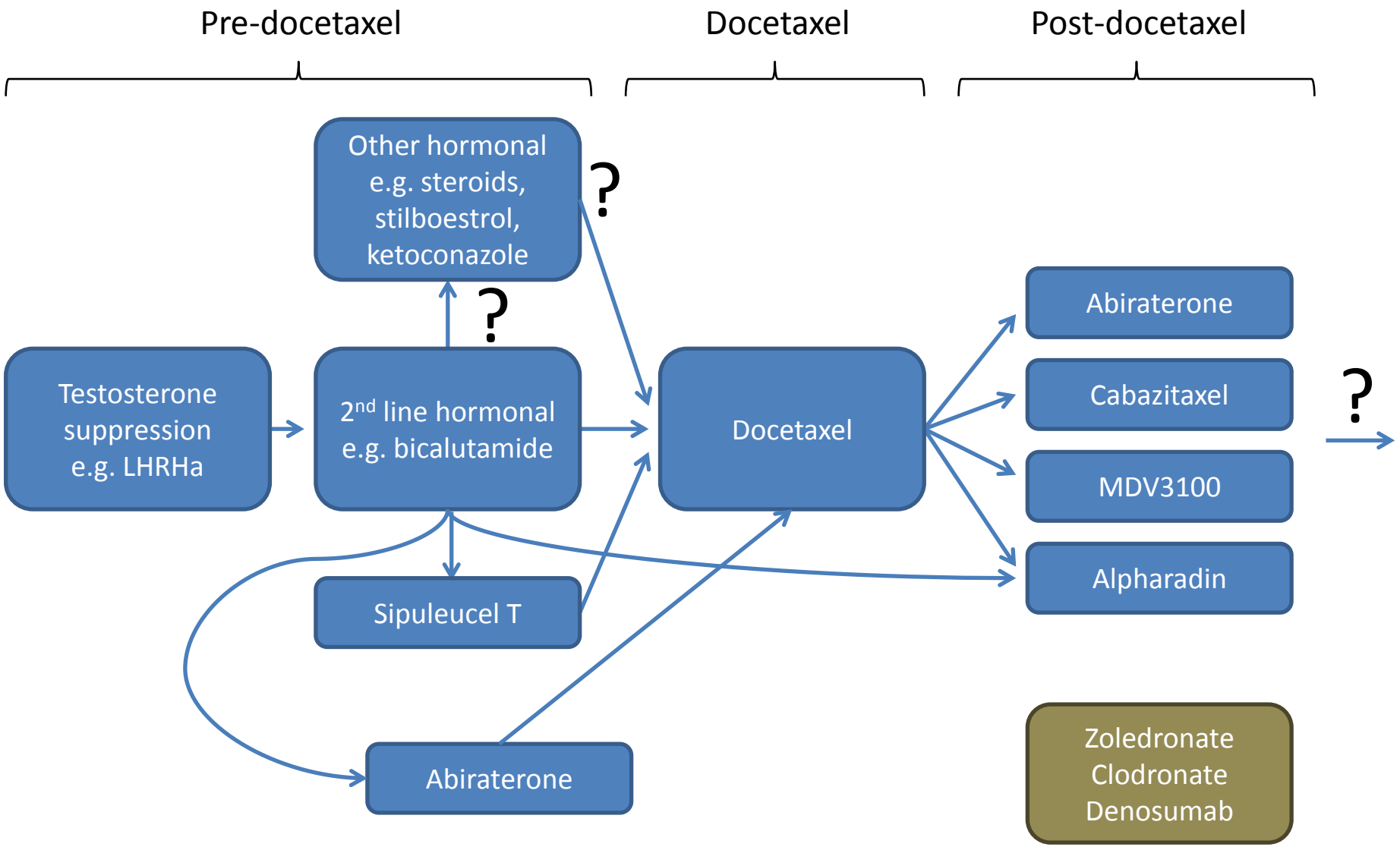
Metastatic prostate cancer – 2010

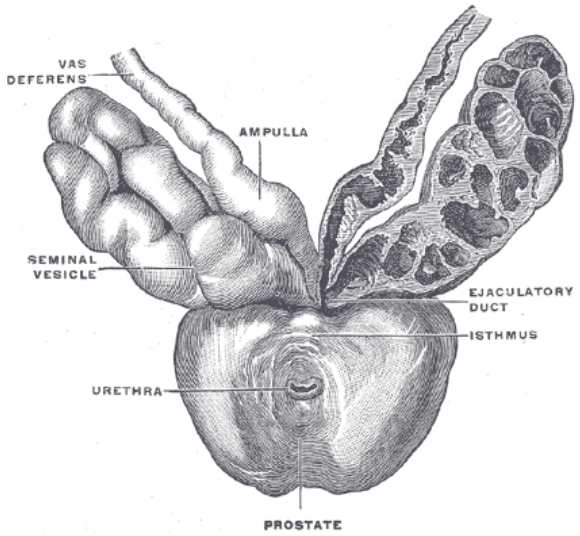


Metastatic prostate cancer – 2012



Metastatic prostate cancer – 2013

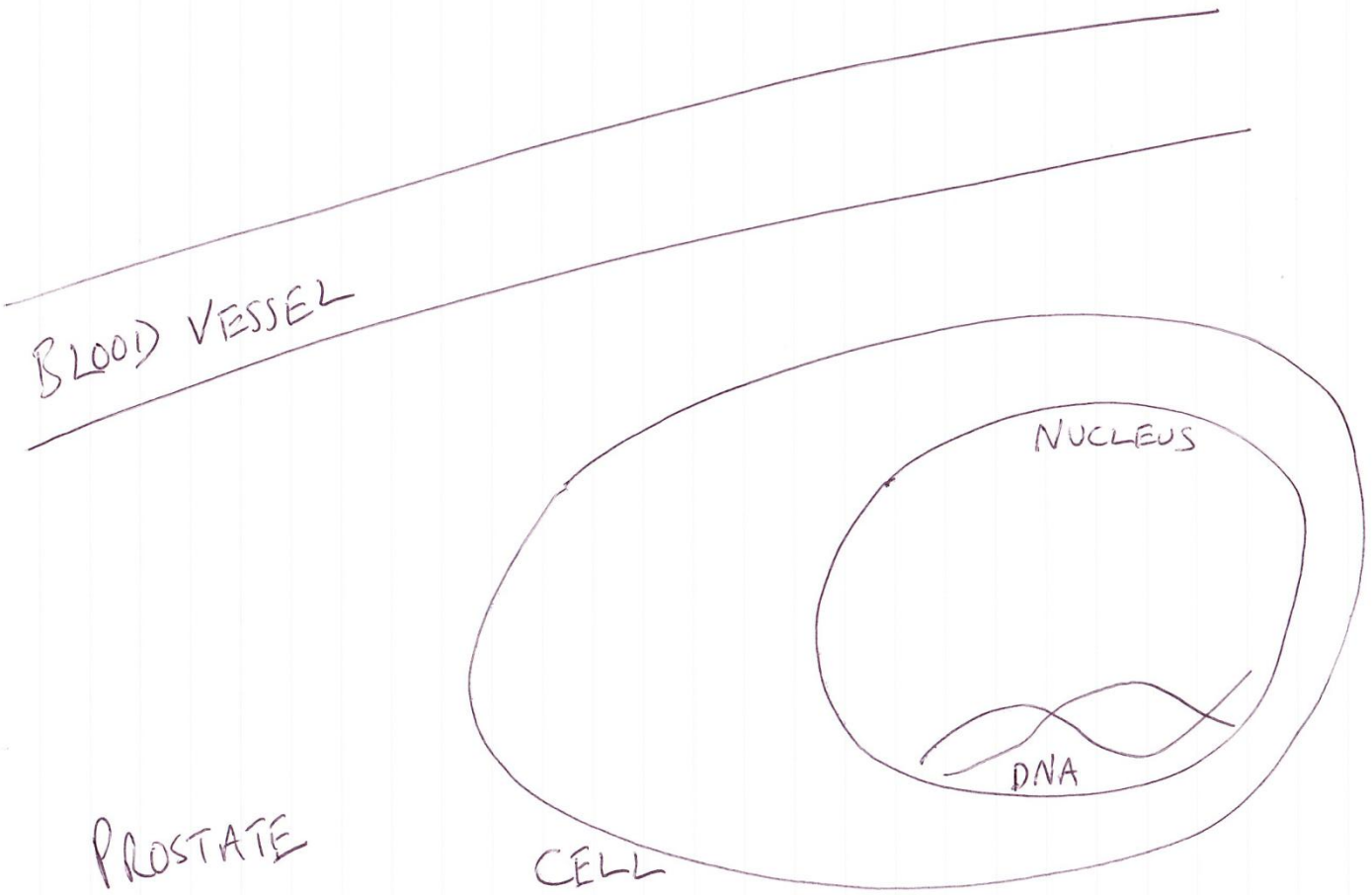


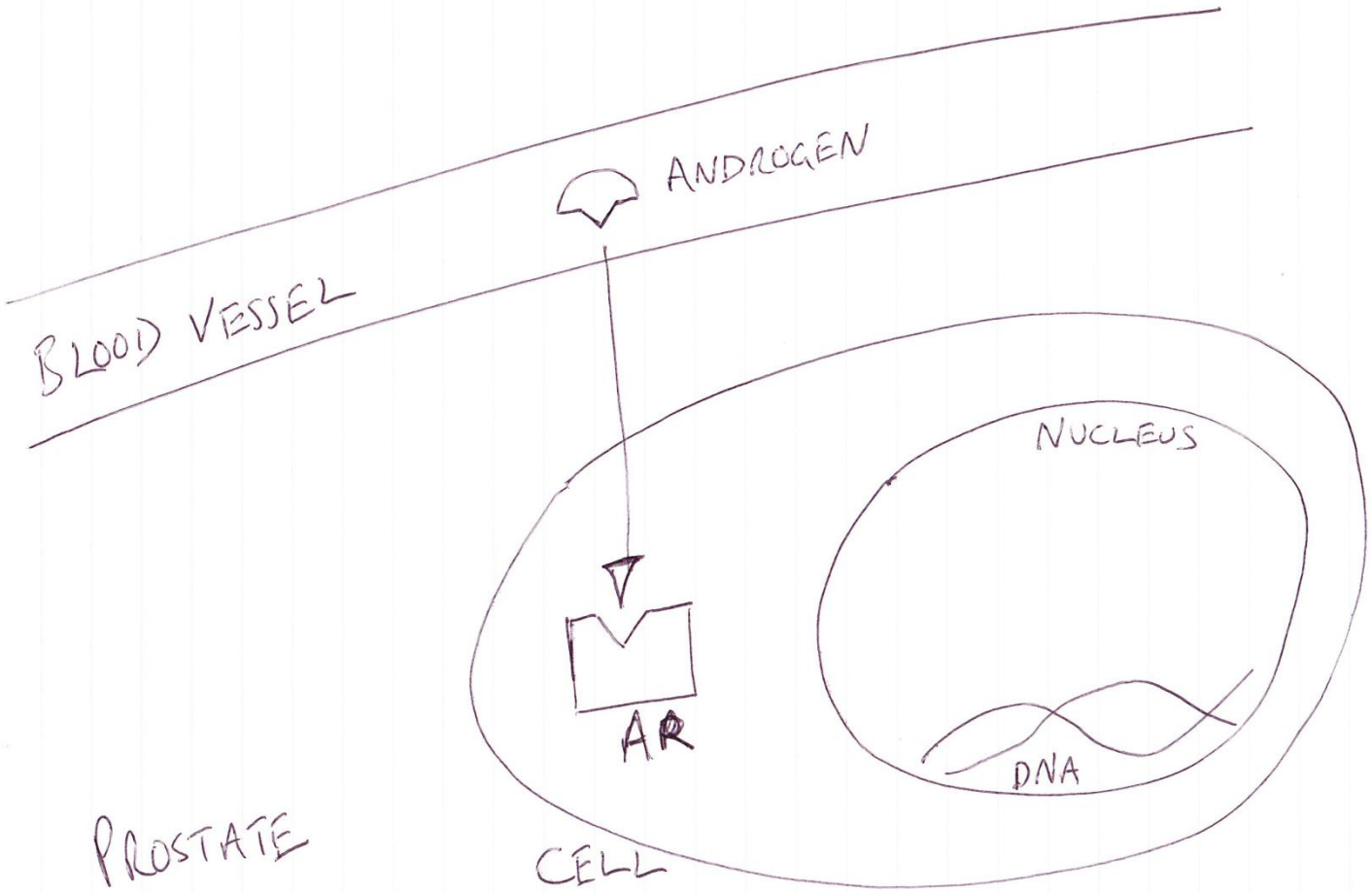


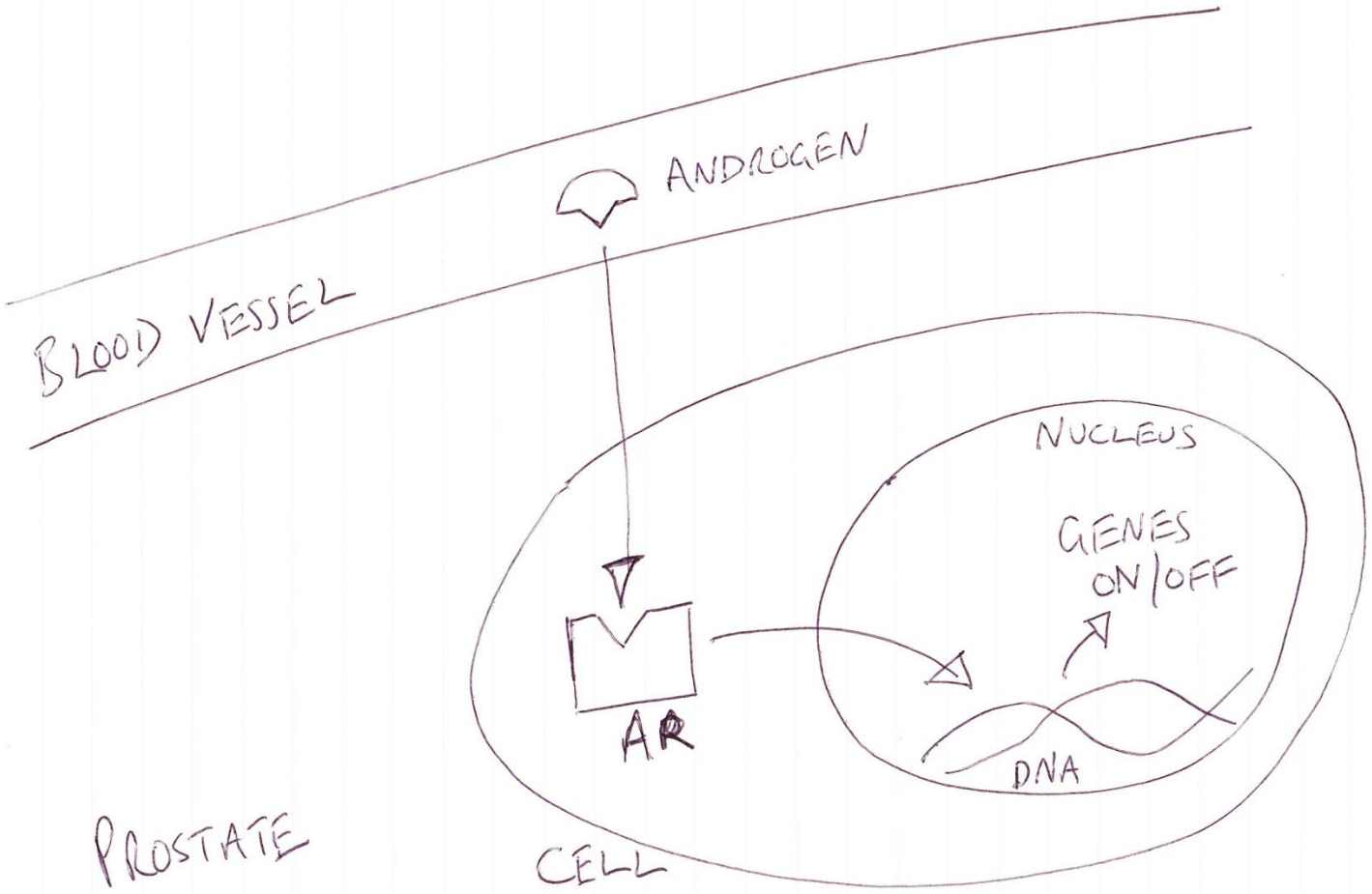
A BIT OF BIOLOGY

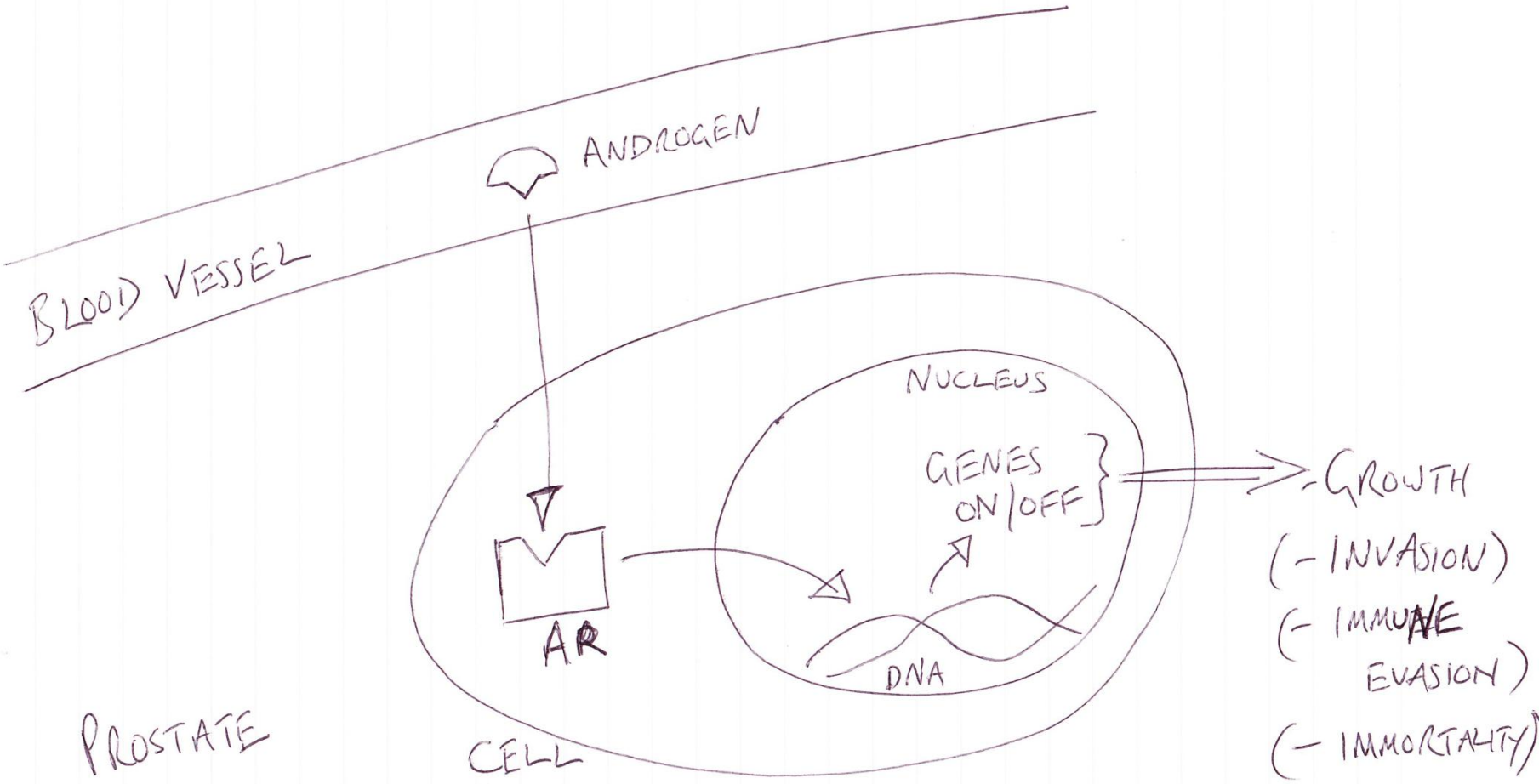
Androgen Receptor

- Central mediator of male reproductive function and development (also impacts on bone, skin, muscle, brain…)
- Nuclear hormone receptor
- 5α-dihydrotestosterone >>> testosterone
- Involved in all stages of prostate cancer


BLOOD VESSEL
NUCLEUS
DNA
CELL
PROSTATE

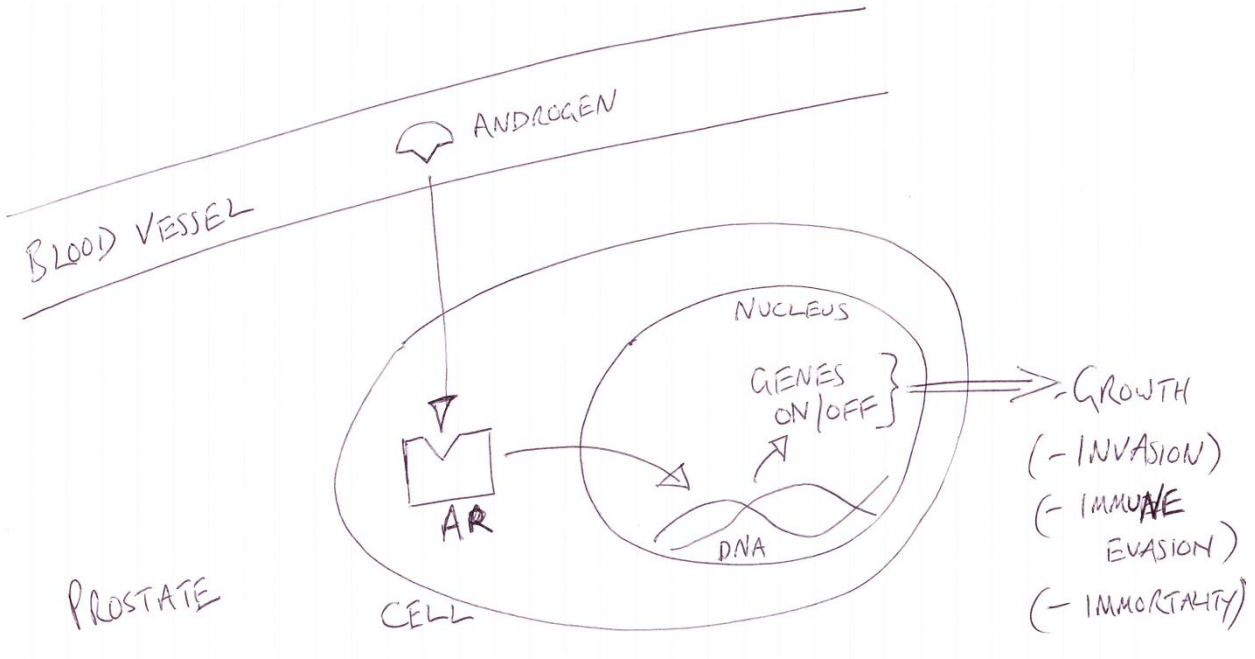

BLOOD VESSEL
ANDROGEN
NUCLEUS
AR
DNA
PROSTATE
CELL


BLOOD VESSEL
ANDROGEN
NUCLEUS
GENES
ON/OFF
AR
DNA
PROSTATE
CELL

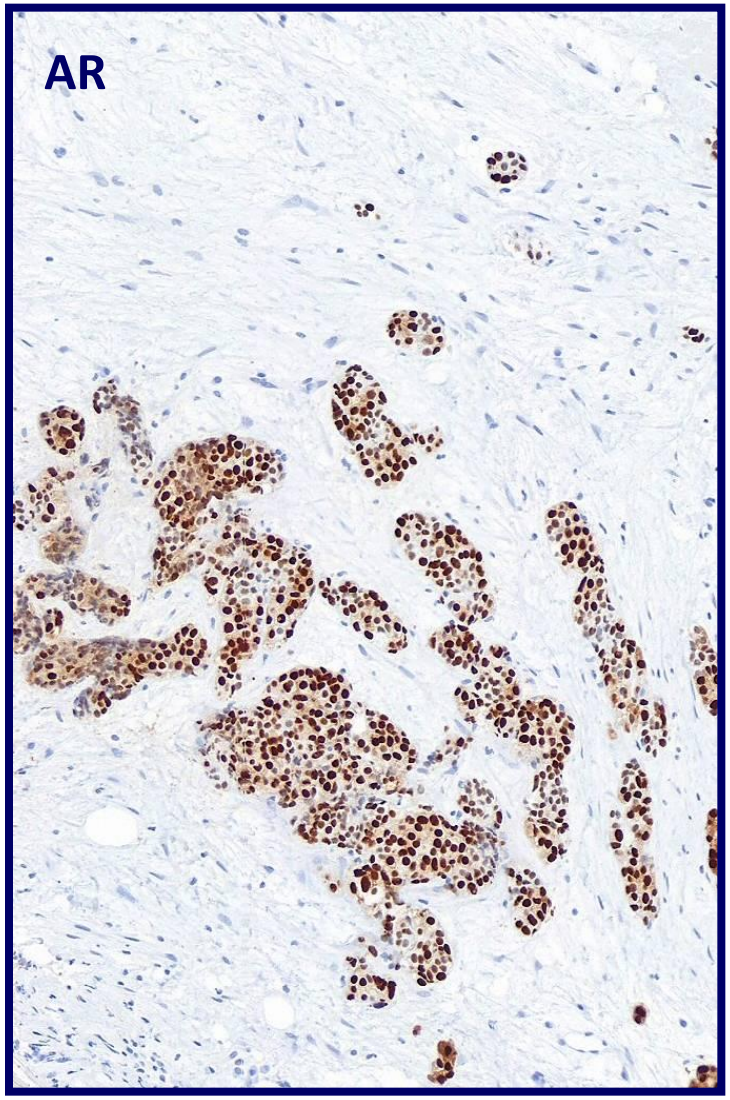

BLOOD VESSEL
ANDROGEN
NUCLEUS
GENES ON/OFF
AR
DNA
PROSTATE
CELL
GROWTH
(- INVASION)
(- IMMUNE EVASION)
(- IMMORTALITY)

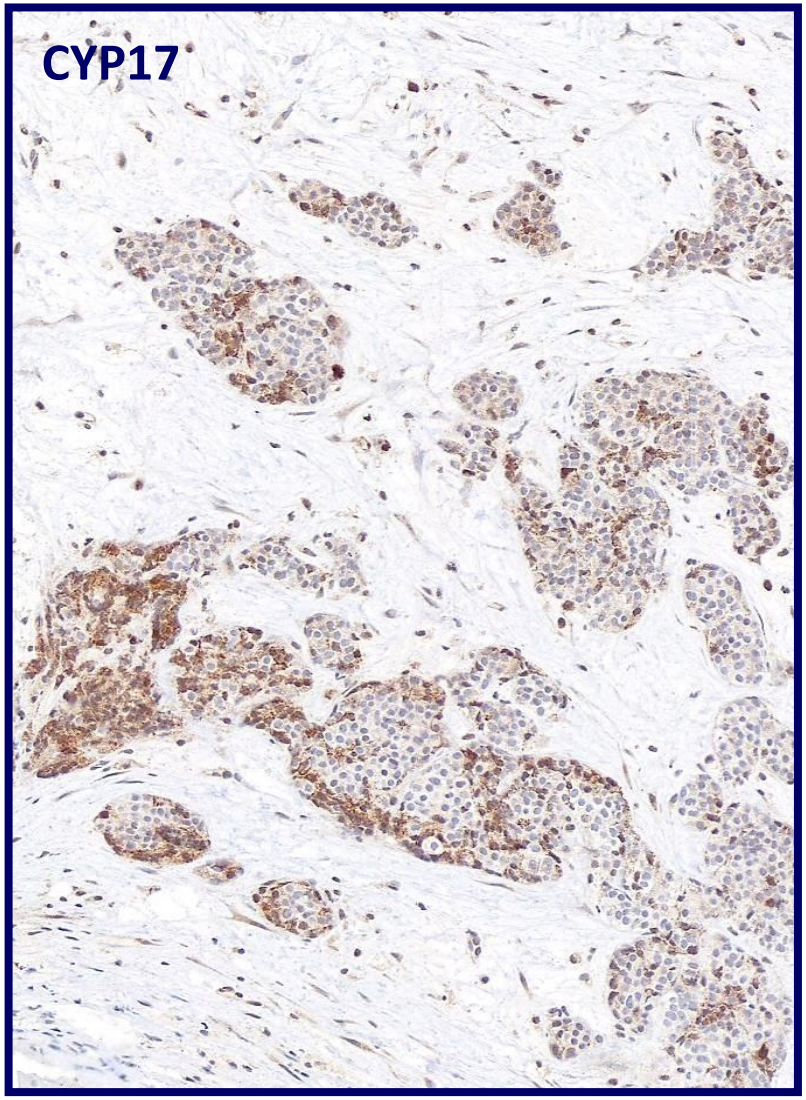
Potential post ADT mechanisms

- AR becomes ‘promiscuous’
- AR gets over-expressed
- Cancer cells make their own androgens
- AR mutates to become active without hormone
- Other signalling pathways activate abnormally
- Other

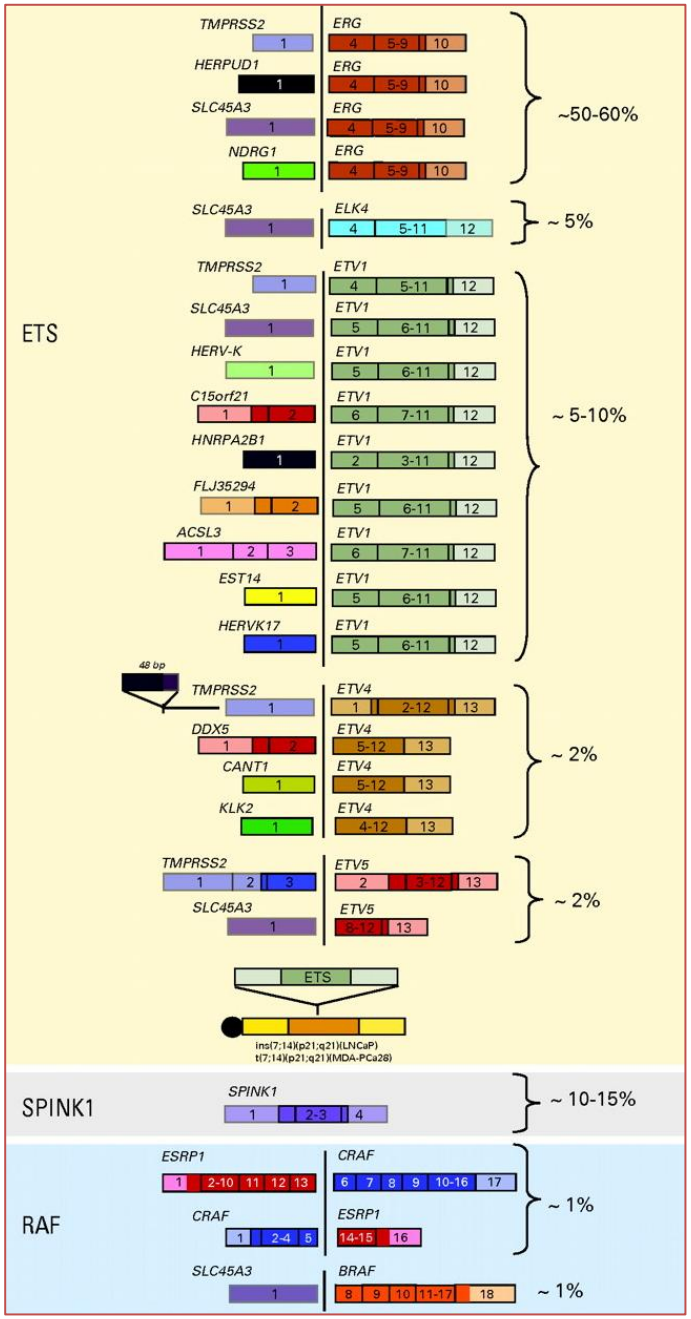


Persistent Androgen Signaling in CRPC With Bone Metastases





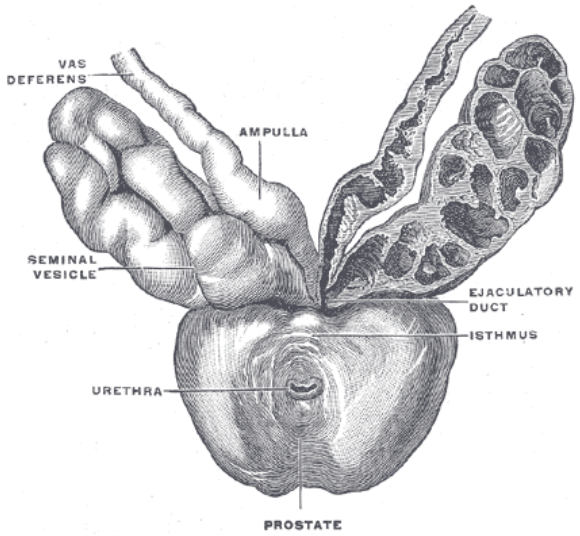
Efstathiou JCO 2012



Rubin JCO 2011

Biology conclusions

- Prostate cancer is driven by abnormal hormone signalling by androgens
- This is the case in virtually all stages of the disease pathway
- Hormonal therapy is central to this disease as a result
- Other signalling pathways are coming into focus with potential therapeutic implications



PATIENT SELECTION

Treatment selection

- Performance status
- PSA
- PSA velocity
- ‘Clinical velocity’
- Metastatic sites
- Prior therapy
- Response to prior therapy
- Small cell/neuroendocrine differentiation
- Co-morbidities
- Drug access?
- Age???

Treatment selection

- Performance status
- PSA
- PSA velocity
- [illegible]
- [illegible]
- [illegible]
- Response to prior therapy
- Small cell/neuroendocrine differentiation
- Co-morbidities
- Drug access?
- Age???

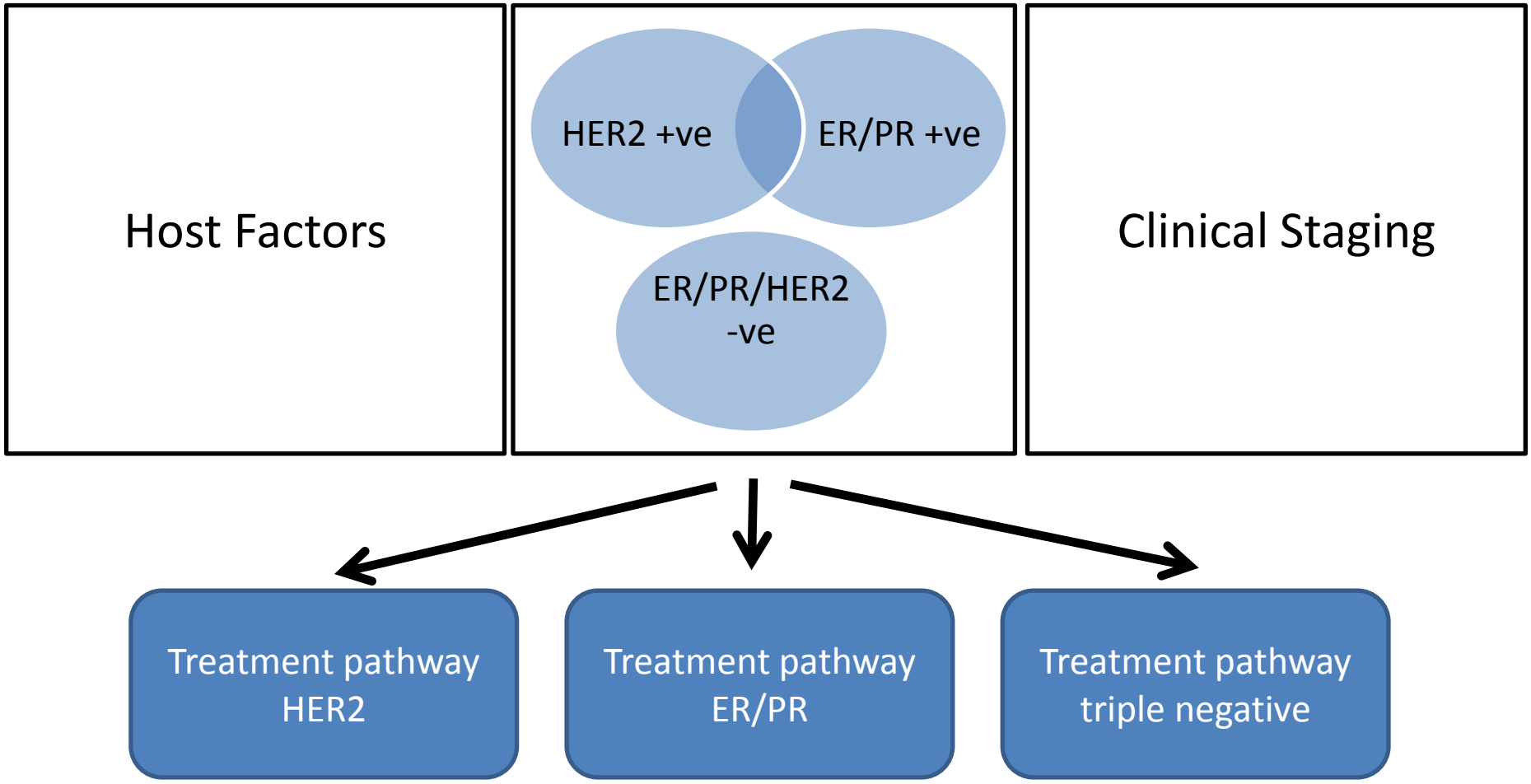
Patient choice

Treatment selection

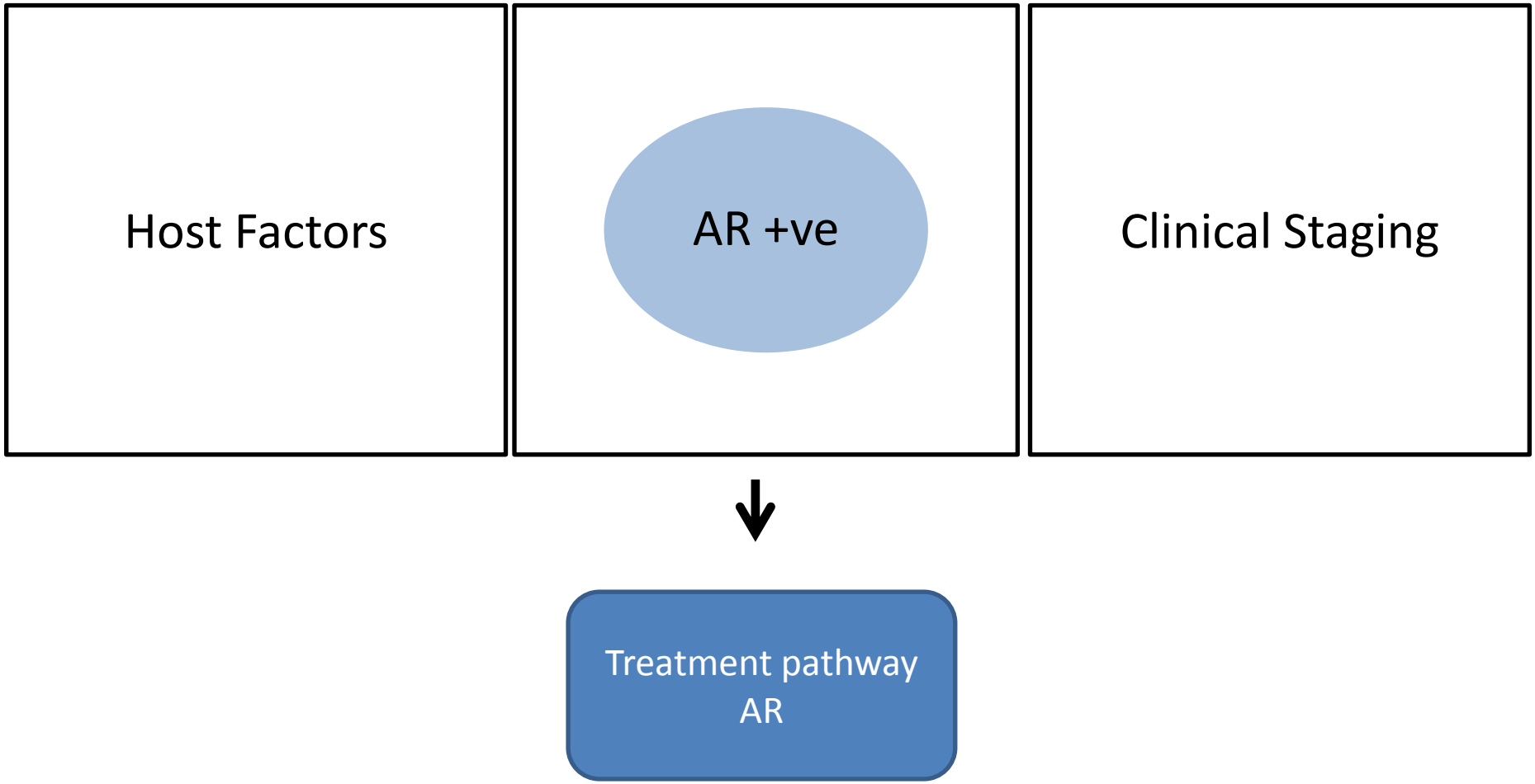
- Performance status
- PSA
- PSA
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- Age???

Patient's wife's choice?

Clever breast cancer treatment



Less clever prostate cancer treatment



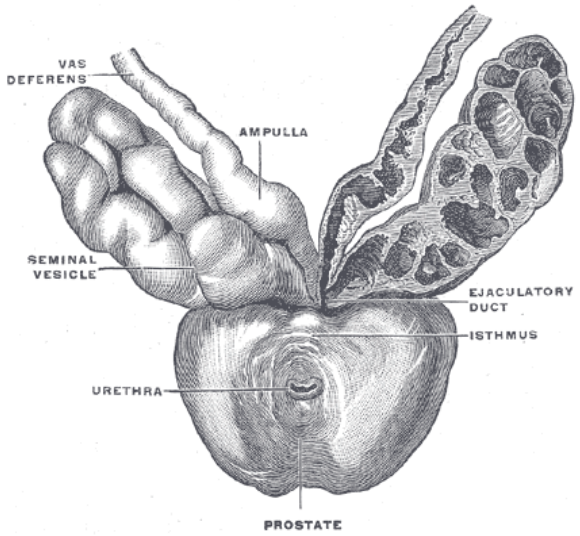
Best supportive care (alone) is always a treatment option.

Should we treat M0 disease that is biochemically progressive through ADT?

There is no evidence that doing this is of value.
But we do it a lot.
We should test this in clinical trials.

Patient selection conclusions

- Treatment selection is primarily driven by clinical factors
- We cant generally select by biology (yet)
- Selection strategies are perhaps our key research need
- When to treat in M0 disease is unclear



SECOND LINE HORMONAL THERAPY (OLD DRUGS)

Second line hormone therapies

- ADT effective for ~1-3 years on average
- No survival or QOL advantage proven for any conventional (i.e. older) second line agents
- Addition of an anti-androgen is ‘standard’
  - e.g. bicalutamide, flutamide, nilutamide
- Other old options
  - stilboestrol, ketoconazole, low dose steroids…

Bicalutamide post ADT (+/- F)

TABLE 2. *Effect of bicalutamide therapy*

Pt. No.	Age	Primary Hormone Therapy	Duration of Primary Hormonal Therapy Response (mos.)	Flutamide Withdrawal Response	Flutamide Response for Androgen Independent Prostate Ca	Starting PSA (ng./ml.)	% Decline PSA*	Change Karnofsky Performance Status†	Change Analgesic Use‡	Response Duration (mos.)
1	66	LHRH + flutamide for mo. 1 only	15	–	–	1,522	–	−10	5⇒5	–
2	71	LHRH + flutamide	20	No	–	411	86	+20	1⇒0	4
3	82	LHRH + flutamide	6	No	–	508	68	nc	1⇒1	3
4	64	Orchiectomy + flutamide	36	No	–	65	10	−10	1⇒2	–
5	68	LHRH + flutamide	12	No	–	1,328	25	−30	1⇒2	–
6	59	LHRH + flutamide	24	No	–	1,137	30	−20	3⇒4	–
7	71	Orchiectomy	36	–	12 Mos.	5,300	–	−10	1⇒3	–
8	54	LHRH + flutamide	10	No	–	260	–	−40	2⇒3	–
9	64	LHRH	24	–	No	1,458	–	−10	4⇒5	–
10	57	LHRH	18	–	No	430	–	−10	1⇒2	–
11	78	LHRH	6	–	No	195	–	−20	0⇒1	–
12	68	LHRH + flutamide	24	12 Mos.	–	32	Greater than 99	+10	3⇒0	13+§
13	47	LHRH + flutamide	48	No	–	139	–	−30	1⇒2	–
14	71	LHRH + flutamide	20	No	–	1,848	51	−20	1⇒2	4
15	87	Orchiectomy	24	No	No	176	44	nc	1⇒0	–
16	67	Orchiectomy	12	–	–	352	–	−10	1⇒1	–
17	84	LHRH	60	No	No	46	–	nc	0⇒1	–
18	80	Orchiectomy + flutamide	12	No	–	196	54	nc	1⇒1	3
19	79	Orchiectomy	18	No	No	1,160	–	nc	0⇒0	–
20	64	LHRH + flutamide	2	No	–	67	–	−30	2⇒3	–
21	90	Orchiectomy	42	–	–	365	–	nc	1⇒1	–
22	67	LHRH	42	–	–	173	–	−10	1⇒4	–
23	65	LHRH	40	–	–	18	94	nc	1⇒0	8
24	59	Orchiectomy	12	–	–	220	–	−20	2⇒3	–
25	82	Orchiectomy	54	–	–	621	–	−10	1⇒2	–
26	54	LHRH + flutamide	25	3 Mos.	No	55	Greater than 99	+10	1⇒0	9
27	79	Orchiectomy + flutamide	22	3 Mos.	–	138	10	+10	2⇒1	–
28	54	LHRH	2	–	–	189	–	−15	1⇒3	–
29	55	LHRH + flutamide	10	No	No	2,422	–	−10	5⇒5	–
30	78	Orchiectomy	18	–	–	54	–	−10	1⇒1	–
31	65	LHRH	16	–	–	146	–	−10	2⇒3	–

* Determined from initial of bicalutamide therapy

PSA response rate (>50%) = 22.5%

No QOL data

Joyce et al, J Urol, 1998

Nilutamide post ADT (+/- F or B)

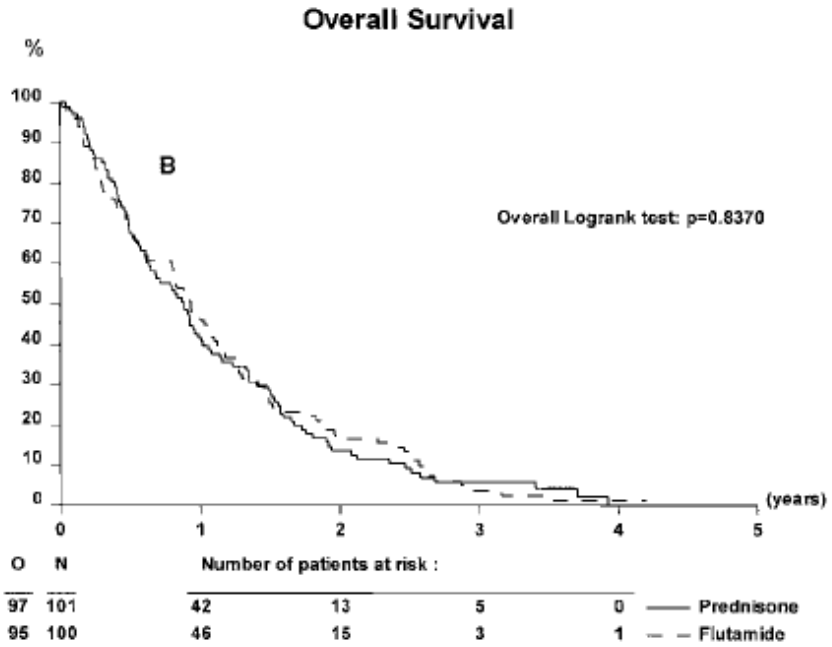
TABLE 2. *Study outcomes*

No. greater than 50% PSA response with nilutamide (%)	12 (43%)
No. greater than 50% PSA response with nilutamide and initial maximal androgen blockade	8
No. sustained greater than 50% PSA response with nilutamide for 3 mos. or more (%)	8 (29)
Overall mos. median followup (range)	26 (4–44)
Median mos. followup time of responders (range)	28 (8–33)

No QOL data

Kassouf et al, J Urol, 2003

Flutamide v prednisone post ADT



Parameter	Prednisone Group (n = 101)	Flutamide Group (n = 100)	Total (N = 201)
Response*,†	56	45	101
No change†	21	29	50
Progression†	16	21	37
Early death, malignant disease	1	0	1
Early death, other cause	1	1	2
Not assessable	4	2	6
Ineligible	2	2	4
Duration of response, months	4.8‡	4.2	4.6
Progression-free survival, months§	3.4‡	2.3	2.9
Overall survival, months	10.6‡	11.2	10.9

QOL data favoured prednisone

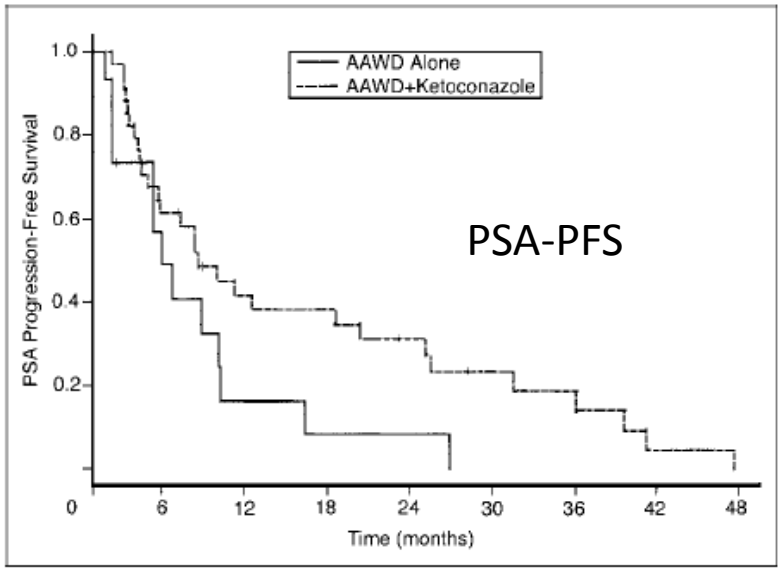
Fossa et al, JCO, 2001

Anti-androgen withdrawal response

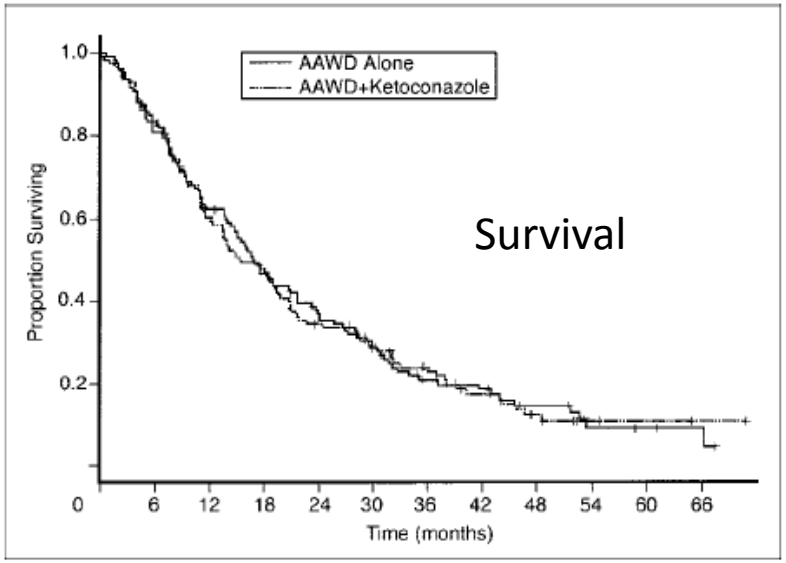
- 210 patients
  - 64% flutamide
  - 32% bicalutamide
  - 3% nilutamide
- 21% had confirmed PSA decrease > 50%
- No radiographic responses
- Median PFS 3 months (19% >12)
- Longer anti-androgen use predicted PSA response
- No QOL data

Sartor et al, Cancer, 2008

Ketoconazole



PSA-PFS



Survival

Table 4. Treatment-Related Grade 3 and 4 Toxicities

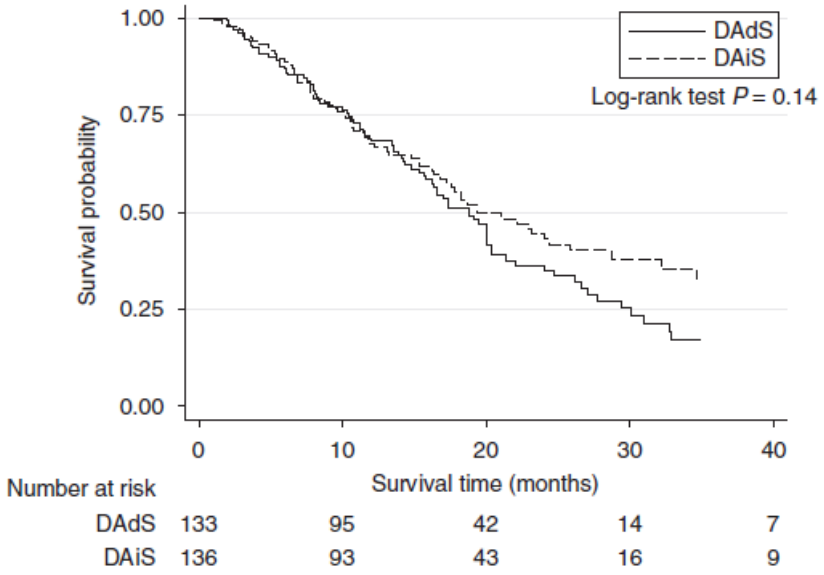
	% of Patients	
	AAWD Alone (n = 124)	AAWD and Ketoconazole (n = 124)
Hepatic toxicity	4	2
Anorexia	0	2
Neurotoxicity	0	4
Cardiotoxicity	0	1
Pulmonary	0	2
Coagulation	0	1
Nausea/vomiting	0	1
Malaise/fatigue	0	4

Abbreviation: AAWD, antiandrogen withdrawal.

No QOL data

Small et al, JCO, 2004

Stilboestrol



No QOL difference

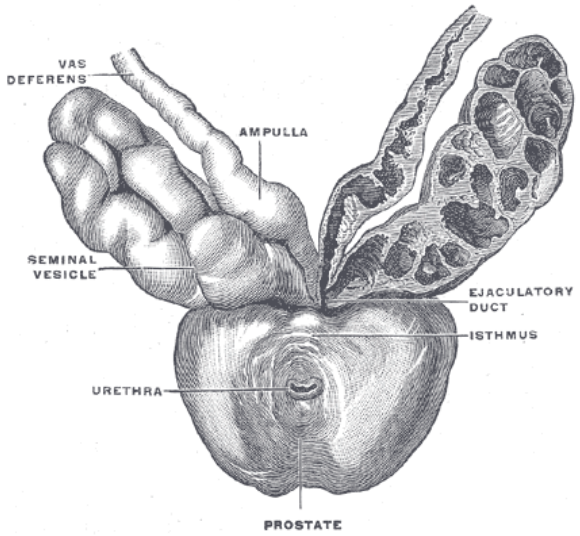
Table 4 Comparison of toxicity between DA and DAiS

Toxicity	All (*N* = 257) *N* (%)	DA (*N* = 128) *N* (%)	DAiS (*N* = 129) *N* (%)	*P*-value
Painful gynaecomastia	52 (20)	1 (01)	51 (40)	<0.001
Headaches	28 (11)	16 (13)	12 (09)	0.31
Skin	134 (52)	59 (46)	65 (50)	0.52
Fluid retention	117 (46)	54 (42)	63 (49)	0.26
Weight gain	32 (13)	14 (11)	18 (14)	0.47
Myopathy	5 (02)	4 (03)	1 (01)	0.25
Hyperglycaemia	4 (02)	3 (02)	1 (01)	0.51
VTE	42 (16)	14 (11)	28 (22)	0.02
DVT	20 (08)	3 (03)	17 (13)	
PE	21 (08)	11 (09)	10 (08)	
TIA	1 (0.5)	0 (0)	1 (01)	

Shamash et al, BJC, 2011

Second line hormones conclusions

- No survival or QOL benefit (other than prednisone> flutamide)
- 2nd line anti-androgen ('MAB') is 'standard' (but not-evidence based)
- None of this would not be approved today
- Some patients probably do benefit!



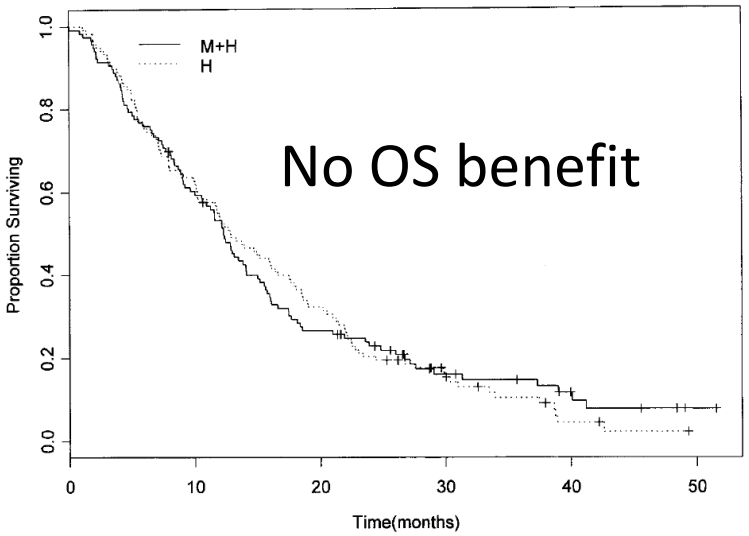
CHEMOTHERAPY

Mitoxantrone

mHRPC
Documented progression
n=242

R

- Hydrocortisone
- Hydrocortisone + Mitoxantrone



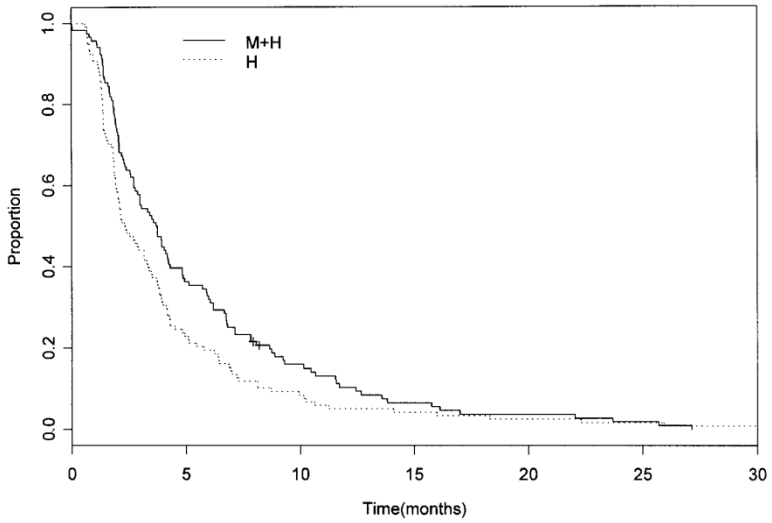
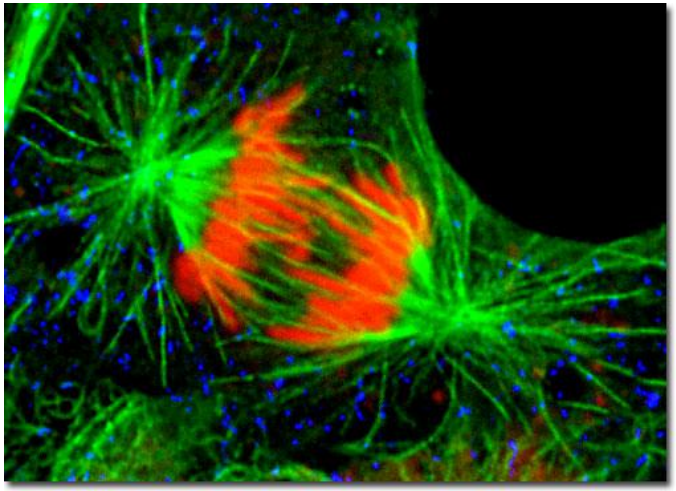


Table 5. Estimated Treatment Effects, Adjusting for Baseline Score and Stratification Factors

QOL Outcome	Estimated Difference*	SE	*P*
FLIC: total	− 4.34	2.74	.12
Symptom distress: total	0.05	0.92	.96
Sexual and urological function: total	0.08	0.57	.89
Problems in daily life: total	− 1.25	0.97	.20
Impact of pain: total	− 1.87	2.12	.38
FLIC: physical well-being	− 1.90	1.79	.29
FLIC: emotional state	− 1.42	0.69	.04
FLIC: family disruption	− 0.93	0.39	.02
FLIC item: pain from cancer	0.35	0.31	.26
FLIC item: pain interferes	− 0.18	0.22	.43
Symptom distress item: pain, how often	− 0.30	0.15	.06
Symptom distress item: pain, how severe	− 0.28	0.13	.03
Symptom distress item: appetite	0.08	0.14	.59
Symptom distress item: fatigue	− 0.06	0.14	.68

Kantoff et al, JCO, 1999

Docetaxel



mHRPC

Documented progression

PS 0-2

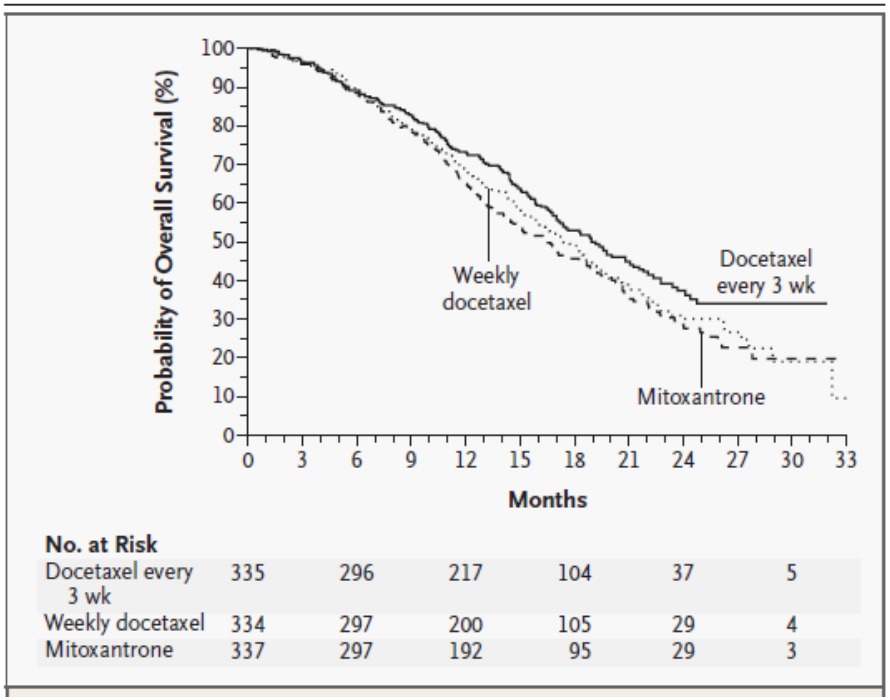
n=1006

R

- Mitoxantrone + Prednisolone
- Docetaxel 3 weekly + Prednisolone
- Docetaxel weekly + Prednisolone

Tannock et al, NEJM, 2004

Docetaxel



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Median survival

- D3 – 19.2 months
- D1 – 17.8 months
- M – 16.3 months

Improvements also seen in:

- QOL
- Pain
- PSA response

Berthold et al, JCO, 2008
Tannock et al, NEJM, 2004

Docetaxel

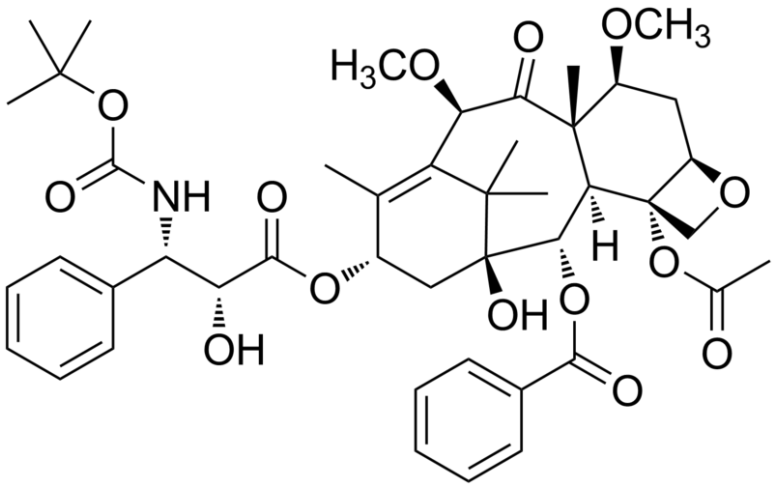
Table 4. Adverse Events of Any Grade, or of Grade 3 or 4, That Occurred or Worsened during Treatment.

Adverse Event	Docetaxel Every 3 Wk (N=332)	Weekly Docetaxel (N=330)	Mitoxantrone Every 3 Wk (N=335)
		percent	
Grade 3 or 4 anemia	5	5	2
Grade 3 or 4 thrombocytopenia	1	0	1
Grade 3 or 4 neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF‡	10†	8†	22
Major decrease	1†	2*	7
Fatigue	53†	49†	35
Grade 3 or 4	5	5	5
Alopecia	65†	50†	13
Nausea, vomiting, or both	42	41	38
Diarrhea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral edema	19†	12†	1
Epistaxis	6	17†	2
≥1 Serious adverse event	26	29	20
Treatment-related death	0.3	0.3	1

Tannock et al, NEJM, 2004

Cabazitaxel

- Semi-synthetic taxane
- Anti-tumour activity in models resistant to paclitaxel and docetaxel



mCRPC

Documented progression

Prior docetaxel

PS 0–2

N=755

R

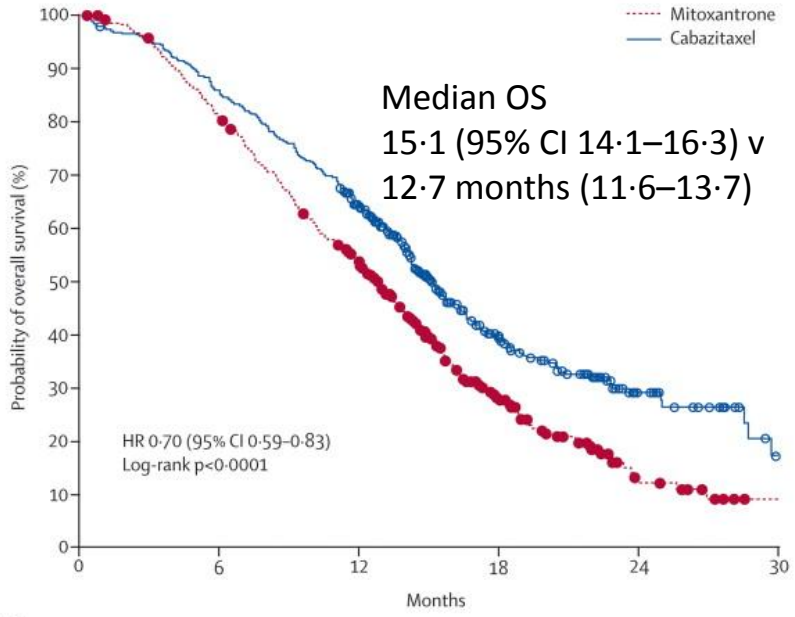
Cabazitaxel + prednisoline

Mitoxantrone + prednisolone

De Bono et al, Lancet, 2010

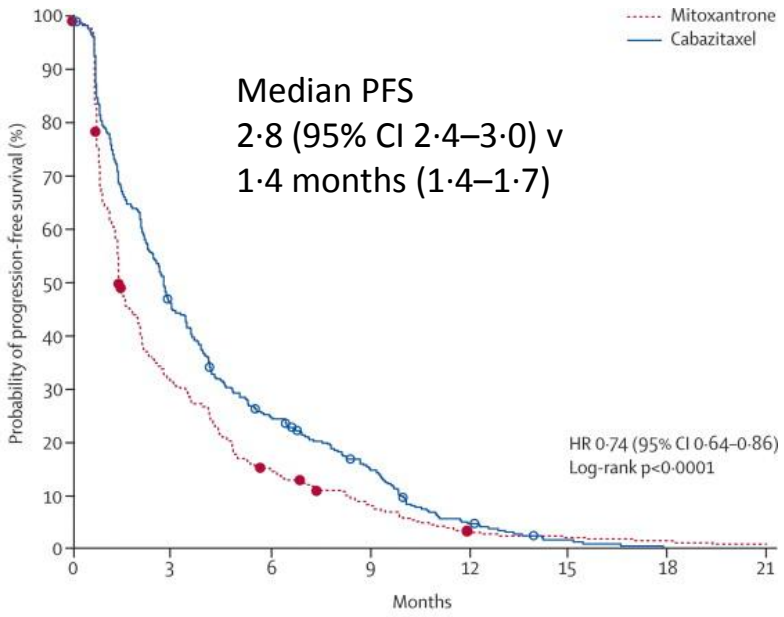
Cabazitaxel

A



Median OS
15·1 (95% CI 14·1–16·3) v
12·7 months (11·6–13·7)

Number at risk						
Mitoxantrone	377	300	188	67	11	1
Cabazitaxel	378	321	231	90	28	4



Median PFS
2·8 (95% CI 2·4–3·0) v
1·4 months (1·4–1·7)

Number at risk								
Mitoxantrone	377	115	52	27	9	6	4	2
Cabazitaxel	378	168	90	52	15	4	0	0

De Bono et al, Lancet, 2010

	Mitoxantrone	Cabazitaxel	Hazard ratio (95% CI)	p value for comparison
Tumour response rate*				
Number of evaluable patients	204	201	..	..
Response rate (%)	4·4% (1·6–7·2)	14·4% (9·6–19·3)	..	0·0005
PSA response rate†				
Number of evaluable patients	325	329	..	..
Response rate (%)	17·8% (13·7–22·0)	39·2% (33·9–44·5)	..	0·0002
Pain response rate‡				
Number of evaluable patients	168	174	..	..
Response rate (%)	7·7% (3·7–11·8)	9·2% (4·9–13·5)	..	0·63
Progression				
Number of patients in intention-to-treat analysis	377	378	..	..
Median time to tumour progression (months)	5·4 (2·3–10·0)	8·8 (3·9–12·0)	0·61 (0·49–0·76)	<0·0001
Median time to PSA progression (months)	3·1 (0·9–9·1)	6·4 (2·2–10·1)	0·75 (0·63–0·90)	0·001
Median time to pain progression (months)§	Not reached	11·1 (2·9–not reached)	0·91 (0·69–1·19)	0·52

No QOL data in this trial

De Bono et al, Lancet, 2010

	Mitoxantrone (n=371)		Cabazitaxel (n=371)	
	All grades	Grade ≥3	All grades	Grade ≥3
Haematological†				
Neutropenia	325 (88%)	215 (58%)	347 (94%)	303 (82%)
Febrile neutropenia	..	5 (1%)	..	28 (8%)
Leukopenia	343 (92%)	157 (42%)	355 (96%)	253 (68%)
Anaemia	302 (81%)	18 (5%)	361 (97%)	39 (11%)
Thrombocytopenia	160 (43%)	6 (2%)	176 (47%)	15 (4%)
Non-haematological				
Diarrhoea	39 (11%)	1 (<1%)	173 (47%)	23 (6%)
Fatigue	102 (27%)	11 (3%)	136 (37%)	18 (5%)
Asthenia	46 (12%)	9 (2%)	76 (20%)	17 (5%)
Back pain	45 (12%)	11 (3%)	60 (16%)	14 (4%)
Nausea	85 (23%)	1 (<1%)	127 (34%)	7 (2%)
Vomiting	38 (10%)	0	84 (23%)	7 (2%)
Haematuria	14 (4%)	2 (1%)	62 (17%)	7 (2%)
Abdominal pain	13 (4%)	0	43 (12%)	7 (2%)
Pain in extremity	27 (7%)	4 (1%)	30 (8%)	6 (2%)
Dyspnoea	17 (5%)	3 (1%)	44 (12%)	5 (1%)
Constipation	57 (15%)	2 (1%)	76 (20%)	4 (1%)
Pyrexia	23 (6%)	1 (<1%)	45 (12%)	4 (1%)
Arthralgia	31 (8%)	4 (1%)	39 (11%)	4 (1%)
Urinary-tract infection	11 (3%)	3 (1%)	27 (7%)	4 (1%)
Pain	18 (5%)	7 (2%)	20 (5%)	4 (1%)
Bone pain	19 (5%)	9 (2%)	19 (5%)	3 (1%)

De Bono et al, Lancet, 2010

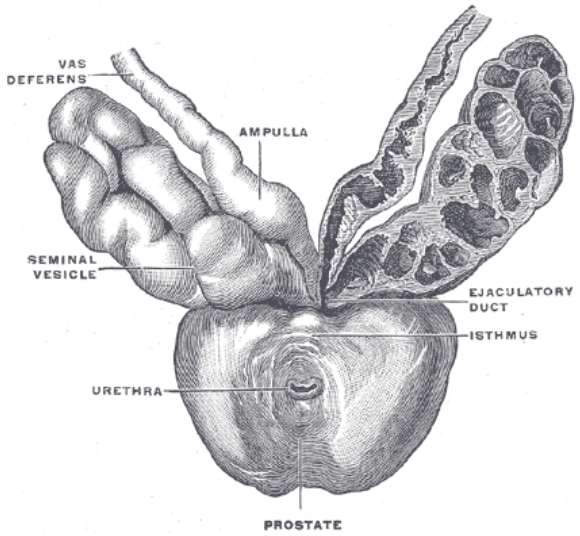
Causes of death

	Mitoxantrone (n=371)	Cabazitaxel (n=371)
Total deaths during the study	275 (74%)	227 (61%)
Deaths ≤30 days after last dose of study drug	9 (2%)	18 (5%)
Causes of death ≤30 days after last dose of study drug		
Disease progression	6 (2%)*	0
Adverse events		
Neutropenia and clinical consequences/sepsis	1 (<1%)	7 (2%)
Cardiac	0	5 (1%)
Dyspnoea†	1 (<1%)	0
Dehydration/electrolyte imbalance	0	1 (<1%)
Renal failure	0	3 (1%)
Cerebral haemorrhage	0	1 (<1%)
Unknown cause	0	1 (<1%)
Motor vehicle accident	1 (<1%)	0
Deaths >30 days after last dose of study drug	266 (72%)	209 (56%)

De Bono et al, Lancet, 2010

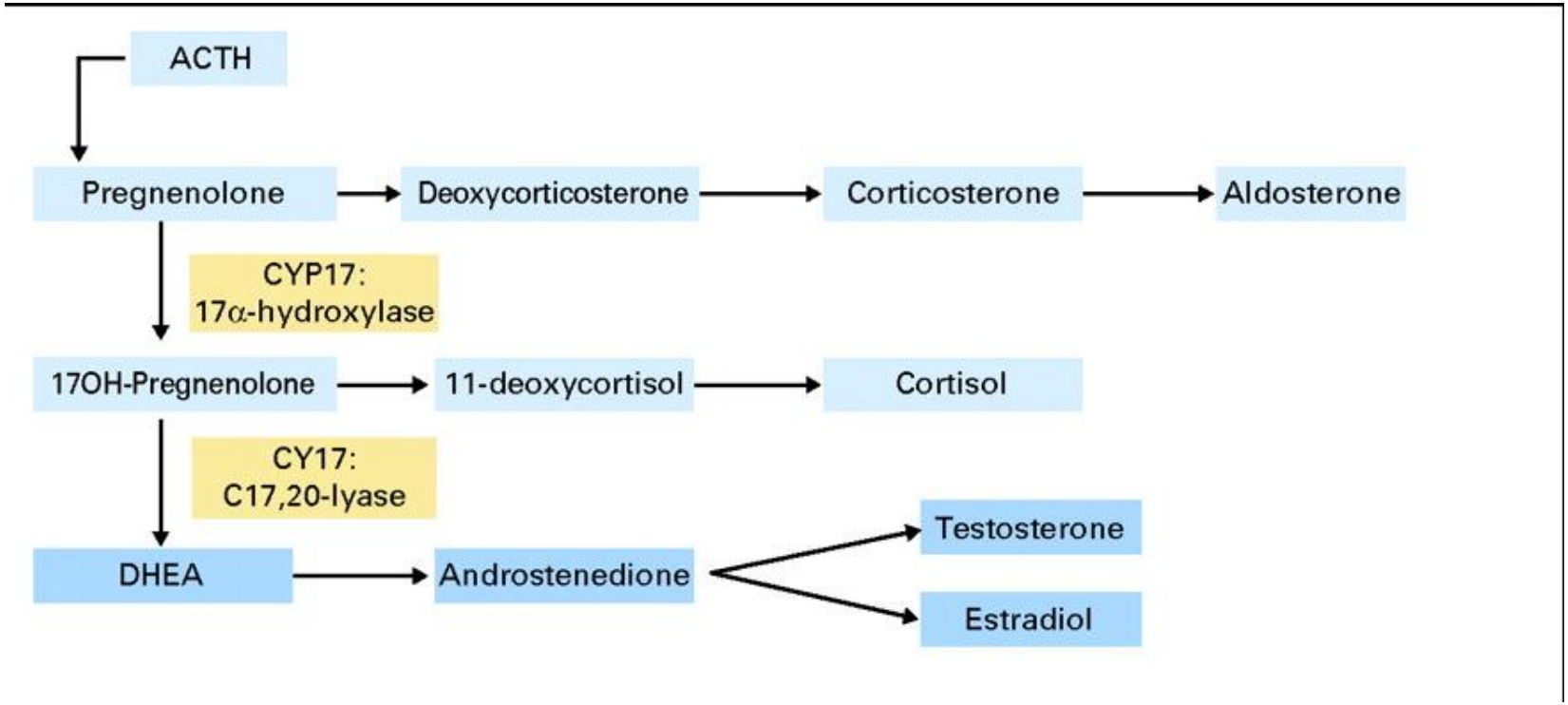
Chemotherapy conclusions

- Docetaxel remains the first line standard of care
  - Only viable in about 50% of patients
  - Modest improvement in survival
- Cabazitaxel now 2nd line standard for chemotherapy
- Predictors of toxicity and benefit required
- Unclear how to sequence with new drugs



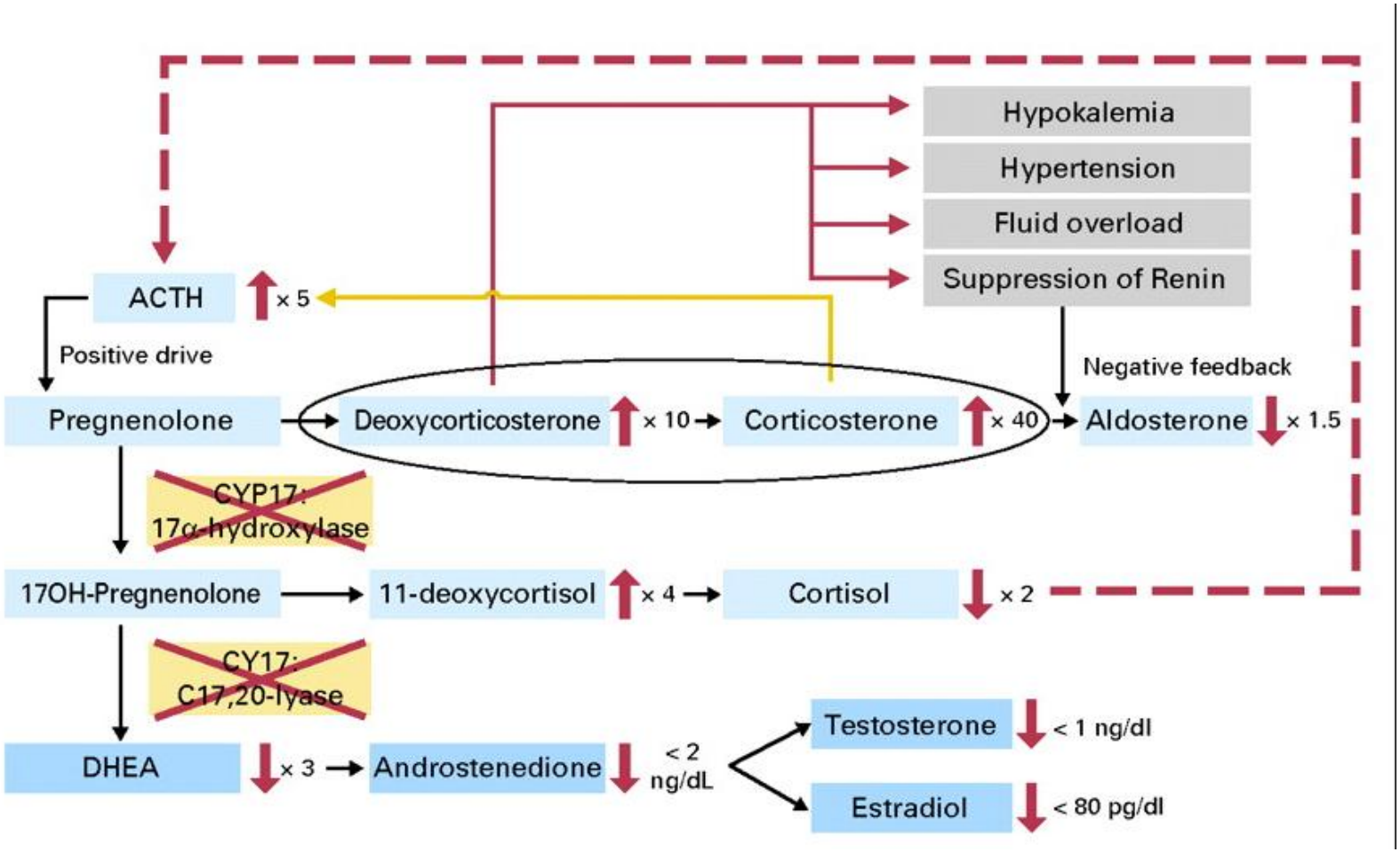
NEW HORMONAL THERAPIES

Steroid Hormone Synthesis



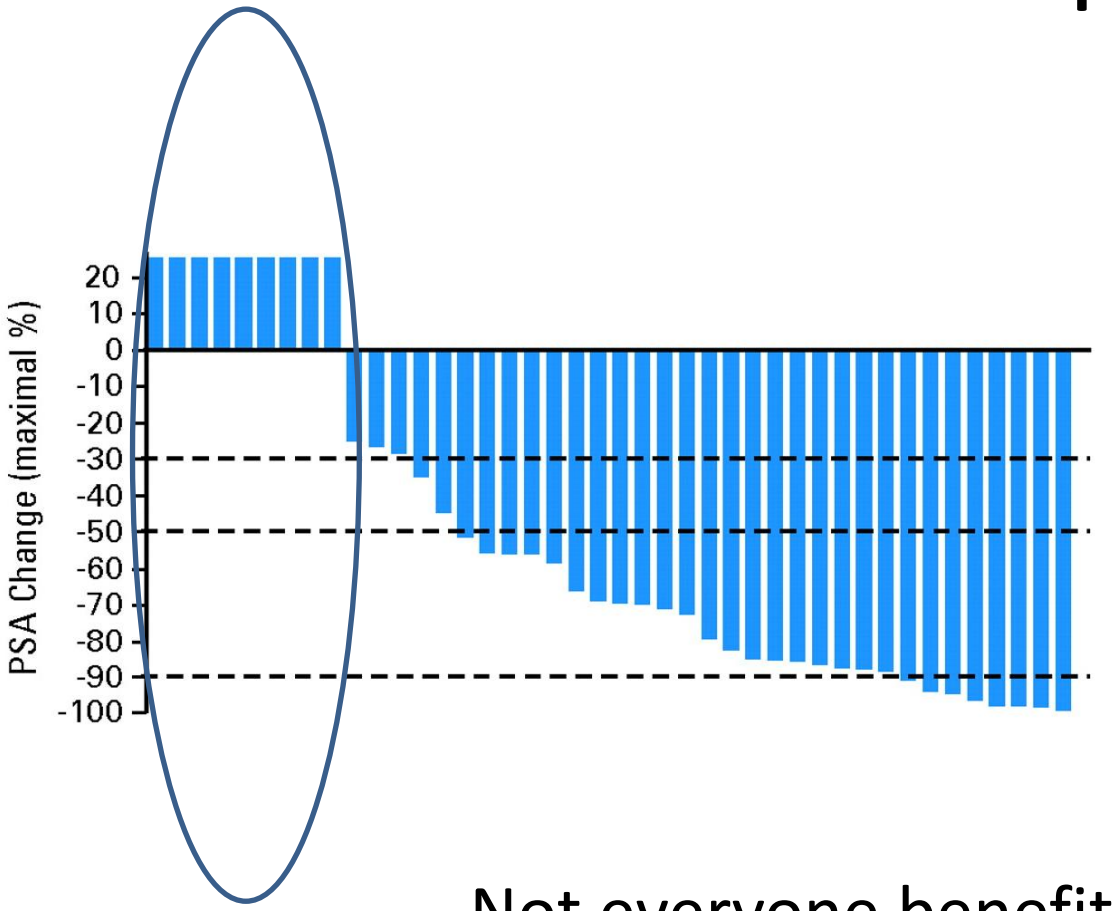
Attard, G. et al. J Clin Oncol; 26:4563-4571 2008

Abiraterone Mechanism



Attard, G. et al. J Clin Oncol; 26:4563-4571 2008

Phase II abiraterone PSA responses

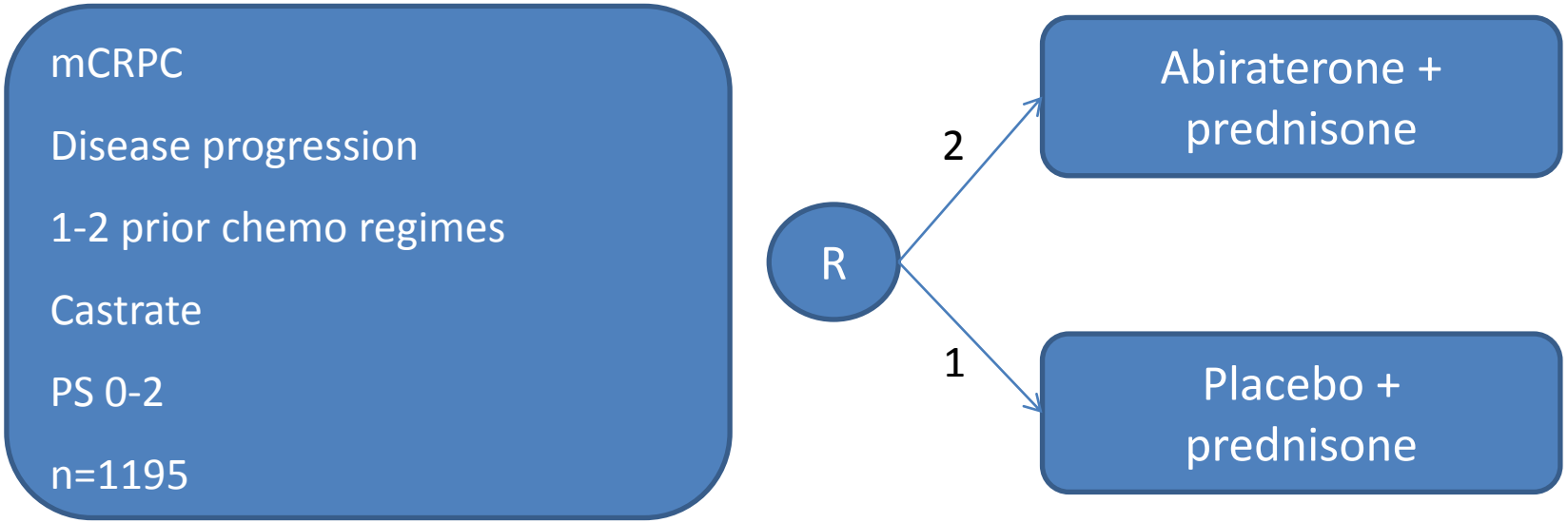


Not everyone benefits

BUT this is CRPC after chemo!

Attard, G. et al. J Clin Oncol; 26:4563-4571 2008

COU-AA-301 design



de Bono et al, NEJM 2011

COU-AA-301 survival outcome

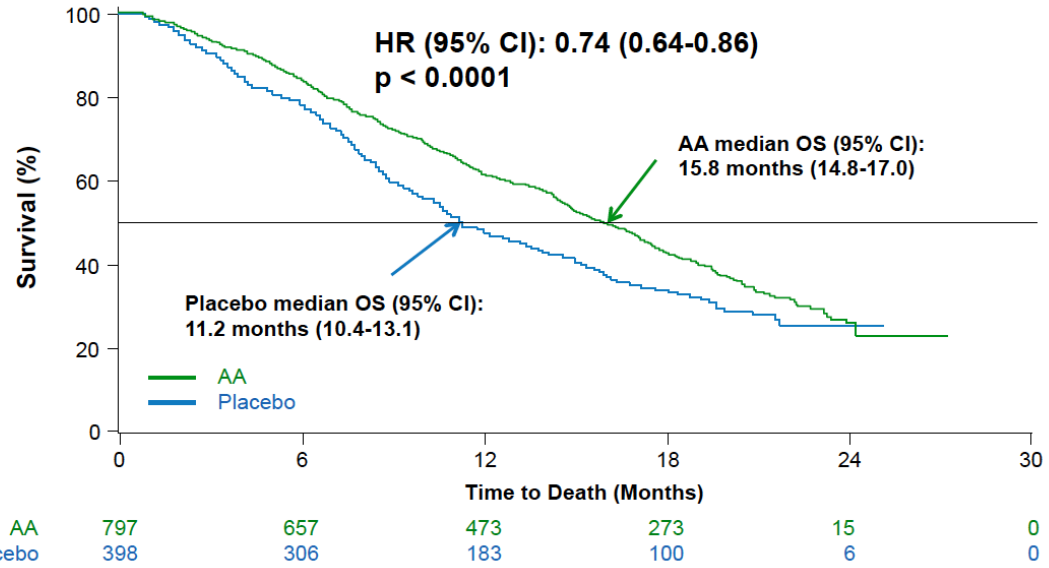


Table 3. Secondary End Points.*

Variable	Abiraterone Acetate (N=797)	Placebo (N=398)	Hazard Ratio (95% CI)	P Value
Time to PSA progression (mo)	10.2	6.6	0.58 (0.46–0.73)	<0.001
Progression-free survival according to radiographic evidence (mo)	5.6	3.6	0.67 (0.59–0.78)	<0.001
PSA response rate (%)				
Total	38.0	10.1		<0.001
Confirmed response on the basis of the PSA concentration	29.1	5.5		<0.001
Objective response on the basis of imaging studies	14.0	2.8		<0.001

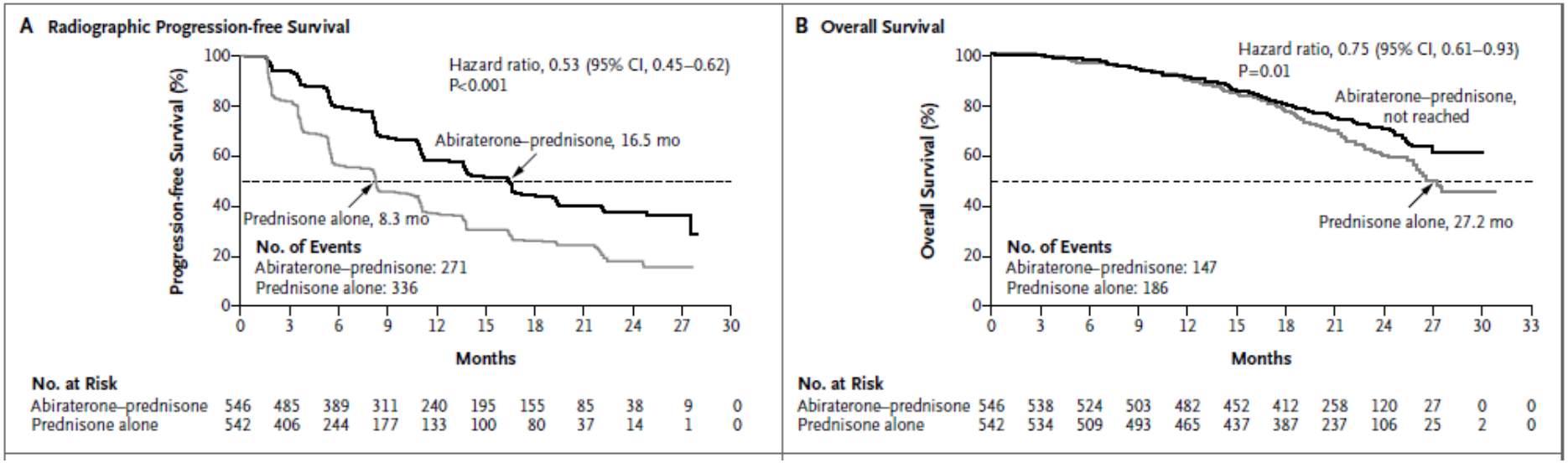
de Bono et al, NEJM 2011

Table 4. Adverse Events.

Event	Abiraterone Acetate (N=791)			Placebo (N=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number (percent)					
Anemia	178 (23)	51 (6)	8 (1)	104 (26)	23 (6)	6 (2)
Thrombocytopenia	28 (4)	8 (1)	3 (<1)	13 (3)	1 (<1)	1 (<1)
Neutropenia	7 (1)	1 (<1)	0	1 (<1)	1 (<1)	0
Febrile neutropenia	0	0	0	0	0	0
Diarrhea	139 (18)	5 (1)	0	53 (14)	5 (1)	0
Fatigue	346 (44)	64 (8)	2 (<1)	169 (43)	36 (9)	3 (1)
Asthenia	104 (13)	18 (2)	0	52 (13)	7 (2)	1 (<1)
Back pain	233 (30)	44 (6)	3 (<1)	129 (33)	37 (9)	1 (<1)
Nausea	233 (30)	12 (2)	1 (<1)	124 (32)	10 (3)	0
Vomiting	168 (21)	13 (2)	1 (<1)	97 (25)	11 (3)	0
Hematuria	65 (8)	11 (1)	0	31 (8)	9 (2)	0
Abdominal pain	95 (12)	16 (2)	0	44 (11)	6 (2)	0
Pain in arm or leg	134 (17)	18 (2)	1 (<1)	79 (20)	20 (5)	0
Dyspnea	102 (13)	8 (1)	2 (<1)	46 (12)	7 (2)	2 (<1)
Constipation	206 (26)	8 (1)	0	120 (31)	4 (1)	0
Pyrexia	71 (9)	3 (<1)	0	35 (9)	5 (1)	0
Arthralgia	215 (27)	33 (4)	0	89 (23)	16 (4)	0
Urinary tract infection	91 (12)	17 (2)	0	28 (7)	2 (<1)	0
Pain	13 (2)	5 (1)	0	19 (5)	6 (2)	1 (<1)
Bone pain	194 (25)	42 (5)	2 (<1)	110 (28)	25 (6)	4 (1)
Fluid retention and edema	241 (31)	16 (2)	2 (<1)	88 (22)	4 (1)	0
Hypokalemia	135 (17)	27 (3)	3 (<1)	33 (8)	3 (1)	0
Cardiac disorder*	106 (13)	26 (3)	7 (1)	42 (11)	7 (2)	2 (<1)
Liver-function test abnormalities	82 (10)	25 (3)	2 (<1)	32 (8)	10 (3)	2 (<1)
Hypertension	77 (10)	10 (1)	0	31 (8)	1 (<1)	0

de Bono et al, NEJM 2011

COU-AA-302



Ryan et al, NEJM, 2012

COU-AA-302

Table 1. Prespecified Secondary and Exploratory Efficacy End Points.*

End Point	Abiraterone–Prednisone (N = 546)	Prednisone Alone (N = 542)	Value (95% CI)†	P Value
Secondary end points				
Median time to opiate use for cancer-related pain — mo	NR	23.7	0.69 (0.57–0.83)	<0.001
Median time to initiation of cytotoxic chemotherapy — mo	25.2	16.8	0.58 (0.49–0.69)	<0.001
Median time to decline in ECOG performance score by ≥1 point — mo	12.3	10.9	0.82 (0.71–0.94)	0.005
Median time to PSA progression — mo‡	11.1	5.6	0.49 (0.42–0.57)	<0.001
Exploratory end points§				
Median time to increase in pain — mo¶	26.7	18.4	0.82 (0.67–1.00)	0.049
Median time to functional-status decline measured as FACT-P total score — mo‖	12.7	8.3	0.78 (0.66–0.92)	0.003
Patients with decline of ≥50% in PSA level — %**	62	24	2.59 (2.19–3.05)††	<0.001
Patients with a RECIST response — %‡‡				
Defined objective response	36	16	2.27 (1.59–3.25)††	<0.001
Stable disease	61	69		
Progressive disease	2	15		

Ryan et al, NEJM, 2012

AFFIRM design

mCRPC

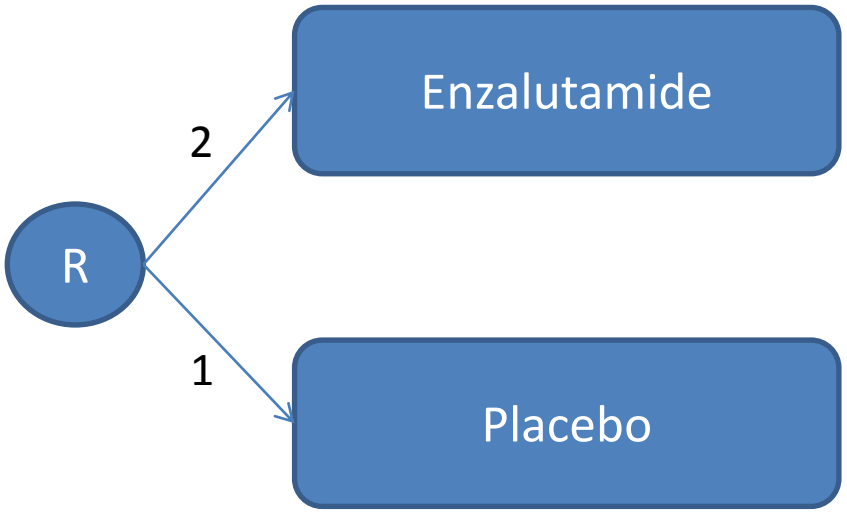
Disease progression

1 or more prior chemo regimes

Castrate

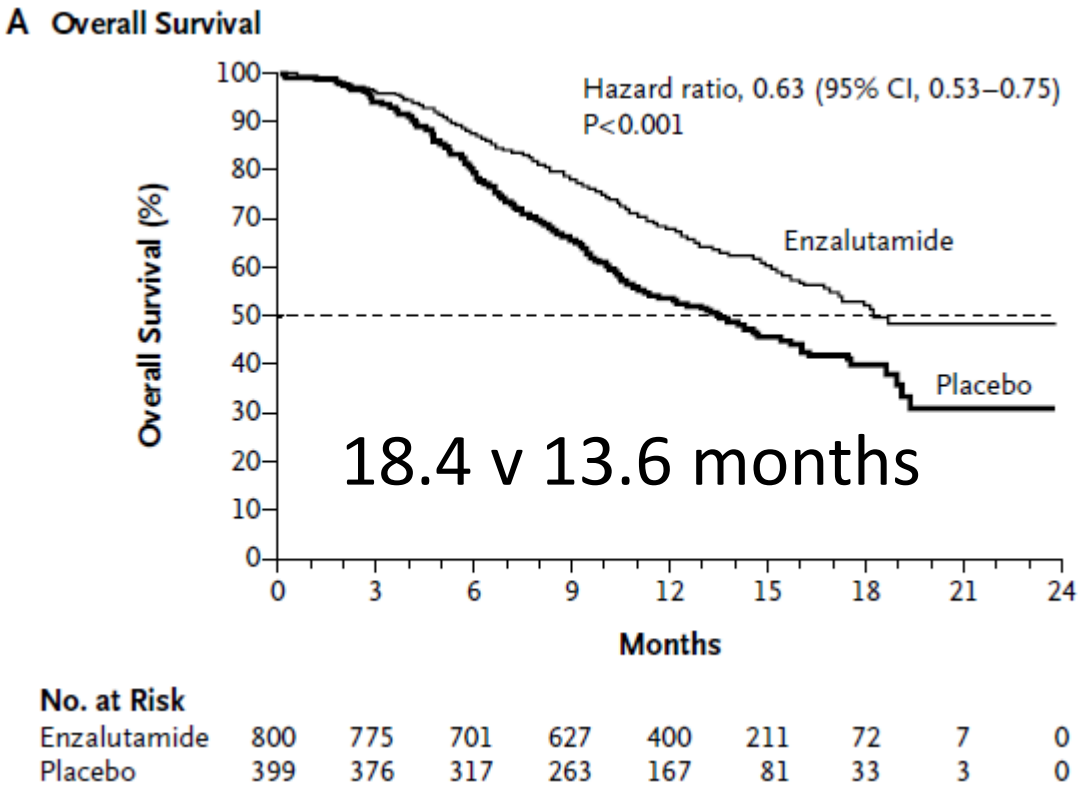
PS 0-2

n=1199

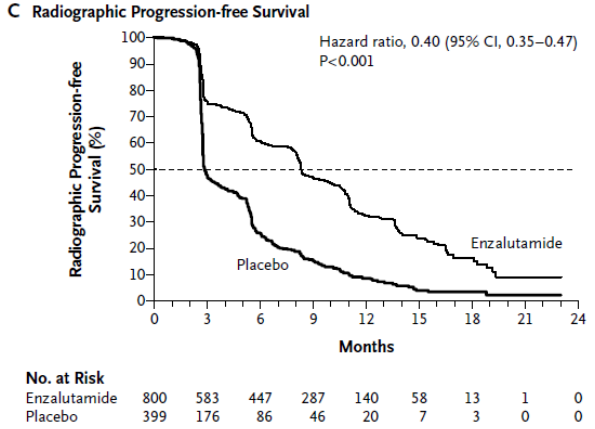


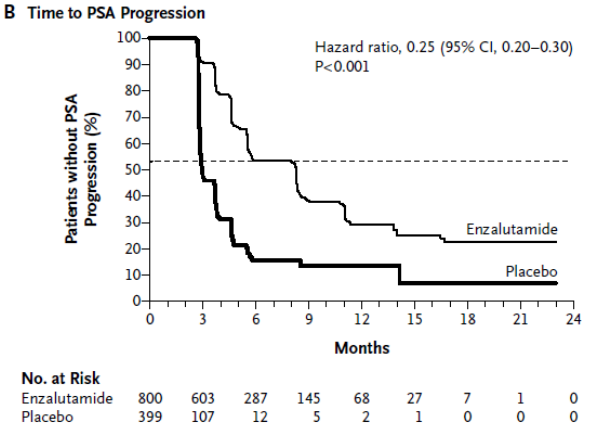
Scher et al, NEJM 2012

Enzalutamide (MDV3100)



18.4 v 13.6 months





QOL benefit also seen

Scher et al, NEJM 2012

Enzalutamide (MDV3100)

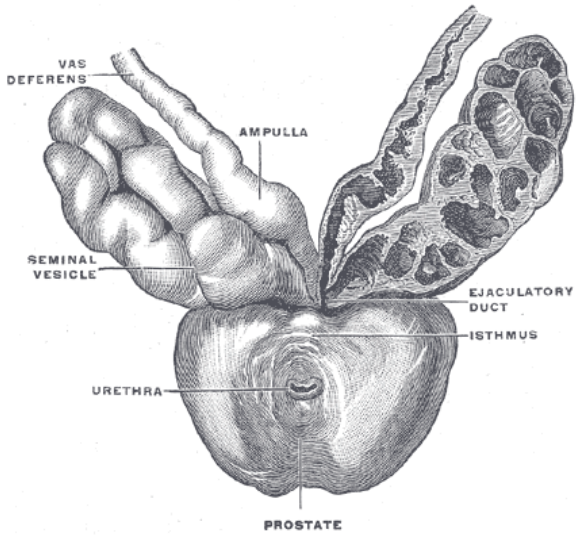
Table 3. Adverse Events, According to Grade.

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

Scher et al, NEJM 2012

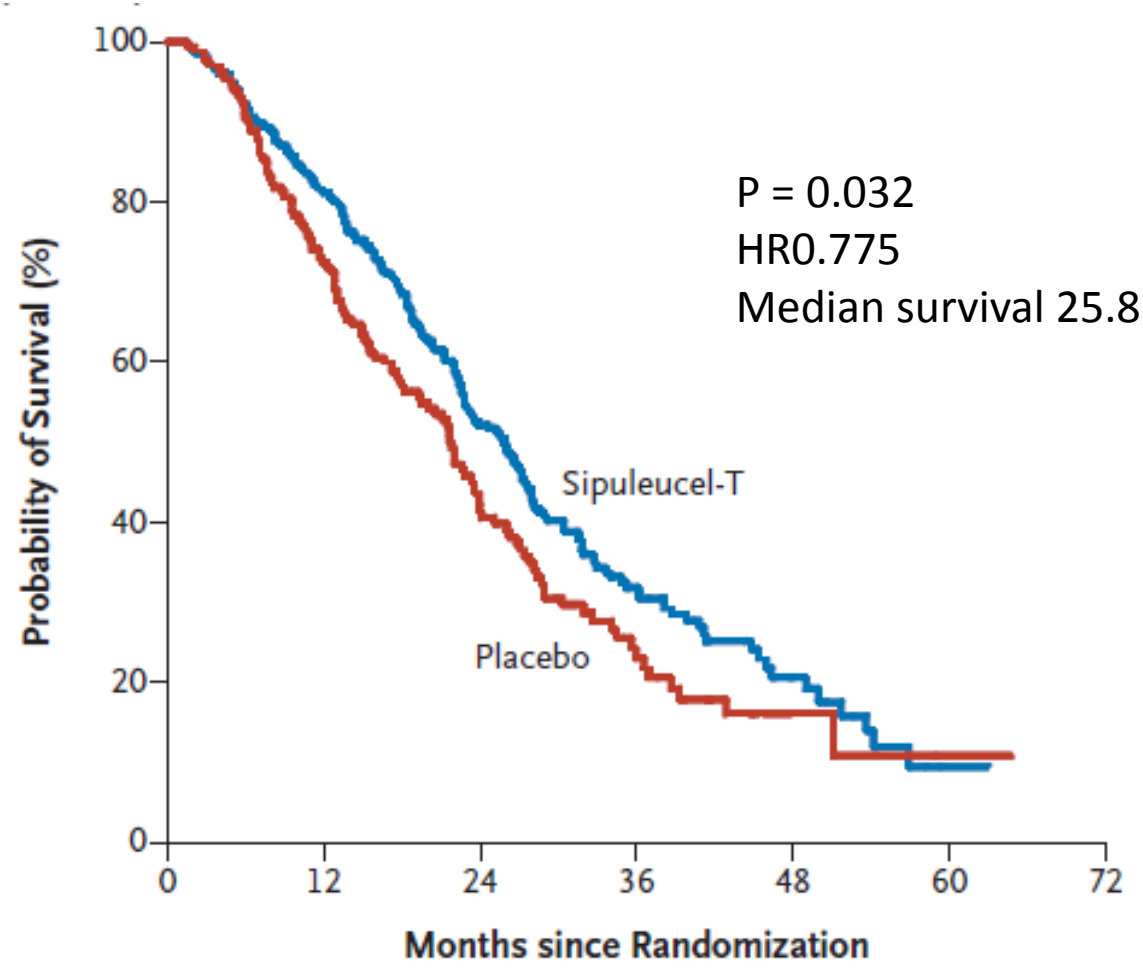
New hormonal therapy conclusions

- Abiraterone and enzalutamide prove AR signalling remains critical throughout
- Relatively easy treatments
- We don’t know when best to use them
- Predictors of benefit required



IMMUNOTHERAPY

Sipuleucel T

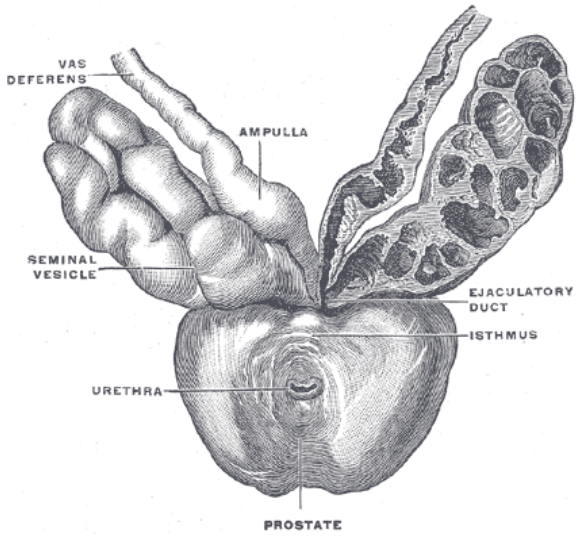


P = 0.032
HR0.775
Median survival 25.8 v 21.7 months

Sipuleucel conclusions

- Proves immunotherapy can work
- Probably in minimally symptomatic patients without visceral disease
- Minimal toxicity

- An irrelevance in the UK? - $93000

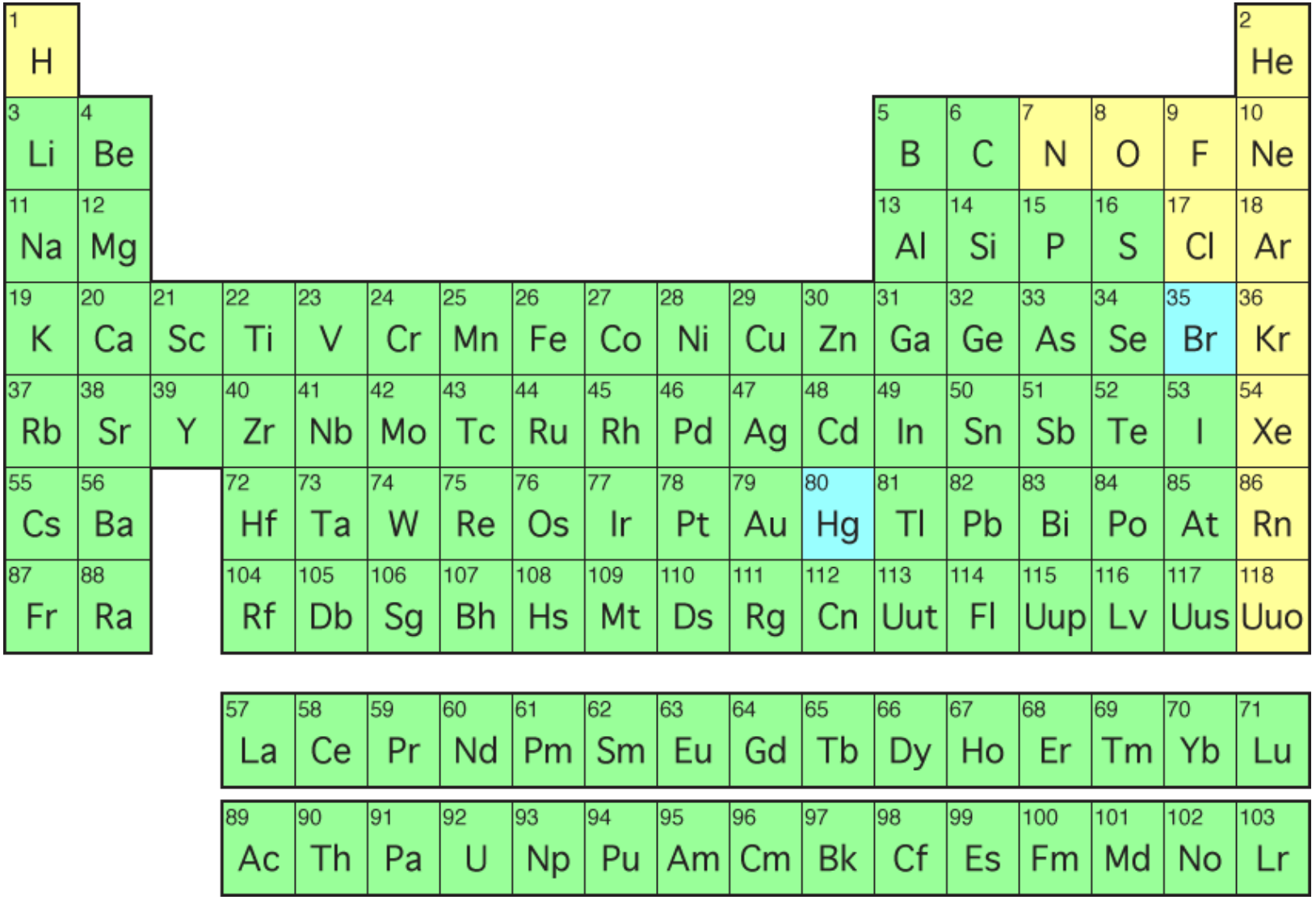


RADIO-PHARMACEUTICALS

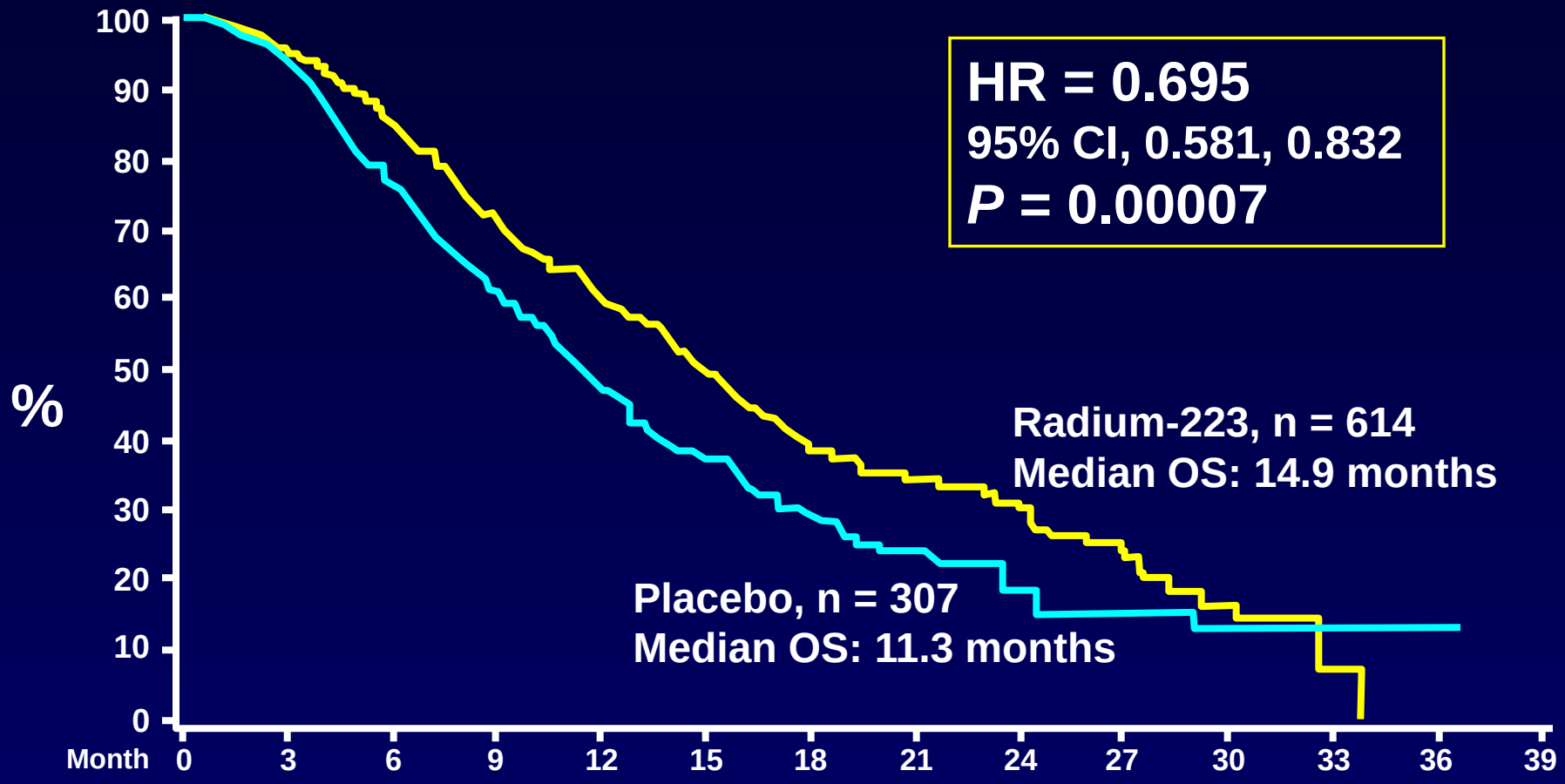
Radionuclides

- Strontium 89
- Samarium 153
- Rhenium 186
- Alpharadin

Periodic table



Alpharadin

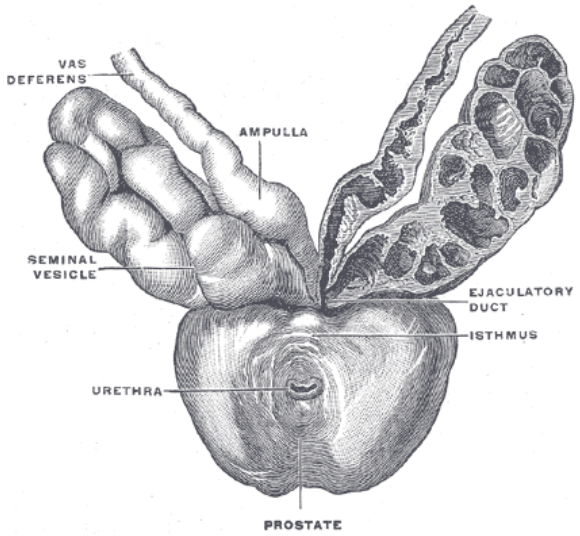


Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Vogelzang, J Clin Oncol 31, 2013 (suppl 6; abstr 11)

Alphardin

- Improvements also seen in
  - QOL
  - Time to first SRE
- Generally good toxicity profile

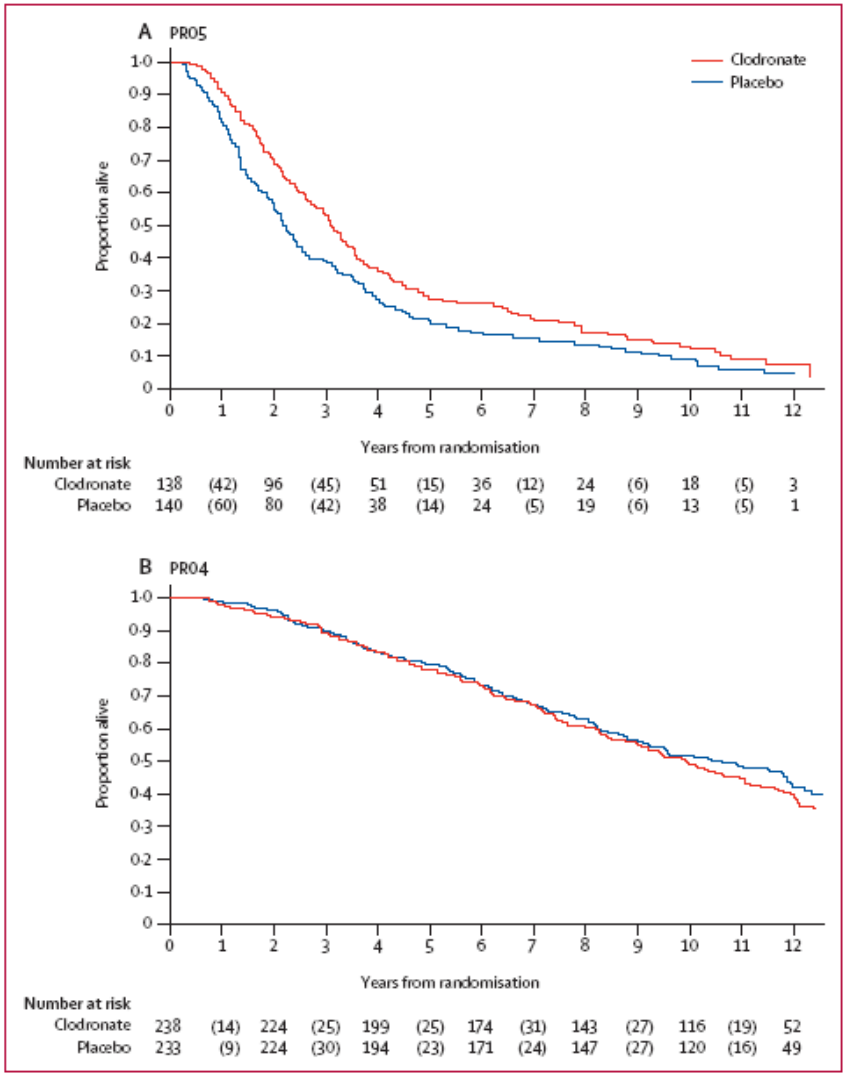


BONE DIRECTED THERAPIES

Bisphosphonates

- Inhibitors of osteoclasts and therefore bone re-absorption
- Used in osteoporosis with proven benefit
- Used to treat malignant hypercalcaemia
- Used for malignant bone pain
- Investigated in a variety of solid malignancies including prostate

Clodronate



PR05

311 with mets on ADT

Clodronate vs placebo 3yrs

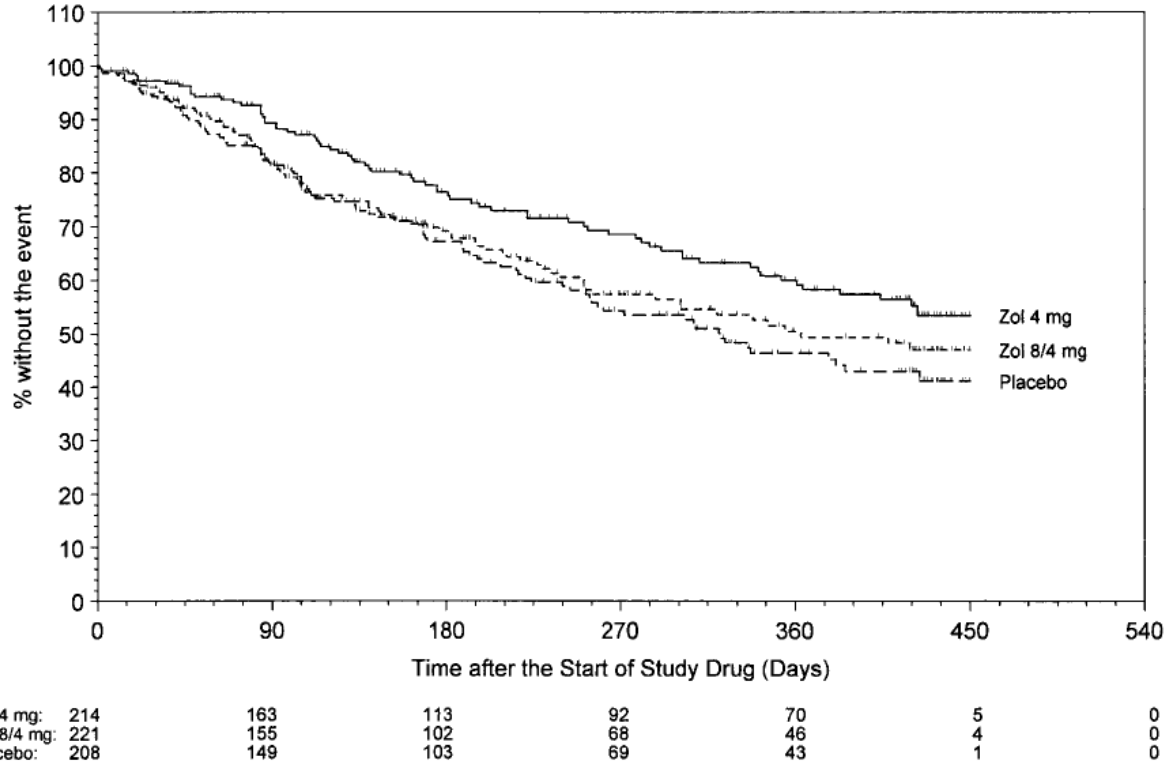
PR04

508 non-mets RT/ADT/both

Clodronate vs placebo 5yrs

Dearnaley et al, Lancet Oncology 2009

Zoledronate



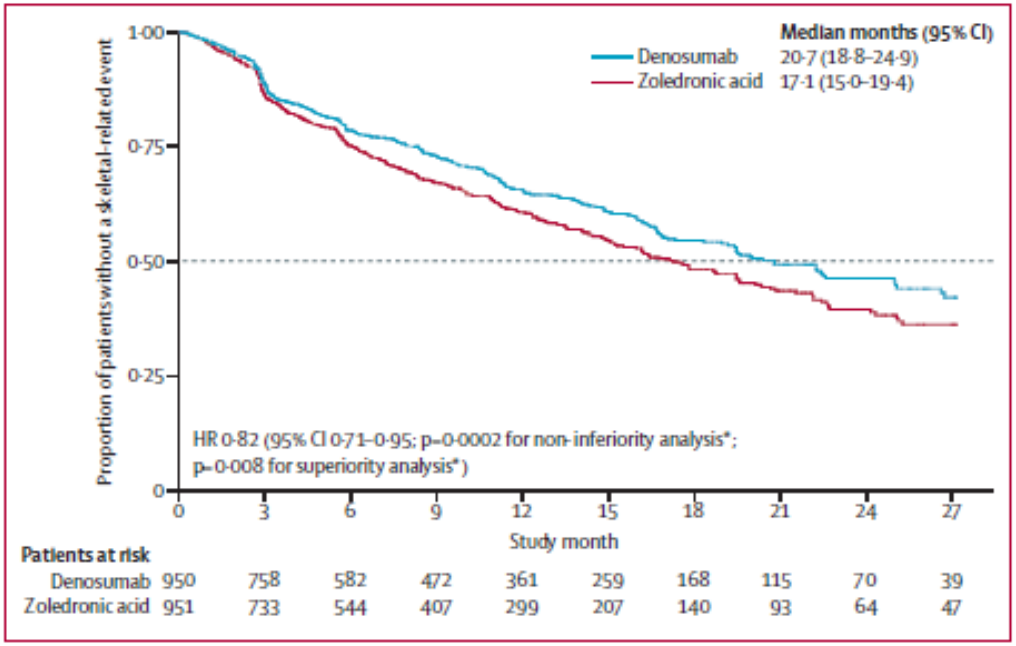
Skeletal-related events:

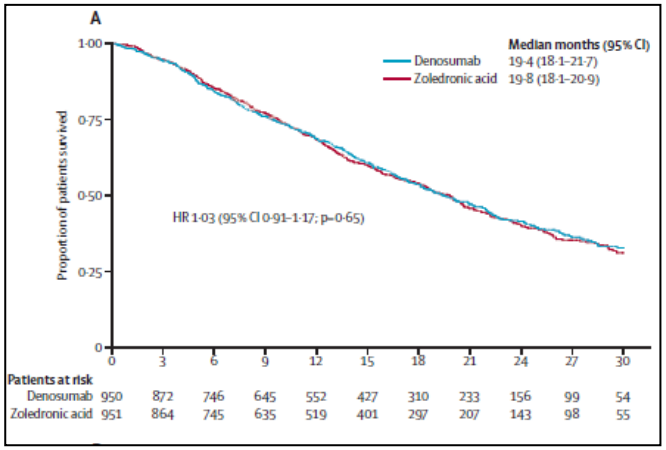
- pathologic bone fractures
- spinal cord compression
- surgery to bone
- radiation therapy to bone
- antineoplastic therapy to treat bone pain

No QOL difference

Saad et al, JNCI 2002

Denosumab v Zoledroante in bony mCRPC





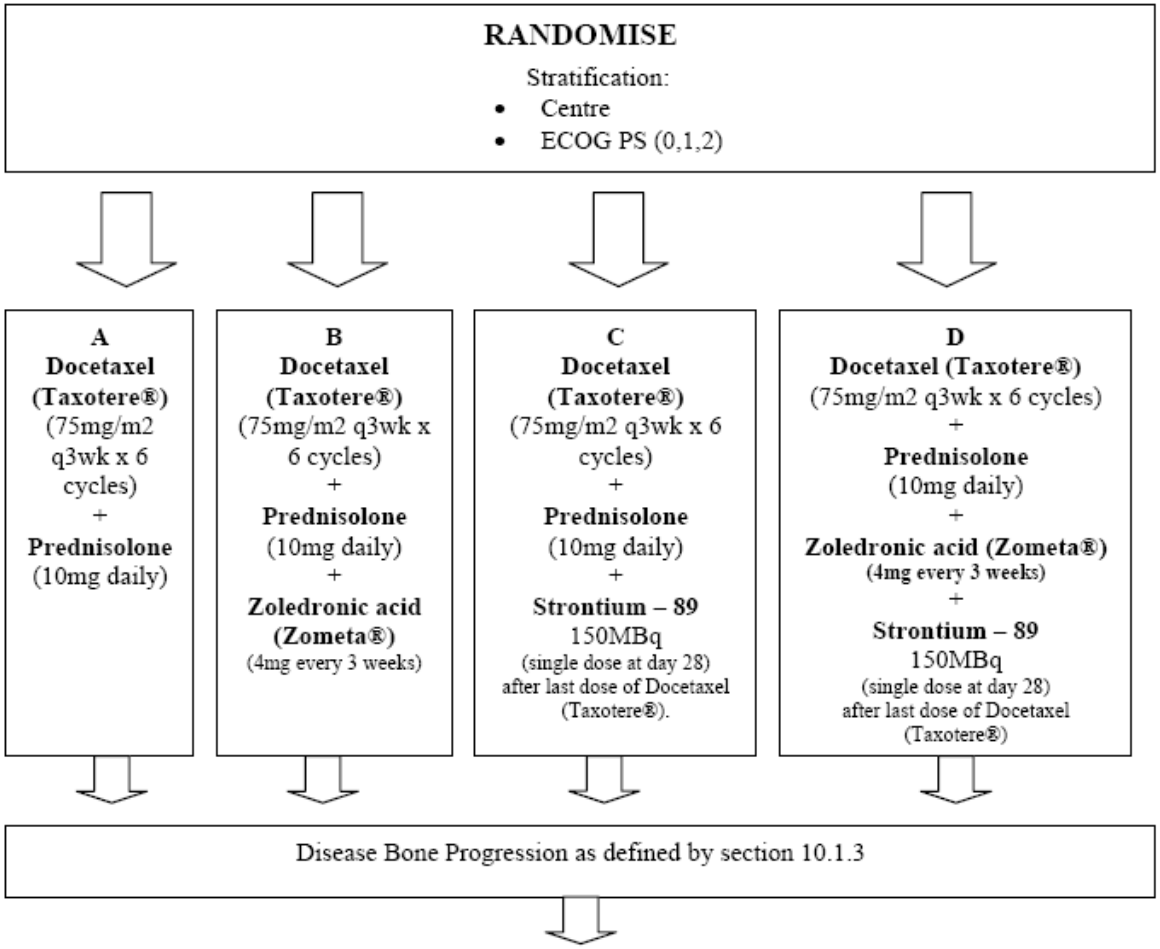
time to first on-study skeletal related event:

- **pathological fracture**
- **radiation therapy**
- **surgery to bone**
- **spinal cord compression**

No QOL difference

Fizazi et al, Lancet, 2011

Trapeze


RANDOMISE
Stratification:
Centre
ECOG PS (0,1,2)
A
Docetaxel (Taxotere®) (75mg/m2 q3wk x 6 cycles) + Prednisolone (10mg daily)
B
Docetaxel (Taxotere®) (75mg/m2 q3wk x 6 cycles) + Prednisolone (10mg daily) + Zoledronic acid (Zometa®) (4mg every 3 weeks)
C
Docetaxel (Taxotere®) (75mg/m2 q3wk x 6 cycles) + Prednisolone (10mg daily) + Strontium – 89 150MBq (single dose at day 28) after last dose of Docetaxel (Taxotere®).
D
Docetaxel (Taxotere®) (75mg/m2 q3wk x 6 cycles) + Prednisolone (10mg daily) + Zoledronic acid (Zometa®) (4mg every 3 weeks) + Strontium – 89 150MBq (single dose at day 28) after last dose of Docetaxel (Taxotere®)
Disease Bone Progression as defined by section 10.1.3

Case history

- 64 year old retired engineer
  - LUTS
  - No PMH, no other medications
  - PSA 12, abnormal DRE
  - TRUS biopsies: Gleason 9 (4+5), vascular invasion
  - No small cell or neuro-endocrine elements
  - MRI pelvis/bone scan: T2c N0 M0

- Radical prostatectomy
  - Tumour fixed to rectum
  - Final pathology showed seminal vesicle involvement and extra-prostatic spread

Case history

- Swift biochemical progression (months)
  - PSA rose from 7 to 13
  - Pelvic MRI lymphadenopathy and bone metastases
  - Commenced CAB (goserelin and bicalutamide)

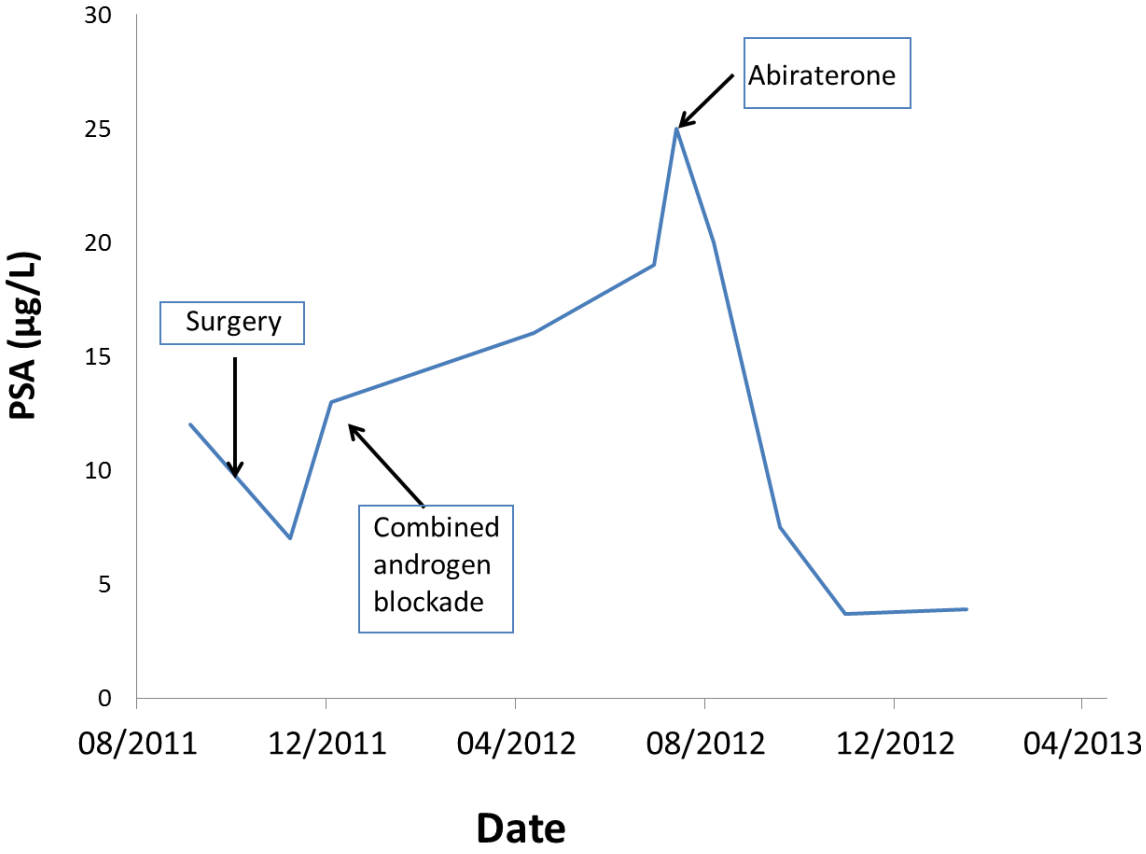
- 4 months later
  - PSA 16
  - PS=0
  - Referred for ‘further palliative systemic therapy’

- Clinically well
  - Restaged: minor increase in pelvic lymphadenopathy and bony metastases
  - PSA 19
  - Left hip pain, moderate severity but patient remained active
  - PS=1
  - Stopped bicalutamide

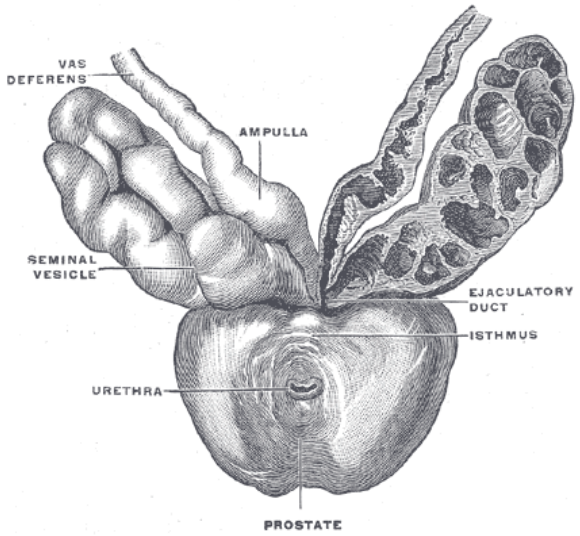
Treatment options

- Observation
- Dexamethasone
- Stilboestrol
- Abiraterone
- Docetaxel chemotherapy
- Ketoconazole
- Sipuleucel–T
- Other

Outcome



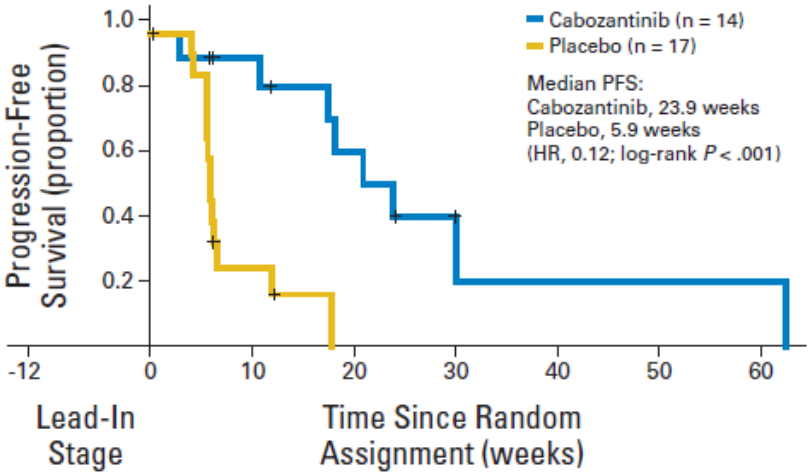
PS=0
Pain free (never had RT to hip)
Reduction in lymphadenopathy
Sclerotic change in bony disease
Transient BP rise

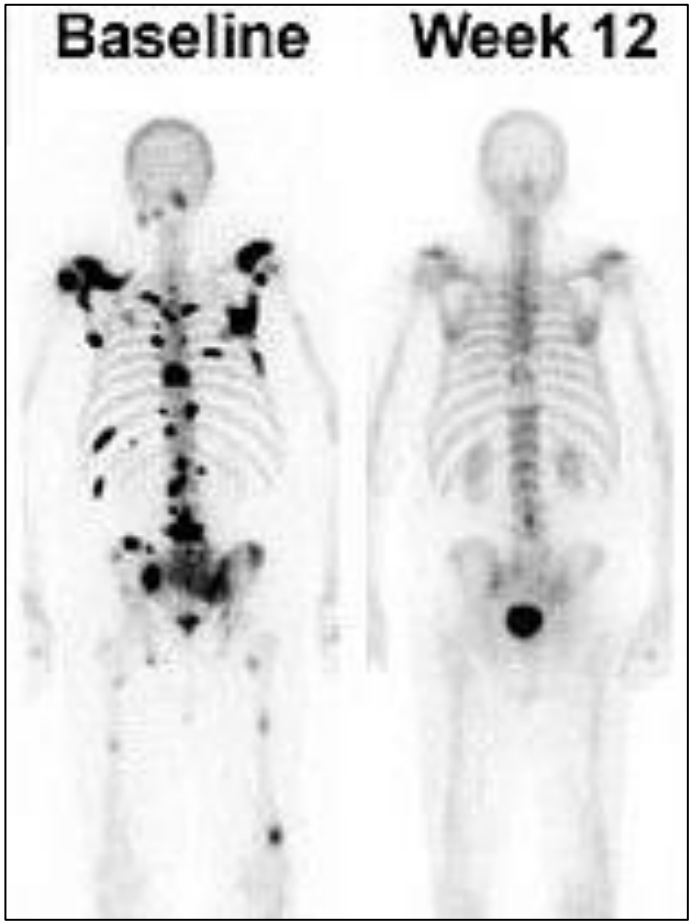


EXPERIMENTAL APPROACHES

Cabozantinib (XL184)

- Oral cMET and VEGFR2 inhibitor
- Phase II
  - At 12 weeks, DCR=80%
  - 72% soft tissue response rate
  - 68% bone scan response rate (12%CR)
  - 67% pain improvement

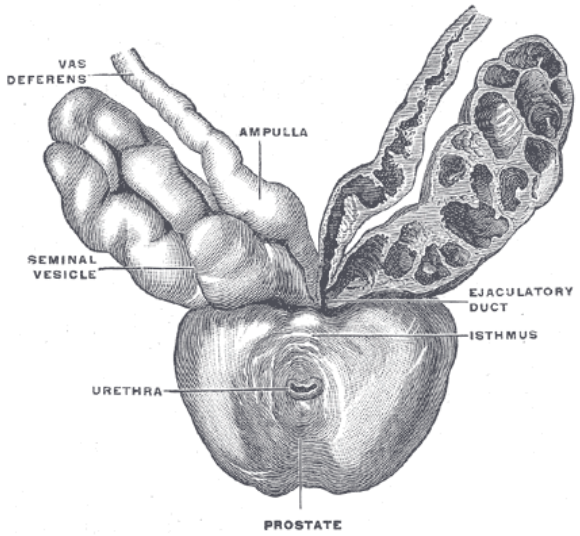




Smith, JCO, 2013

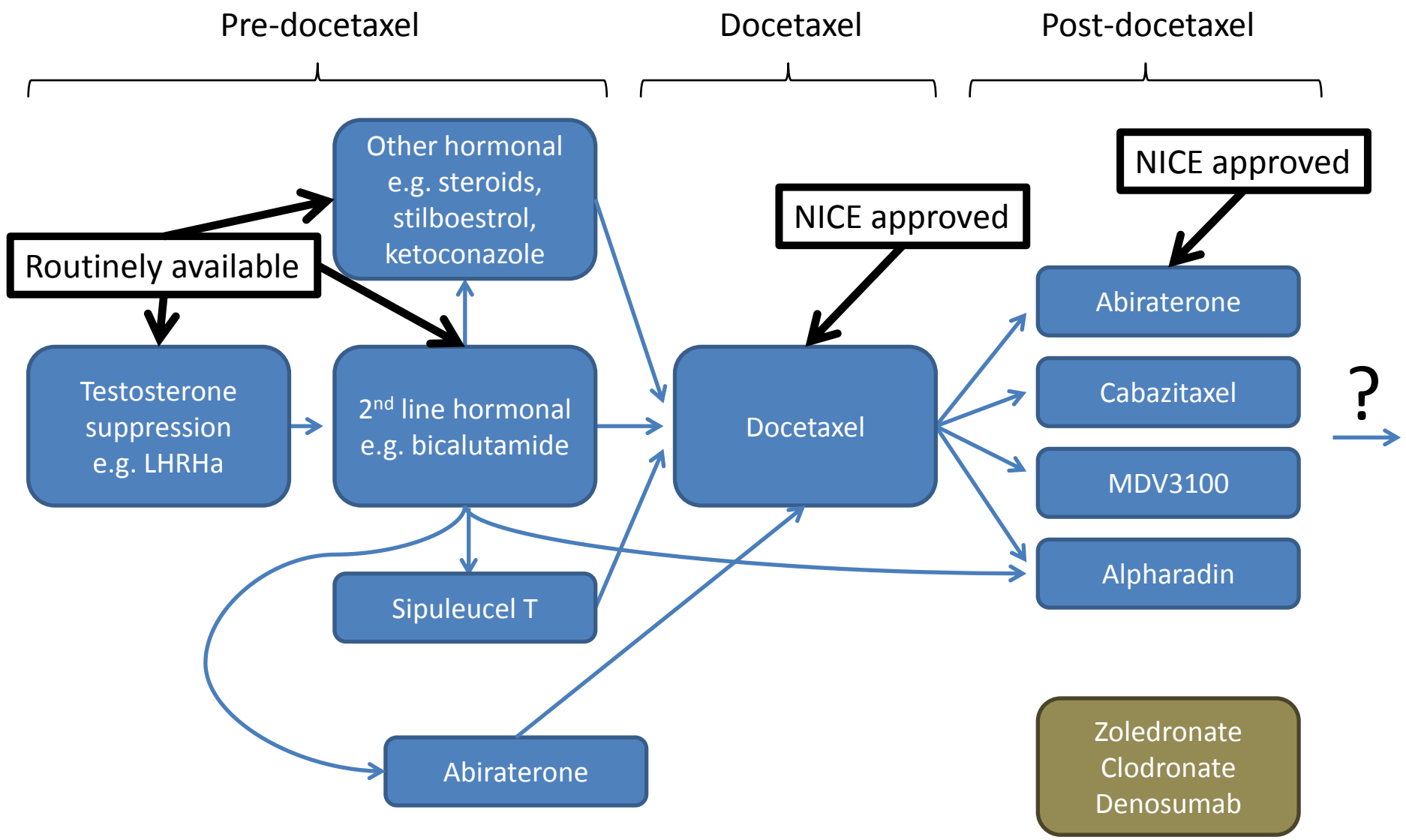
Others in testing

- Ipilimumab
- ~~Lenalidamide~~
- ~~VEGF-Trap~~
- PI3K/AKT inhibitors
- Src inhibitors
  - ~~Dasatinib~~
  - Saracatinib
- ~~Sunitinib~~

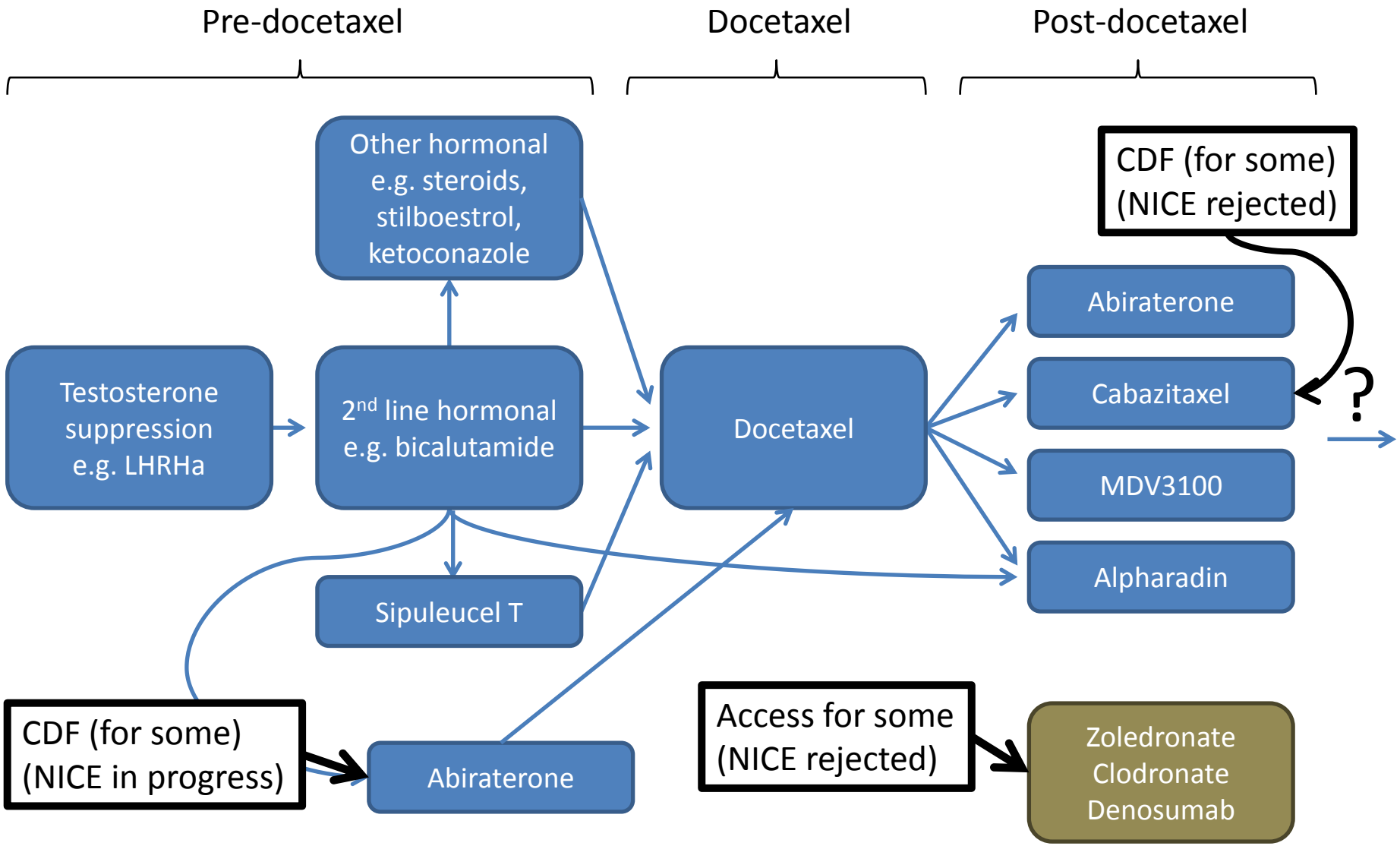

VAS
DEFERENS
AMPULLA
SEMINAL
VESICLE
EJACULATORY
DUCT
ISTHMUS
URETHRA
PROSTATE

DRUG ACCESS

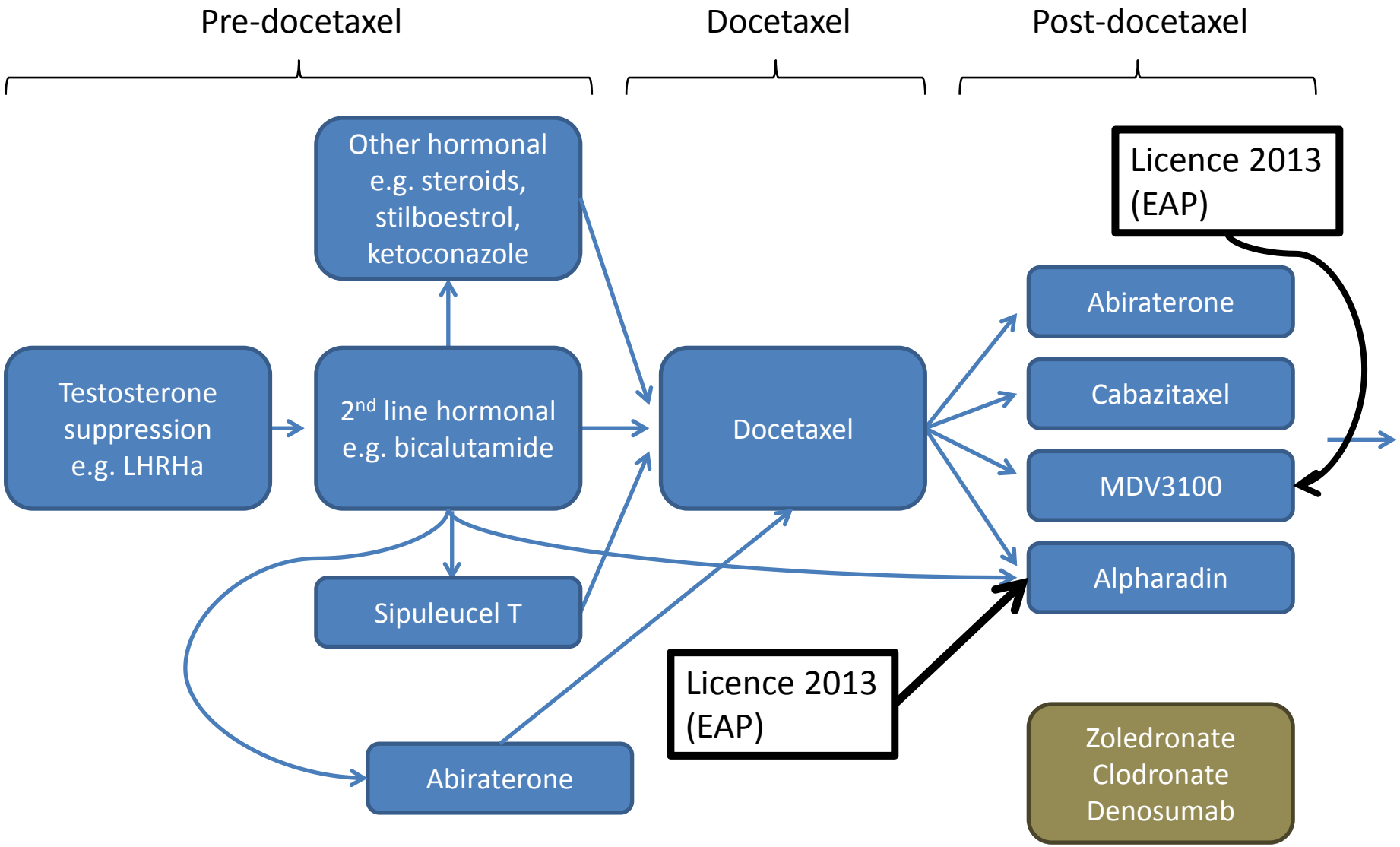
Drug Access – early 2013



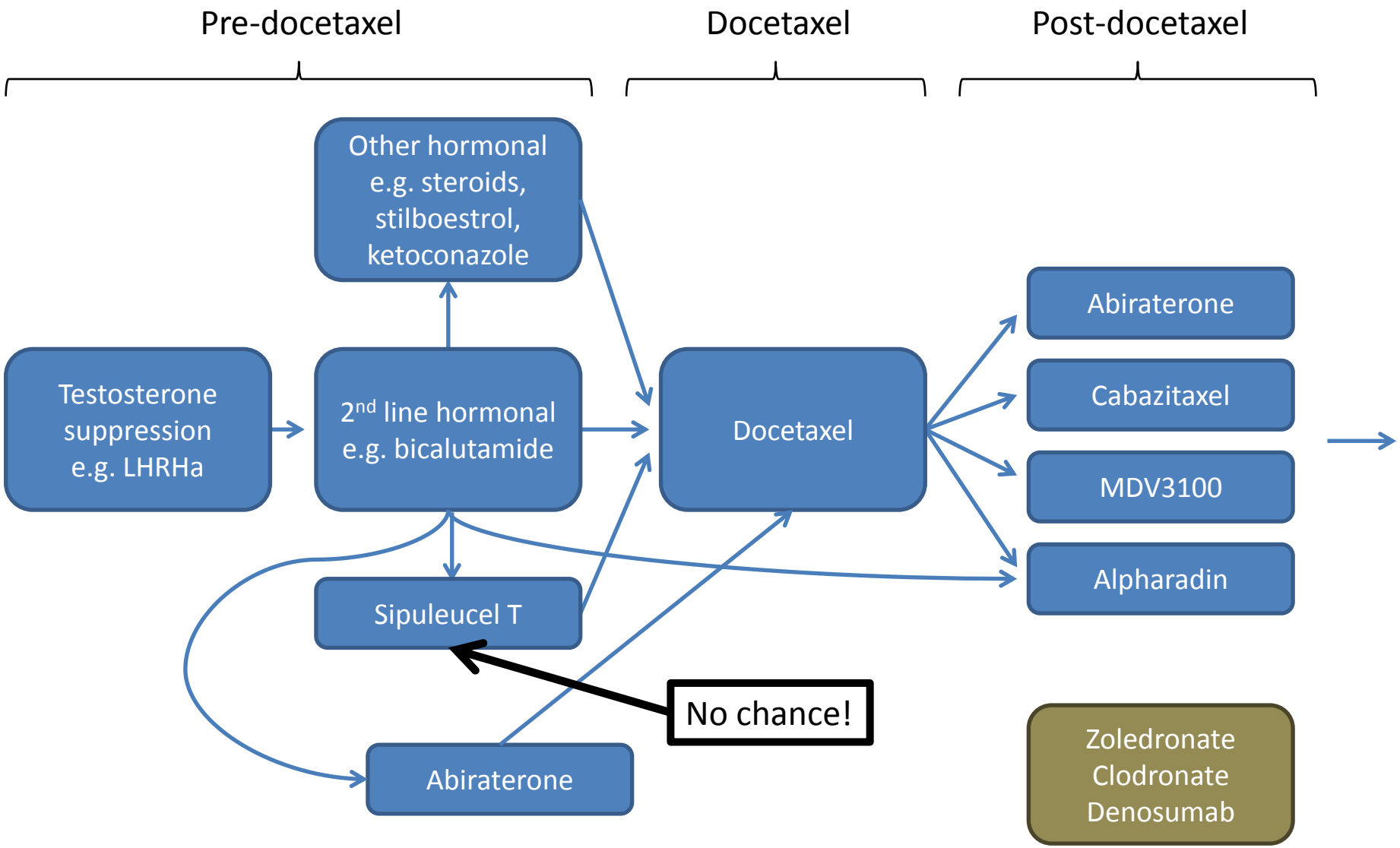
Drug Access – early 2013



Drug Access – early 2013



Metastatic prostate cancer – 2013



General conclusions

- Major changes in treatment options have and are occurring
- Sequencing remains unclear
- Treatment selection strategies urgently needed
- Access remains an issue for many
- Further research needed