Prostate Cancer

PHARMAC SYMPOSIUM - 2016

HR

- 57 year old fireman
- Married, Lynn. Retired. Enjoys sport, travel, wide circle of friends.
- 5 children in a blended family
- PMH: IHD 2 vessel stenting 2011, no angina since.
- Medications: clopidogrel, atorvastatin, metoprolol, candesarten and aspirin

- March 2010
  - Bladder outlet symptoms
- Elevated PSA – 38
- Biopsy of prostate – gleason 4 + 4
- Bone scan – 2 rib lesions

Gosrelin	Zoladex	LHRH agonist (assoc with flare)
Cyproterone Acetate	Androcur	Steroidal Antiandrogen
Flutamide	Eulexin	Non-Steroidal Antiandrogen
Bicalutamide	Cosudex	Non-Steroidal Antiandrogen
Leuprolide	Eligard	LHRH analogue (agonist at pituitary LHRH receptors)
Degarelix	Firmagon	LHRH antagonist. No flare
Ketoconazole		Antiandrogen (via SHBG and cyto p450)
Abiraterone	Zytiga	Cyp17 inhibitor
Enzalutamide	Xtandi	Androgen Receptor Antagonist

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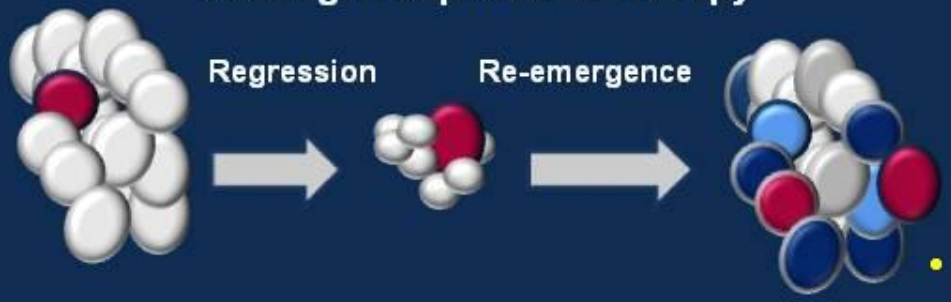
Progress

- Commenced on LHRH agonist therapy
  - “eligard”, Leuprolide
  - PSA dropped to 3, all symptoms resolved. He was well.
  - Bone scan (February 2011) – both bone sites have improved

2016 – we might do something different.

Early Chemo+ADT: A debate in one slide – a need for randomized phase 3 trial



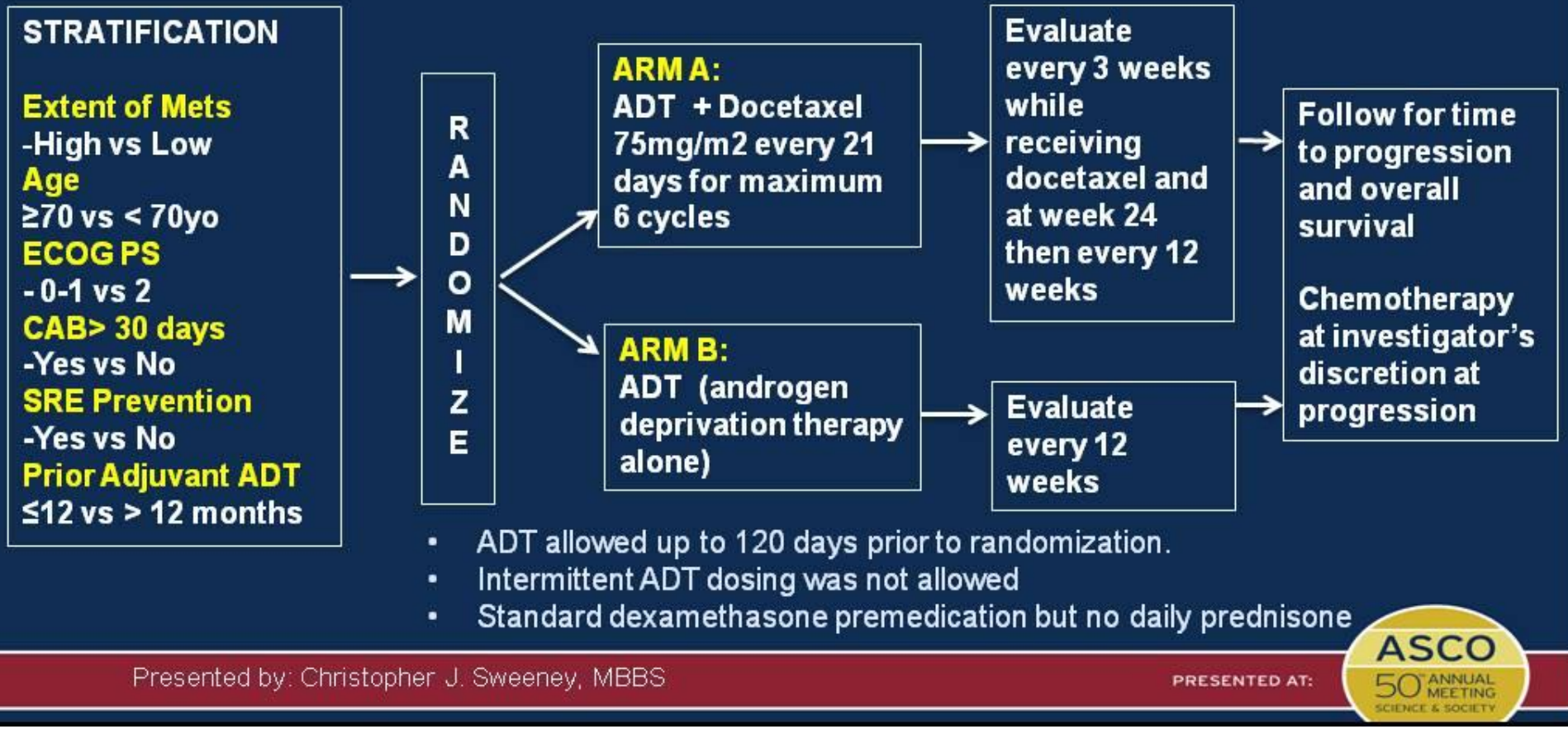
- **Pro**
  - Attack de-novo testosterone independent clones early - allow ADT to keep PrCa in remission longer
  - Some patients at the time of progression are too frail for chemo.
- **Con**
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some patients respond for a long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

Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

- Three trials
  - GETUG15
  - CHARTTED
  - STAMPEDE

E3805 – CHAARTED Treatment



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

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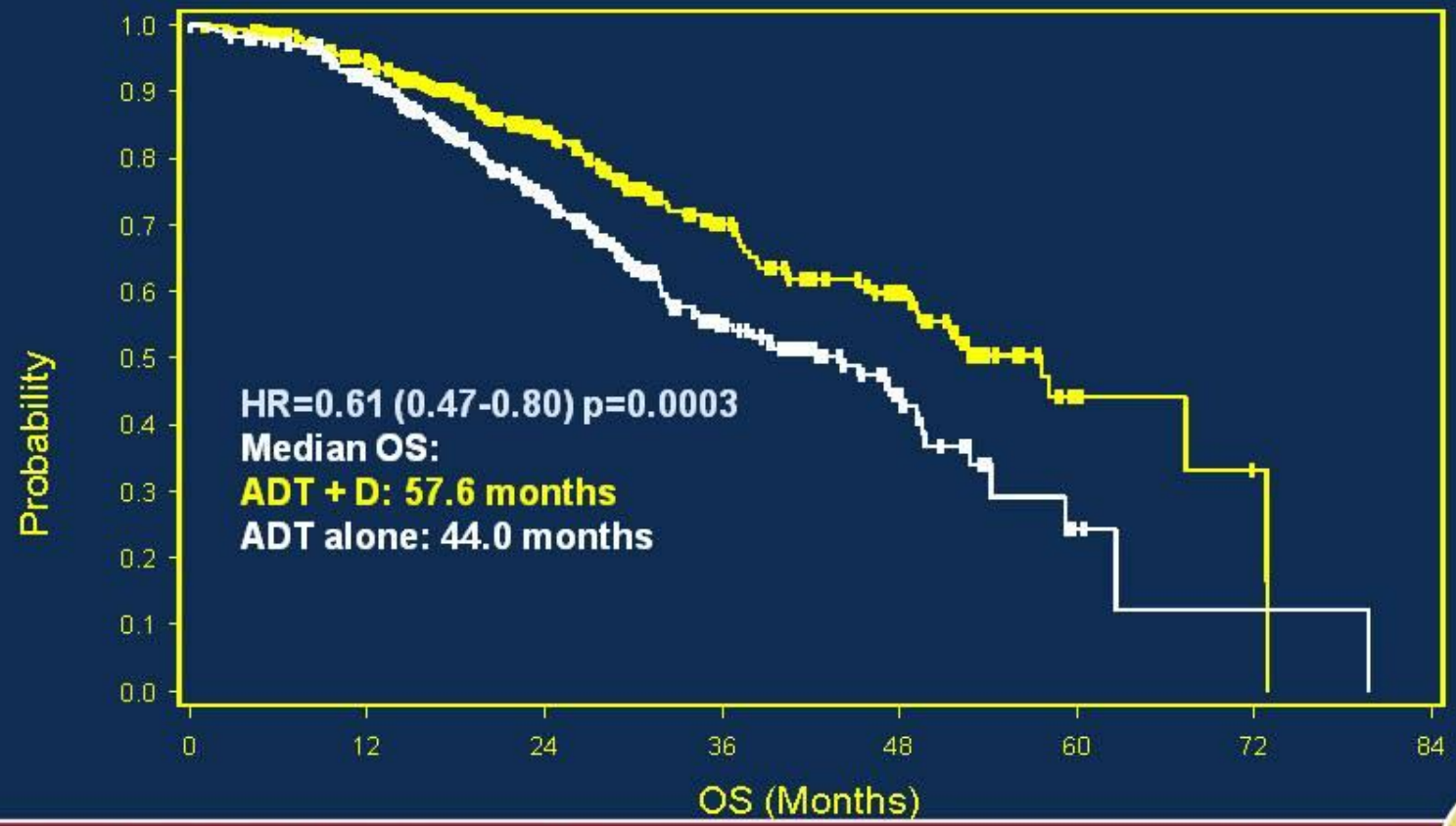
Primary endpoint: Overall survival



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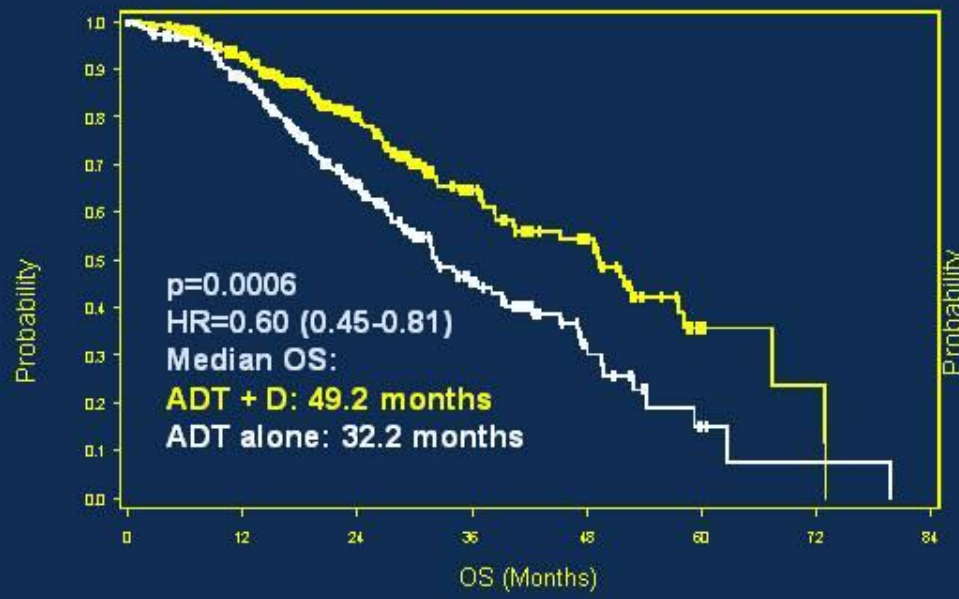
Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

OS by extent of metastatic disease at start of ADT

High volume



Low volume

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

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

Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham
on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O'Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators

PRESENTED AT: ASCO Annual '15 Meeting

Inclusion criteria

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

All patients

Fit for all protocol treatment

Fit for follow-up

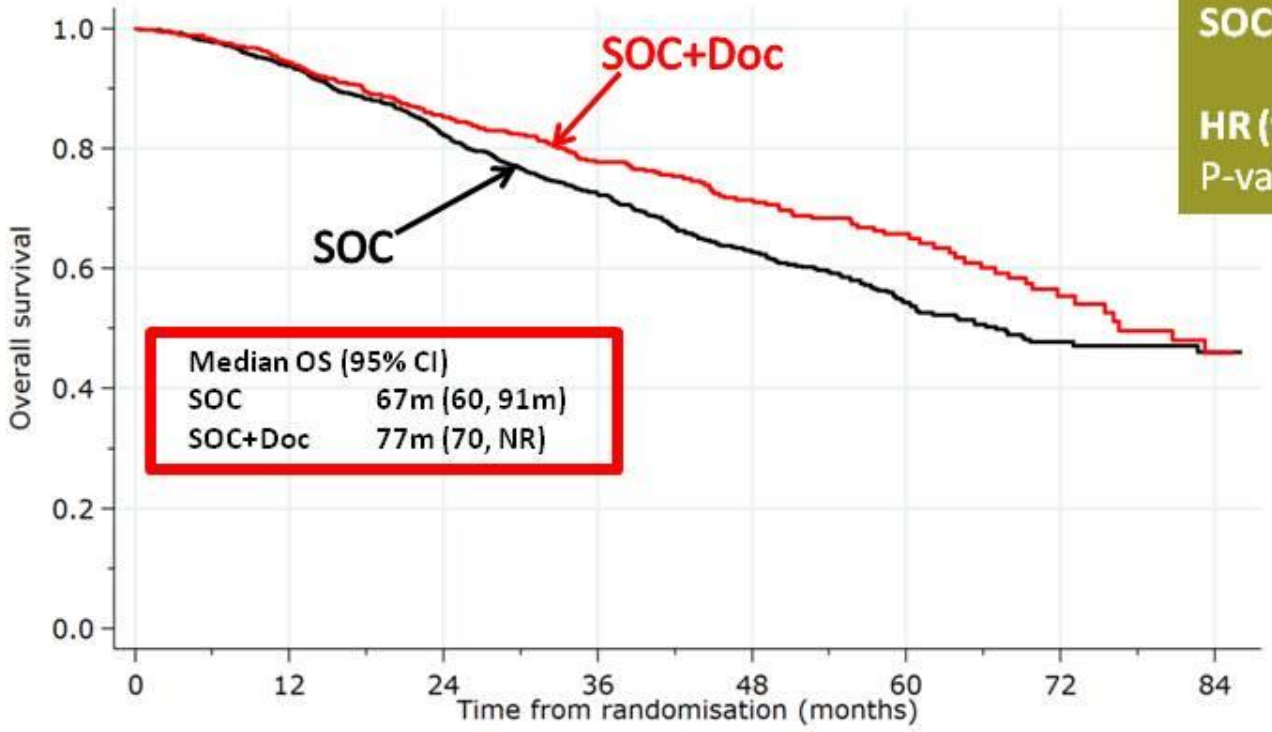
WHO performance status 0-2

Written informed consent

Full criteria

www.stampedetrial.org

Docetaxel: Survival



SOC	405 deaths
SOC+Doc	165 deaths
HR (95%CI)	0.76 (0.63, 0.91)
P-value	0.003

Non-PH p-value 0.51

Group
At risk (events)

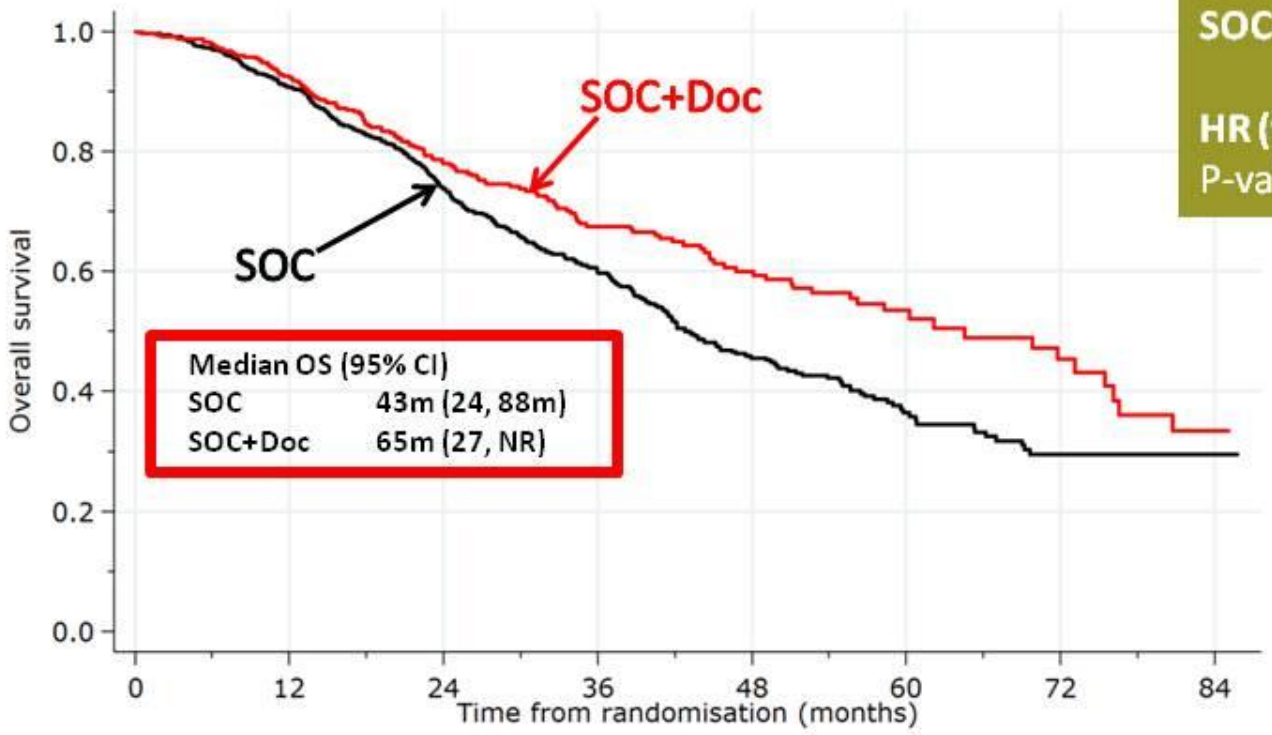
SOC	1184	(73)	1092	(130)	860	(89)	521	(59)	310	(33)	156	(17)	81	(2)	36
SOC+Doc	592	(33)	545	(51)	437	(32)	283	(19)	180	(12)	91	(12)	48	(6)	18

Restricted mean OS time

SOC	58.8m
SOC+Doc	63.4m
Diff (95%CI)	4.6m (1.8, 7.3m)

Presented By Nicholas James at 2015 ASCO Annual Meeting

Docetaxel: Survival – M1 Patients



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

Non-PH p-value 0.23

Restricted mean OS time

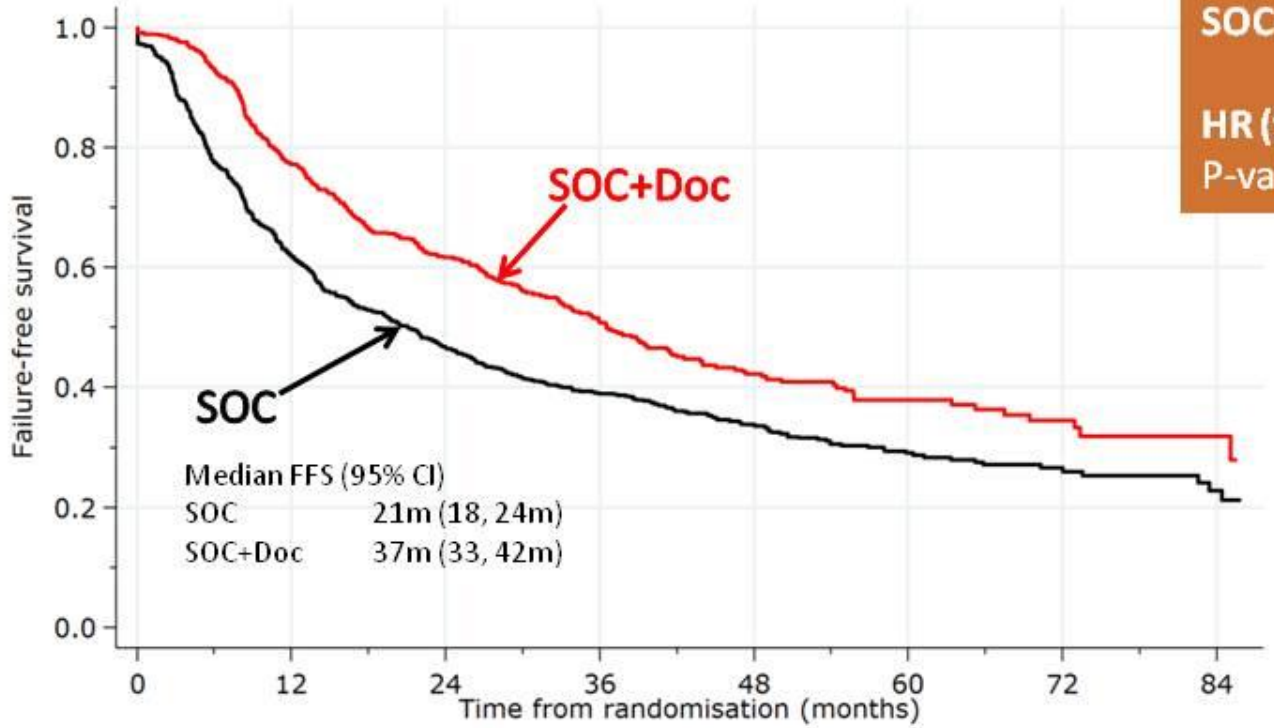
SOC	49.3m
SOC+Doc	56.1m
Diff (95%CI)	6.8m (2.8, 11.0m)

Group
At risk (events)

SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC+Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

Presented By Nicholas James at 2015 ASCO Annual Meeting

Docetaxel: Failure-free survival



SOC	750 FFS events
SOC+Doc	371 FFS events
HR (95%CI)	**0.62** (0.54, 0.70)
P-value	**<0.0000000001***

Non-PH p-value 0.0002

Group At risk (events)															
SOC	1184	(446)	713	(173)	488	(70)	287	(31)	161	(19)	84	(6)	45	(4)	17
SOC+Doc	592	(131)	441	(88)	318	(48)	184	(27)	105	(9)	56	(4)	29	(2)	11

Restricted mean FFS time

SOC	35.3m
SOC+Doc	44.4m
Diff (95%CI)	9.1m (6.3, 11.9m)

*exact p-value 0.0000000000002014

Patient characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
65yr	Median age (min 40, max 84)	[s]
61%	Metastatic (85% Bony mets)	[s]
15%	N+M0	
24%	N0M0	

Balanced by arm

[s] Stratification factors + hospital + NSAID/aspirin

Recommendations

- All men with high risk, newly diagnosed prostate cancer, presenting with metastatic disease, who are deemed fit enough should be offered docetaxel in combination with Androgen Deprivation therapy.

- The benefit / risk ratio will be highest in those with high volume disease

Summary

- All men with high risk, newly diagnosed prostate cancer, presenting with metastatic disease, who are deemed fit enough should be offered docetaxel in combination with Androgen Deprivation therapy.
- The benefit – risk ratio will be most significant in those with high volume disease

- Men with localised M0 prostate cancer who are to receive local treatment should not be offered docetaxel in addition to ADT

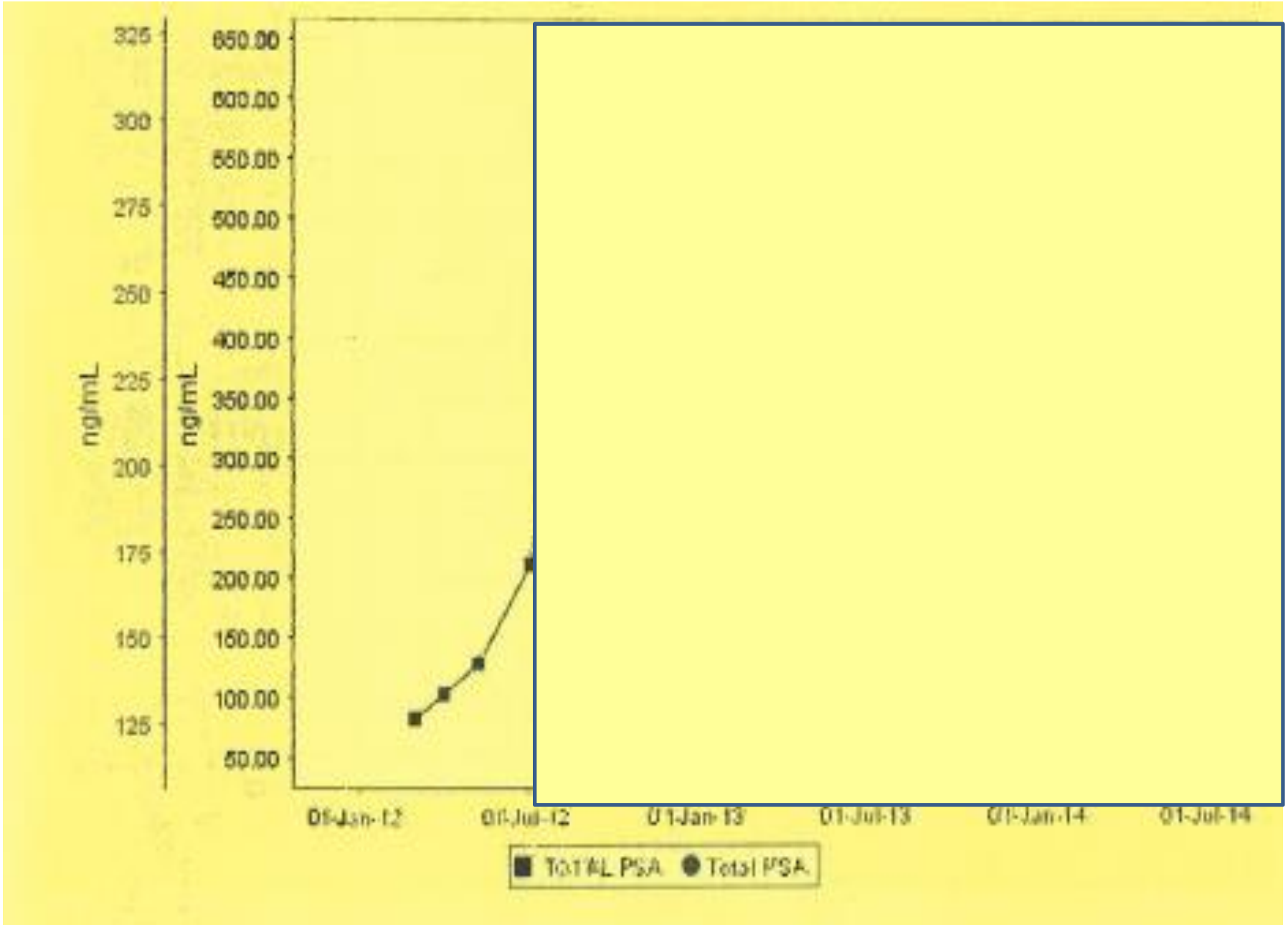
- Selected Men with localised high risk M0 prostate cancer should consider docetaxel chemotherapy in view of the substantial improvement in failure free survival in the Stampede trial

- These last two recommendations may alter with updated results from the key trials.

Progress

- 2010 - Commenced on LHRH agonist therapy
  - “eligard”, Leuprolide
  - PSA dropped to 3, all symptoms resolved. He was well.
  - Bone scan February 2011 – both bone sites have improved
- February 2012
  - PSA rises to 49
  - He is well
  - Commenced Bicalutamide 50mg daily in conjunction with his LHRH agonist.

- July 2012
  - PSA has risen steadily
  - Right rib pain
  - New bone scan – new rib lesion 5th rib on right
  - 8 Gy single fraction to this lesion
  - No other symptoms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01-Jul-13
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01-Jul-14
TOTAL PSA
Total PSA

Survival Advantage in Advanced Prostate Cancer

	Design	POP	N	HR	P value	Med OS months
TAX327	Doc/pred vs Mito/Pred	mCRPC Chemo Naive	1006	0.76	0.009	18.9 vs 16.5
IMPACT	Sipleucel T vs Control	mCRPC, CN	512	0.78	0.03	25.8 vs 21.7
TROPIC	Cabzitaxel/pred vs Mito/pred	mCRPC, prior chemo	755	0.72	<0.0001	15.1 vs 12.7
COU-AA-301	Abi/pred vs placebo/pred	mCRPC pC	1195	0.74	<0.0001	15.8 vs 11.2
Affirm	Enzalutamide	mCRPC Prior doce	1199	0.63	<0.001	18.4 vs 13.6
PREVAIL	Enzalutamide	mCRPC No prior chemo	1717			
Alsympca	Radium 223/BSC vs Plac/BSC	mixed	921	0.70	0.00007	14.9 vs 11.3
COU-AA-302	Abi/pred vs Plac/Pred	mCRPC, CN	1088	0.75	0.01	NR vs 27.2

Mitoxantrone and Prednisone

- Mitoxantrone 12 mg/m2 + prednisone 10 mg daily vs prednisone 10 mg daily alone
- 161 patients
- Primary endpoint – 6 point pain score and QOL
- MP 29% improvement vs 12% P alone p = 0.01
- Duration of palliation 43 weeks vs 18 weeks
  - p < 0.001
- QOL and PSA reduction also significant
- No overall survival advantage

Tannock et al JCO 1996 14:1756-64

Docetaxel Phase III

		OS	Other endpoints	
TAX327 NEJM 2004 1006 patients	Docetaxel (75mg/m2) + pred 5mg bd Vs Vs Docetaxel 30 mg /m2 weekly 5/6 Mitoxantrone 12mg/m2+ pred 5 mg bd	19.2 months vs 17.8 months Vs 16.3 months HR 0.76 (0.62-0.94) P = 0.004	Improvements in PSA Improvements in Pain score Improvement in QOL	
Petrylak et al NEJM 2004 674 patients	Docetaxel (60mg/m2) + estramustine Vs Mitoxantrone 12/mg/ m2+ prednisone	17.5 months vs 15.6 months P = 0.02 HR 0.80 (0.67 – 0.97)	TTP – 3 months advantage P <0.001 PSA decline Pain score No difference	

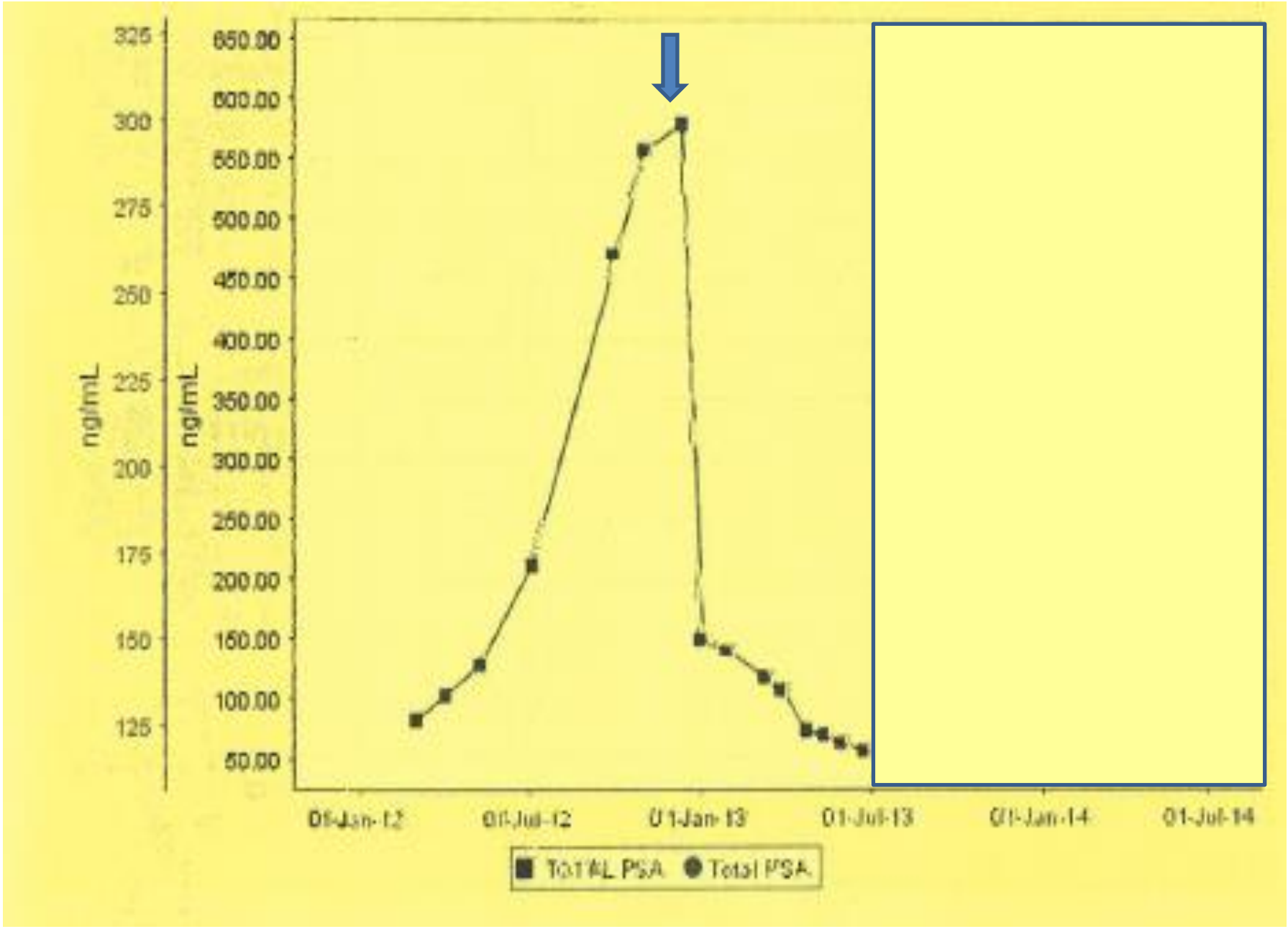
Docetaxel chemotherapy - CRPC

- Doses are low
- Continued for 10 cycles if working
- Concomitant steroids

Well tolerated

Alopecia, Retained Fluid, Peripheral Neuropathy, Myalgia

- Hamish decided
  - To continue zoladex. Stopped bicalutamide.
  - To complete planned travel to Europe and the UK over 3 months
  - We reviewed him closely in the months leading up to the trip
  - He remained well
  - But returned in December 2012 with palpable nodal disease (4 cm) in the left neck
  - Re-staged and also had para-aortic lymphadenopathy.
  - Commenced Docetaxel / Prednisone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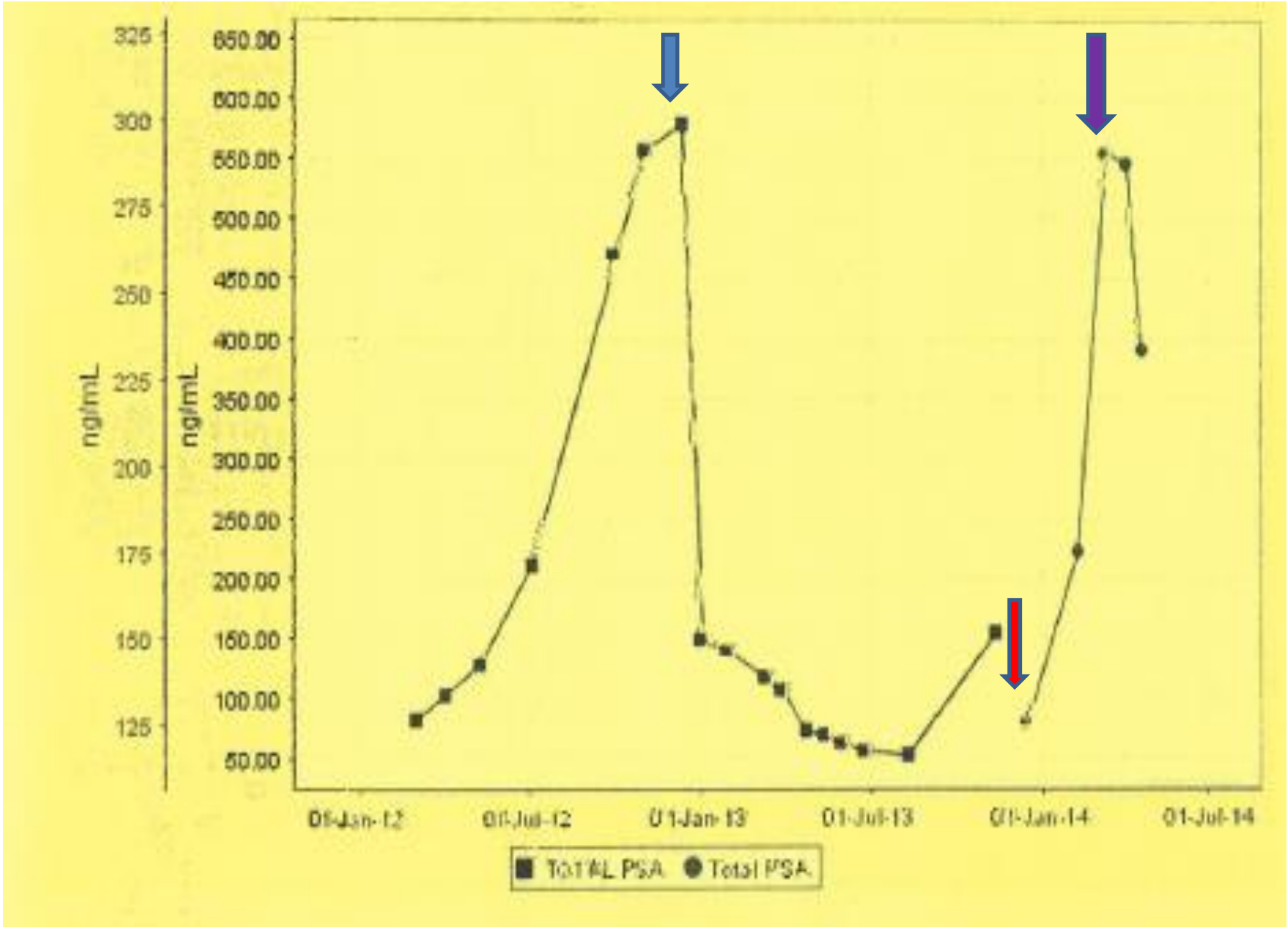
01-Jul-13
01-Jan-14
01-Jul-14
TOTAL PSA
Total PSA

- Nadir PSA 46
- Complete clinical resolution and radiological resolution of all disease
- 10 cycles of docetaxel in all, grade 2 peripheral neuropathy lead to 1 dose reduction
- Completed chemo in July 2013
- January 2013
  - Palpable nodal disease
  - PSA elevated to 176

- Of interest
  - GP commenced prednisone for general achiness over December and to help him get through a cricket match
  - Note PSA

Progress

- Recommenced Docetaxel / Prednisone
- Improvement in the nodal disease
- Reduction in PSA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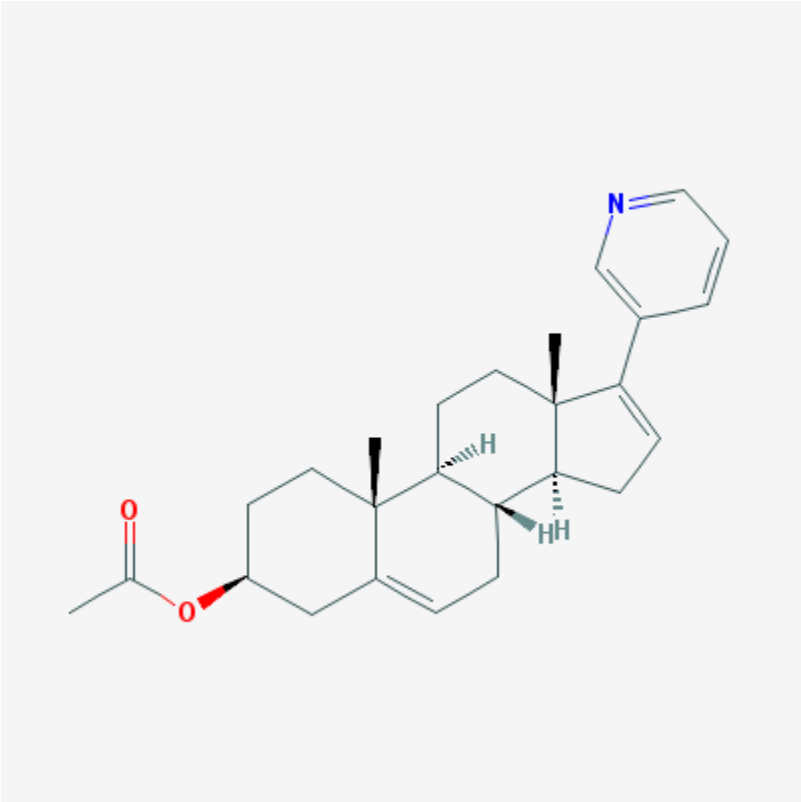
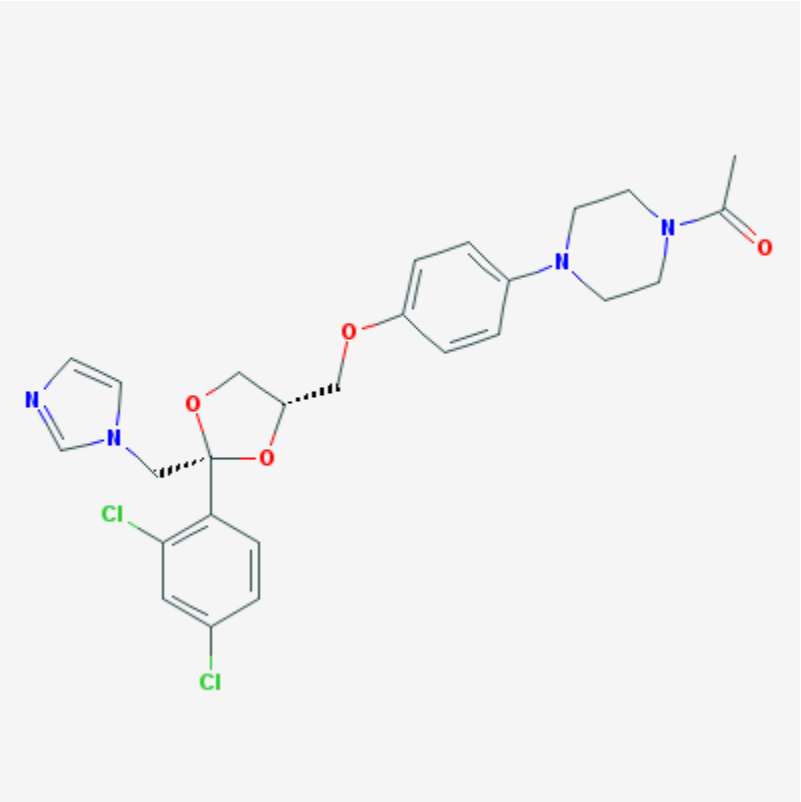


Abiraterone



Ketoconazole

Abiraterone – Phase III

		Population	PFS	OS
COU-aa-302	Pre-chemotherapy	1088 patients Abi + pred vs pred + plac Mildly symptomatic or asymptomatic 1:1	16.5 months vs 8.2 months HR 0.52, 0.45-0.61	35.3 months Vs 30.1 months HR 0.79 (0.66 – 0.95) P = 0.01
COU-AA-301	Post chemotherapy	1195 Abi + pred vs pred + plac 2:1	10.2 months vs 6.6 months P < 0.001	15.8 months Vs 11.2 months P = 0.0001

Ketoconazole

- Retrospective series, single institution
- 1999 – 2010
- 114 patients, 200-400mg / day
- Median F/up 31 months
- 54% had PSA decline, median ttp 8 months
- Grade ¾ toxicity in 22%

Geizman et al, Prostate 2012 7294); 461

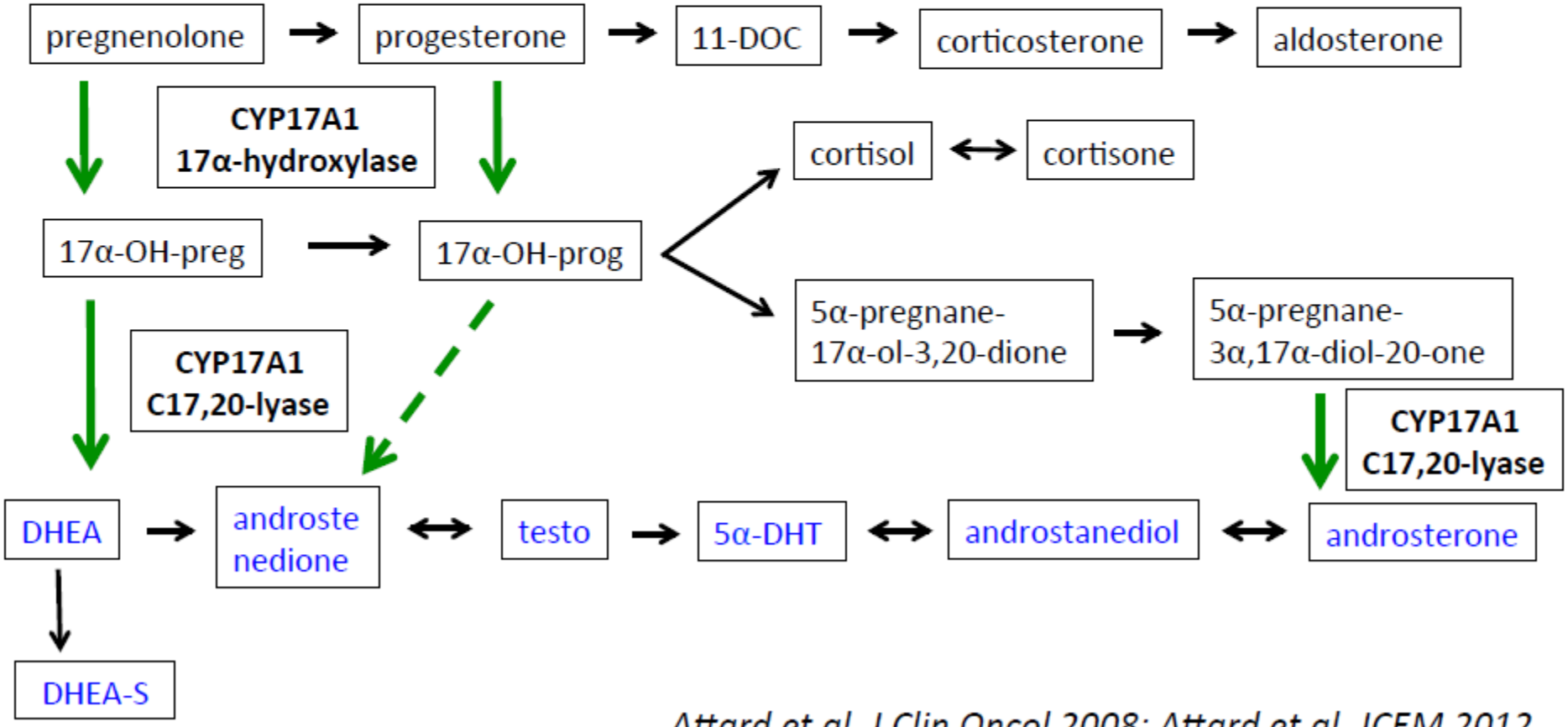
They both use the same mechanism? They both get you from A to B
But which drug do you feel better taking? ???

Ketoconazole

Abiraterone

NEJM April 2014

Mechanism of action of abiraterone in humans



Attard et al, J Clin Oncol 2008; Attard et al, JCEM 2012

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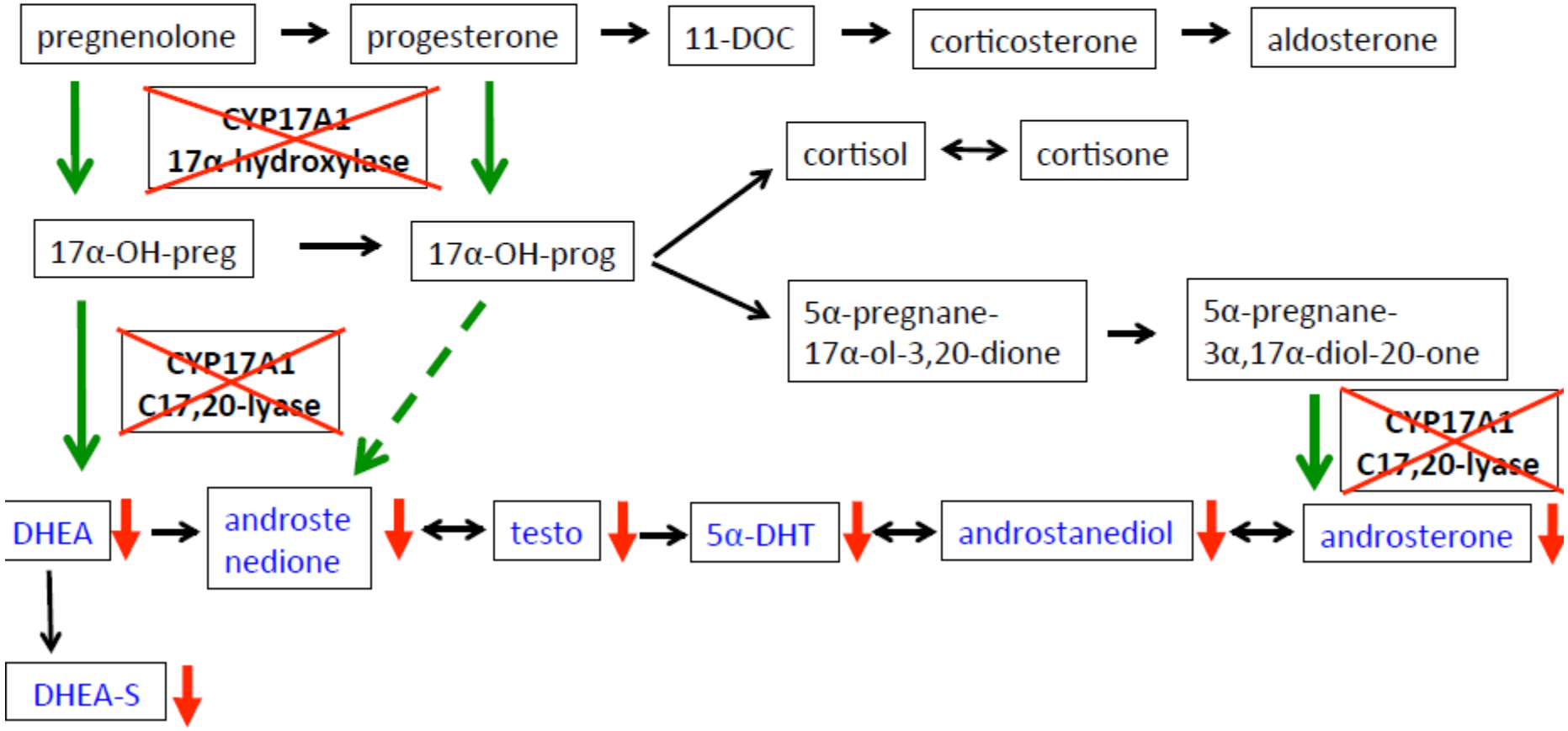

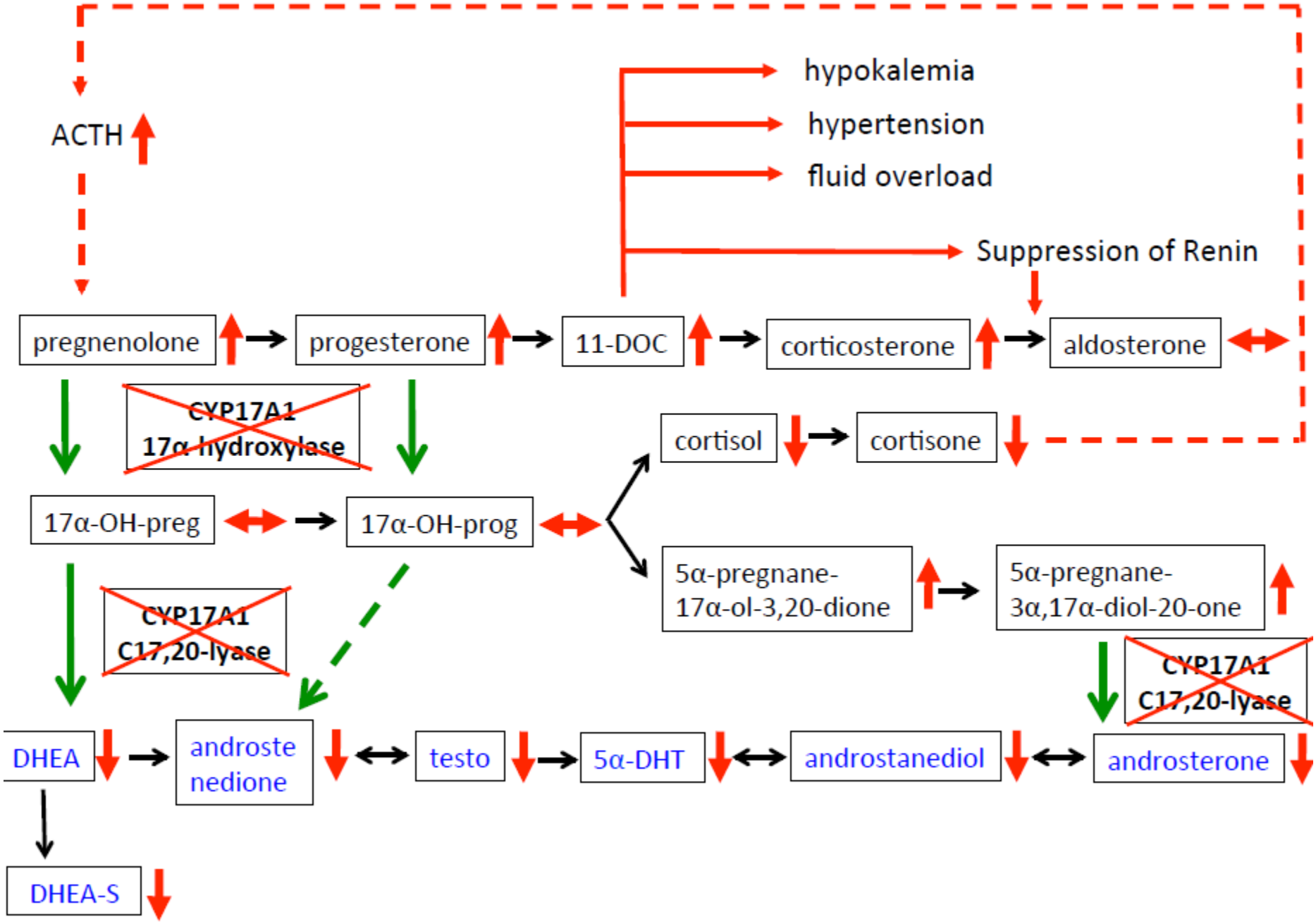
ACTH
hypokalemia
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fluid overload
Suppression of Renin
pregnenolone
progesterone
11-DOC
corticosterone
aldosterone
CYP17A1
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cortisol
cortisone
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17α-OH-prog
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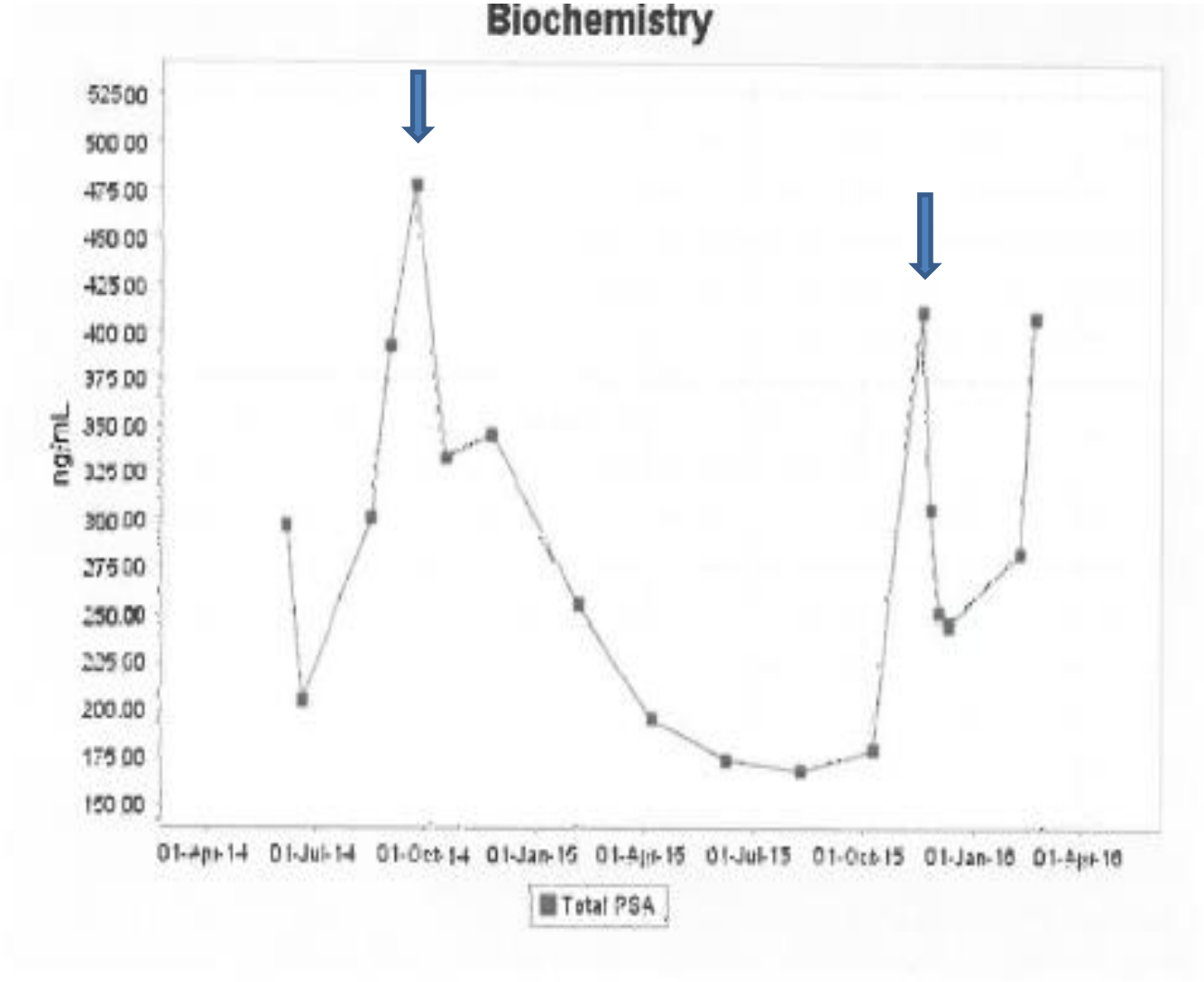


NB initial diagnosis 2010

WHAT ABOUT UNFUNDED OPTIONS?

Sipileucel-T

- Approved in USA for the treatment of asymptomatic or minimally symptomatic mCRPC
- Autologous vaccine – individually collected antigen presenting cells that are exposed to the a fusion protein of prostatic acid phosphatase and granulocyte macrophage CSF
- IMPACT study
  - 512 men
  - Chemo naive
- Median OS 25.8 months vs 21.7 months
- HR 0.78 (0.61- 0.98) p = 0.03

Cabazitaxel

- Second generation tubulin inhibitor
- TROPIC trial
  - Cabazitaxel 25mg/m2/prednisone 5 mg bd vs Mitoxantrone 12 mg/2/prednisone 5mg bd
  - Metastatic castrate resistant prostate cancer
  - All prior therapy with docetaxel
  - 1195 men
- HR 0.72 (0.61-0.84) $p < 0.0001$
- Median OS: 15.1 months versus 12.7 months
- Toxicity of Cabazitaxel (german compassionate access program)
  - Low febrile neutropenia rates over all 7%, anemia 4%
  - Diarrhoea 0.9%

Enzalutamide

- Androgen Receptor (AR) Signalling Inhibitor and pure antagonist of AR
- AFFIRM
  - Enzalutamide vs Placebo
  - Metastatic Castrate Resistant Prostate Cancer
  - All had prior therapy with Docetaxel
  - 1199 patients
- HR for survival 0.63 (0.53 – 0.75)
- $P < 0.001$
- Median OS: 18.4 months vs 13.6 months

- Median time to any adverse event 12.6 months vs 4.6 months
- Toxicity:
  - Seizures (0.6%)
  - Diarrhoea, fatigue, hot flashes

Enzalutamide

- PREVAIL
- Randomised double blind Phase III in castrae resistant prostate cancer – chemo naive
- Study was pre abiraterone
- 1717 patients
- Stopped early – by DSM due to results
- Primary endpoints were to be PFS and OS – unblinded
- Results
  - 12 month rate of Radiographic progression free survival 65% vs 14%
  - CR or PR in soft tissue lesios 59% vs 5%
  - Time to chemotherapy HR 0.35 in favor of enzalutamide

Radium - 223

- Radiopharmaceutical
- Calcium mimic targets new bone growth in and around bone mets via heavy ά particles that are ultra-short range < 100 micrometres

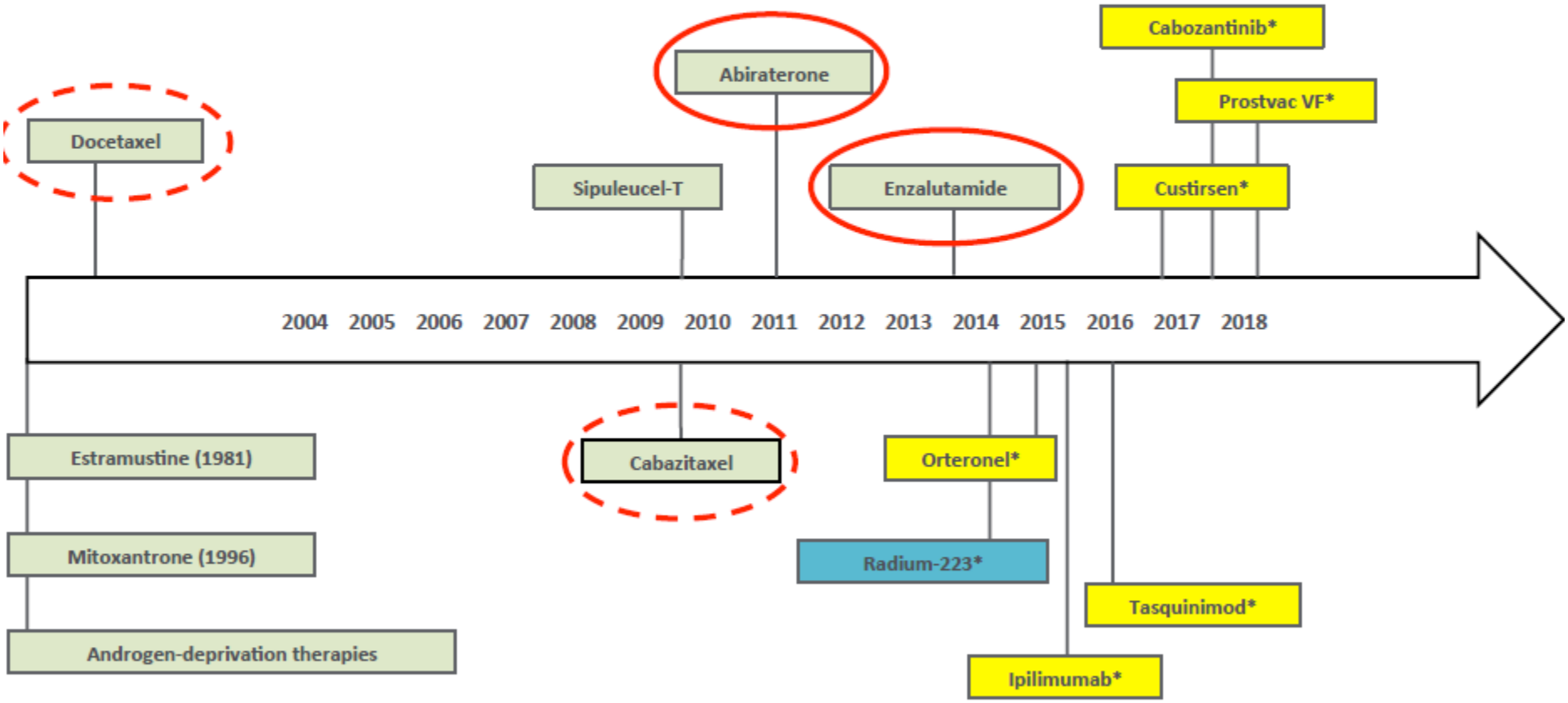
ALYMPCA

- Radium 223 + BSC vs Placebo/BSC
- Median OS 2.8 increased to 3.6 months (trial stopped by DMC)
- Time to first skeletal event 14.9 months vs 11.3 months

Sequencing Therapies

- Many reviews trumpeting the advances in treatments for prostate cancer
- Outside the USA – funded options remain limited
- We have a range of options each of which add “about 3 months”
- Few trials have addressed sequencing to date
- Well reviewed in Asia Pacific Journal of Oncology April 2014, Philip Parente and Howard Gurney

Exciting times for CRPC – and the AR takes center stage



*Denotes products that are not approved for use; approval dates are an estimate only

The referral we want to erradicate from 2016

- Now 70 year old
- 2008 – PSA 9.8, prostate biopsies benign
- 2010 – PSA 12.6 prostate biopsies benign
- 2012 – local bladder symptoms, PSA 42.5, Gleason 4 + 5, PET/CT widespread bone disease
- Commenced Zoladex and XRT Thoracolumbar spine (T4 – L4 to prevent cord compression)
- August 2013 – hip weakness, PSA rising, Add bicalutamide.
- December 2013 – PSA rising, both Bicalutamide and Zoladex stopped. Strontium given
- Late December t7 related pain – further radiation therapy T4- T11, starts regular blood transfusions for anemia
- April 2014 – admission lower limb weakness, Scans show sacral plexopathic carcinomatosis disease, linked to hospice – REFERRED TO MEDICAL ONCOLOGY FOR CONSIDERATION OF CHEMOTHERAPY OPTIONS. PS 2 – 3; platelets 64, HB transfusion dependent

Key points

- Docetaxel chemotherapy should be considered for selected patients at the time of initial diagnosis
  - High risk localised disease not receiving radiation therapy
  - Patients presenting with high risk prostate cancer and metastatic disease at diagnosis

- Third line anti androgen therapy is now standard of care – abiraterone
- We are encouraged by the data for enzalutamide and await funding application
- Docetaxel chemotherapy offers a meaningful clinical benefit to many patients with castrate resistant disease and is well tolerated
- Treatment of advanced prostate cancer is multi-disciplinary – it will also involve the use of radiation therapy, bisphosphonates, and good supportive care

Abiraterone post enzalutamide and docetaxel

- 38 patients, single institution “phase II”
- 8% PSA response >50%
- 18% PSA response >30%
- PFS 2.7 months
- Of the 12 patients with resist measurable disease – 8% had PR

Massard et al Annals of Oncology 2013

Biochemical Recurrence

- Consider Salvage Radical Prostatectomy
  - Especially if no comorbidities,
  - life expectancy of > 10 years,
  - organ confined cancer (<= t2),
  - Gleason Score ≤ 7 and
  - pre-surgical PSA < 10 ng/ml

  - For Cancer Specific Survival rates of 70 – 83% and Overall Survival of 54 – 89%

Chade et al 2012

Cancer of the Prostate Strategic Urologic Research Endeavour
Aggarwal et al

- Post radical radiation therapy plus ADT for biochemical progression

- In the absence of salvage procedures
  - mean time interval from biochemical progression to clinical progression is approximately 3 years

Definition of Recurrence PHOENIX Classification

- Following Radiation therapy
  - PSA of 2 ng/ml above the nadir after RT

- Following radical prostatectomy
  - Confirmed PSA > 0.2 ng/ml on two occasions

With PSA confirmed recurrence

- Do we re-stage via imaging
  - Bone scan
  - CT scan
  - Add no further diagnostic value (add < 5% +) unless the PSA >20ng/ml or PSA velocity is > 2ng/ml
- PET
  - few studies – PSA DT of < 3months strong predictor of + - only considered if salvage lymphadenectomy/RT is being considered
- DO we Re-biopsy
  - Only after RT if salvage radical prostatectomy is indicated.

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