ESMO
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BEST PRACTICE

MANAGEMENT OF HORMONE-SENSITIVE PROSTATE CANCER

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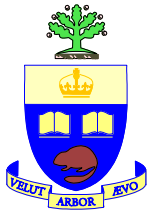


HORMONE-SENSITIVE PROSTATE CANCER

The definition has changed:

- Men with tumour progression after Androgen Deprivation Therapy (ADT) have Castrate-Resistant Prostate Cancer (CRPC)
- Men with CRPC are often still responsive to hormonal agents

This presentation reviews treatment of men with all stages of cancer that may be hormone responsive

INITIAL MANAGEMENT OF METASTATIC PROSTATE CANCER

For ~70 years:

Treatment has been Androgen Deprivation Therapy (ADT):

- Orchiectomy or LHRH agonist (e.g., goserelin; leuprolide)

~90% of men respond with improved symptoms and fall in PSA, for a median duration of 1.5–2 years

Addition of 1st generation anti-androgens (e.g., bicalutamide) leads to further transient response in ~30%

HORMONE SENSITIVITY OF PROSTATE CANCER

Laboratory studies have shown that at progression

- Prostate cancer is often still driven by androgens
- Androgens are produced in prostatic tissue

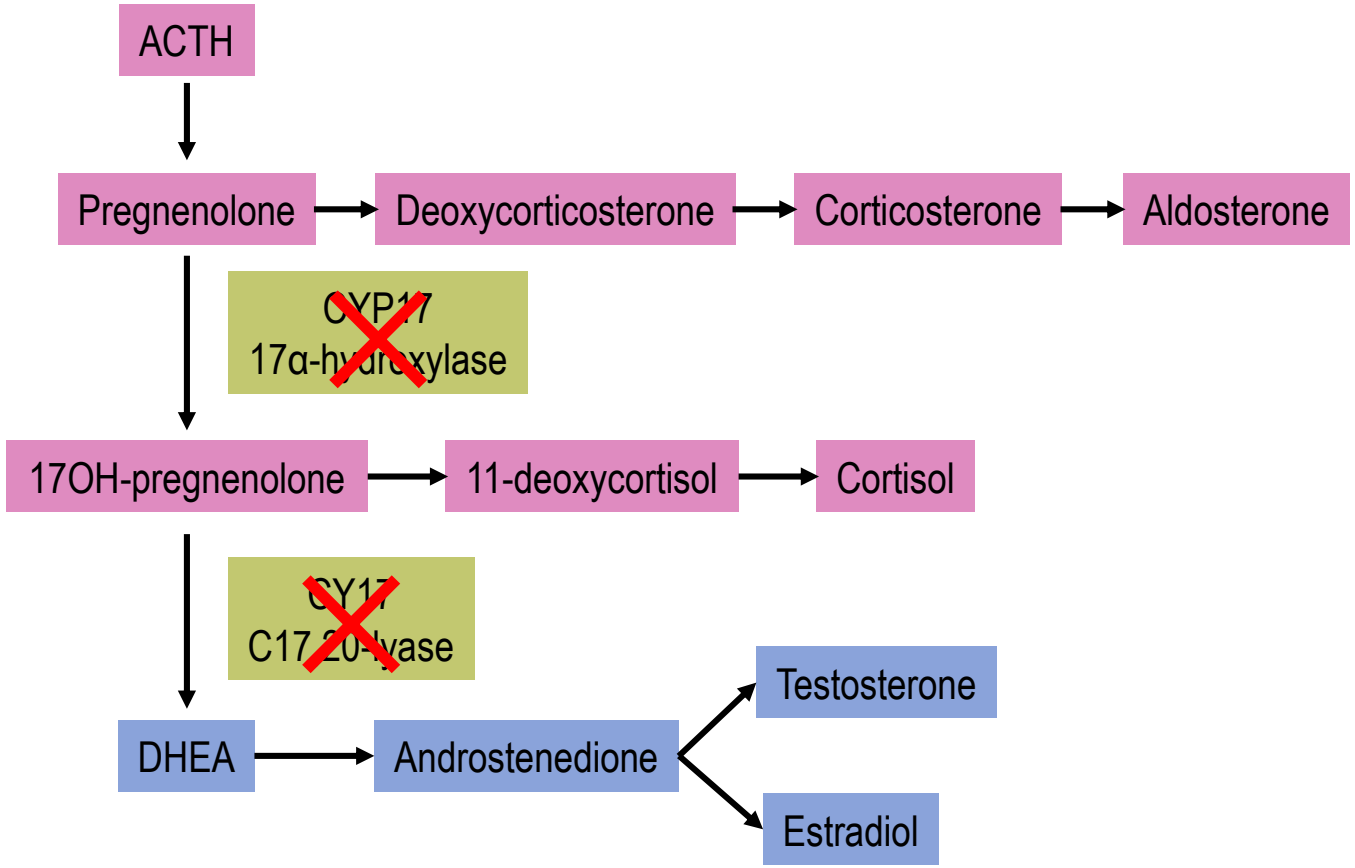
Thus, many men who have progressed on primary ADT remain hormone-sensitive and are referred to as castrate-resistant (CRPC)

Treatment has changed following the development of

- Androgen biosynthesis inhibitors (abiraterone)
- 2nd generation anti-androgens (enzalutamide, apalutamide, darolutamide)

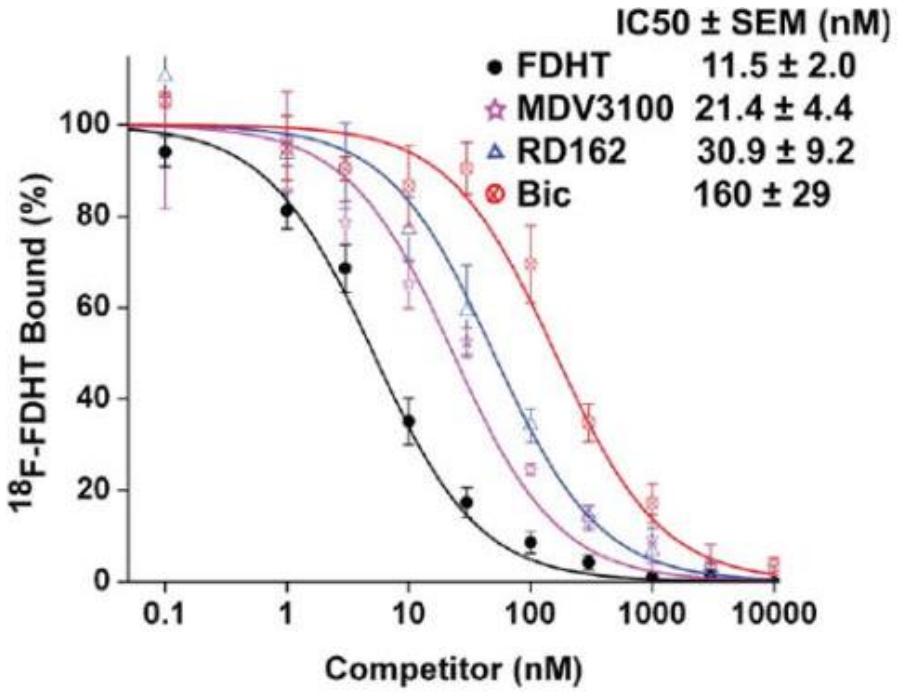
ABIRATERONE ACETATE[1]

Inhibits androgen synthesis



ENZALUTAMIDE (MDV3100)[2]

Enzalutamide (MDV3100) binds 8 times more strongly than bicalutamide to the androgen receptor



1. Attard G,, *et al.* J Clin Oncol 2008;26:4563–71;
2. From Tran C, *et al*. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324(5928):787–90. Reprinted with permission from AAAS

IMPORTANT QUESTIONS

How to manage men with prostate cancer and:

1. Rising PSA without evidence of metastases?
2. Initial treatment of men with distant metastases?
   - With de novo *vs.* later presentation of metastases?
   - With high *vs.* low burden of disease?
   - Is maximal therapy always better than sequential ADT and newer agents?
   - Any role for intermittent ADT?
3. Disease progression while on ADT?
   - (Castrate-resistant but may be hormone-sensitive)

RISING PSA AND NO OVERT METASTASES

Patient numbers are decreasing with improved imaging such as PSMA-PET CT

Radiotherapy to primary site should be used if PSA is rising after surgery

Men with slowly rising (doubling time [DT] >10 mos) and low PSA (<10 ng/mL) do not require immediate treatment

There are new treatments for those with more rapidly rising PSA

RISING PSA ON ADT AND NO OVERT METASTASES

1401/ **1207**/ **1509** men continuing ADT; PSA doubling time <10 mos

2:1 randomisation E or A or D to placebo

Primary endpoint: metastasis-free survival (MFS)

Difference in MFS: **14.6 *vs.* 36.6; 16.2 *vs.* 40.5; 18.4 *vs.* 40.4** months

Improved times to PSA progression and starting other treatments

Trends to improved survival

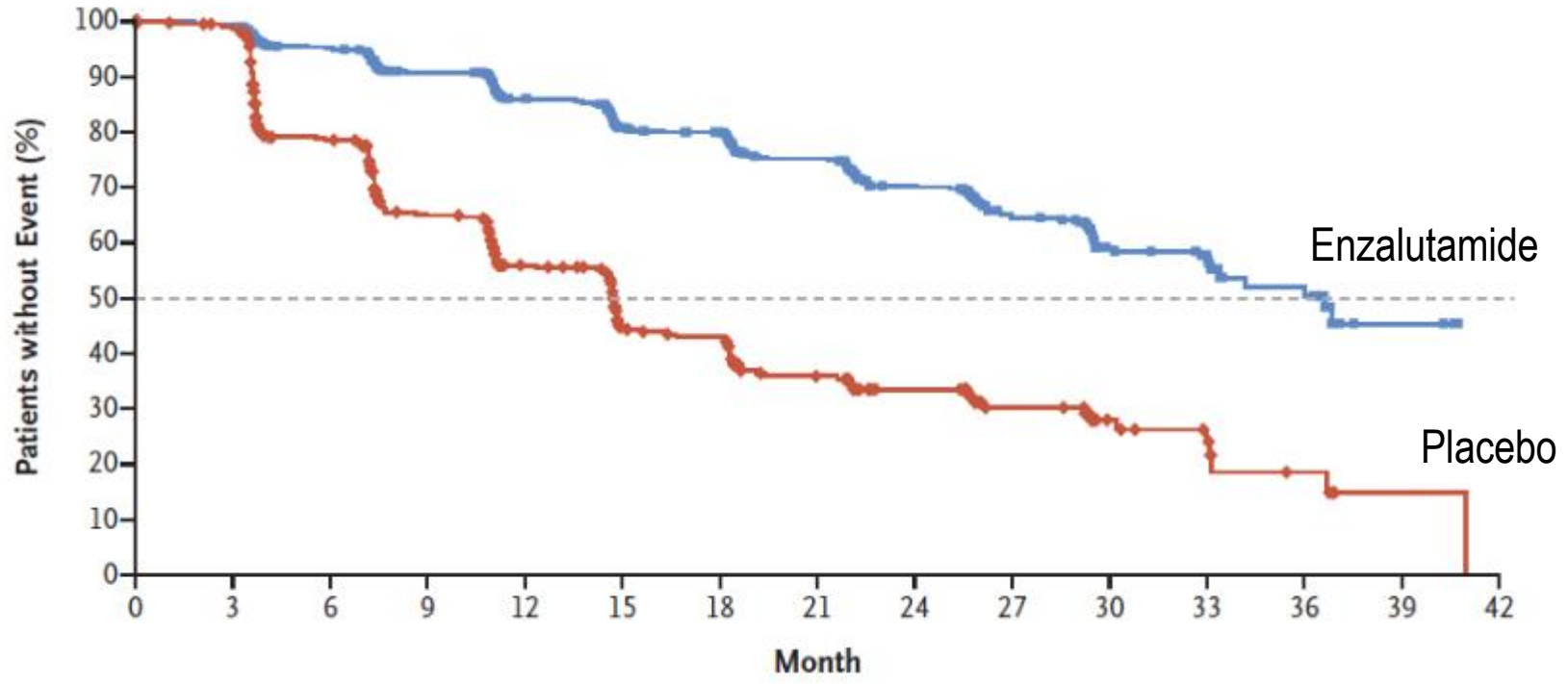
Enzalutamide in Men With Nonmetastatic, Castration-resistant Prostate Cancer
Hussain M, Fizazi K, Saad F, *et al.* N Engl J Med 2018;378:2465–74

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer
Smith MR, Saad F, *et al.* N Engl J Med 2018;378:1408–18

Darolutamide in Nonmetastatic, Castration-resistant Prostate Cancer
Fizazi K, Shore N, Tammela TL, *et al.* N Engl J Med 2019;380:1235–46

Enzalutamide in Men With Nonmetastatic, Castration-resistant Prostate Cancer

Metastasis-free survival in the enzalutamide study



CRITIQUE

Early treatment with AR antagonists in patients with PSA DT <10 months improves metastasis-free survival, but with only small OS benefit, non-significant in 2 of 3 trials

There were rare but increased deaths due to cardiac events in experimental arms of 2 trials – caution is advised in treating men with a history of CV disease

The benefit is obtained at high financial cost

Alternative treatment approaches using agents with a more favourable cost benefit ratio are needed (e.g., low dose abiraterone with food [see slides 32 and 33])

INITIAL TREATMENT OF METASTATIC PROSTATE CANCER

Clinical trials show improved survival when any of the following are added to ADT:

- Docetaxel chemotherapy
- Abiraterone + predniso(lo)ne (5 mg/day)
- Enzalutamide or apalutamide

Key questions:

- Who does and who does not benefit from such combinations?
- Is concurrent treatment always better than sequential use of ADT and new drugs?
- Is there still a role for intermittent ADT as initial treatment?
- If men do need additional treatment, which drug combination is preferred?

DOCETAXEL + ADT FOR HORMONE-SENSITIVE PC

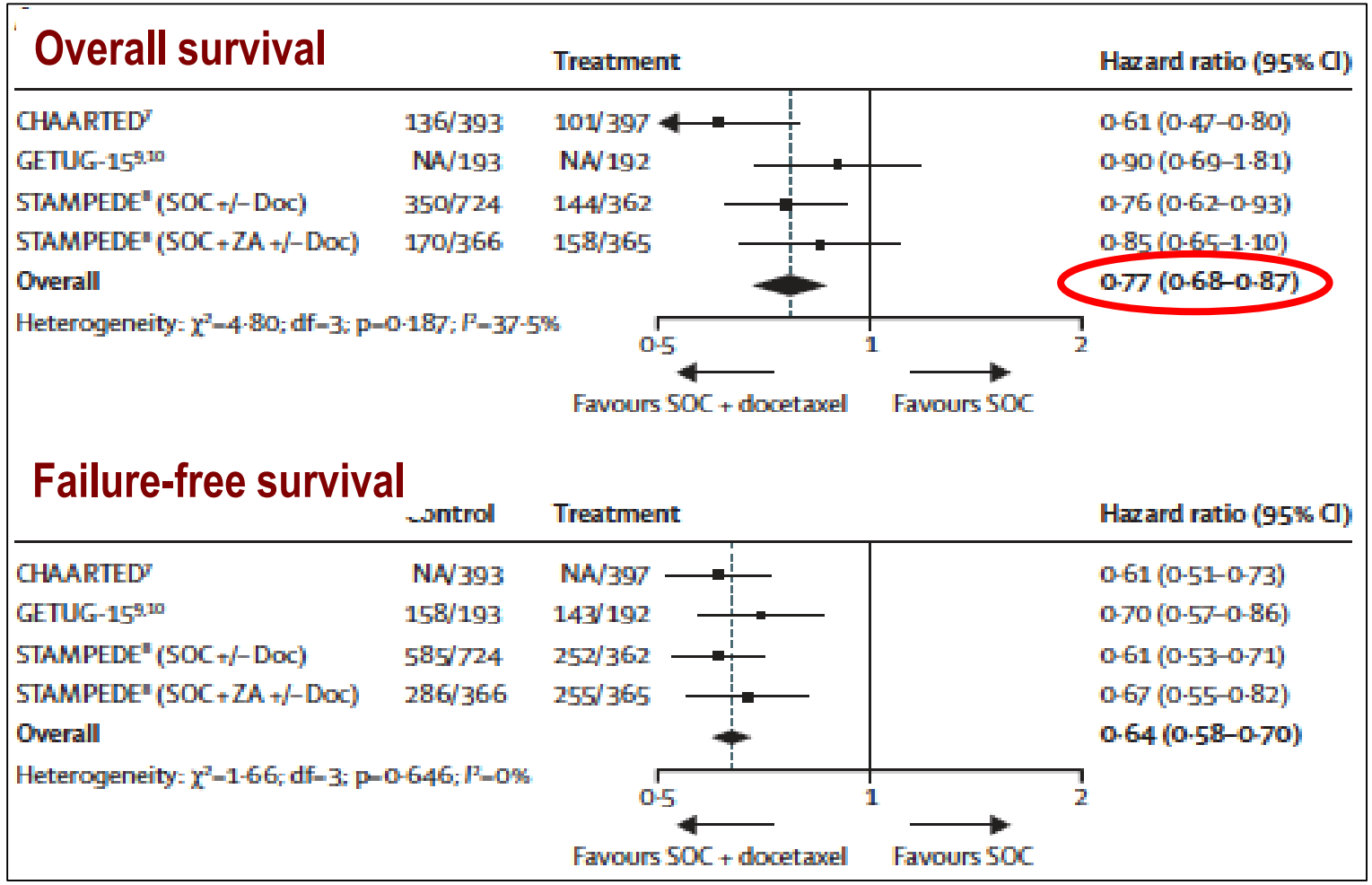
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, Phase 3 trial
Gravis G, Fizazi K, Joly F, *et al.* Lancet Oncol 2013;14:149–58

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial
James ND, Sydes MR, Clarke NW, *et al.* Lancet 2016;387:1163–77

Chemohormonal therapy in metastatic hormone-sensitive prostate cancer
Sweeney CJ, Chen Y, *et al.* N Engl J Med 2015;373:737–46

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data
Vale CL, Burdett S, Rydzewska LHM, *et al*. Lancet Oncol 2016;17:243–56

DOCETAXEL + ADT FOR HORMONE-SENSITIVE PC



THE PATIENTS TREATED IN CHAARTED AND STAMPEDE DO NOT REFLECT THE POPULATION OF MEN PRESENTING WITH METASTASES YEARS AFTER DIAGNOSIS

In these trials:

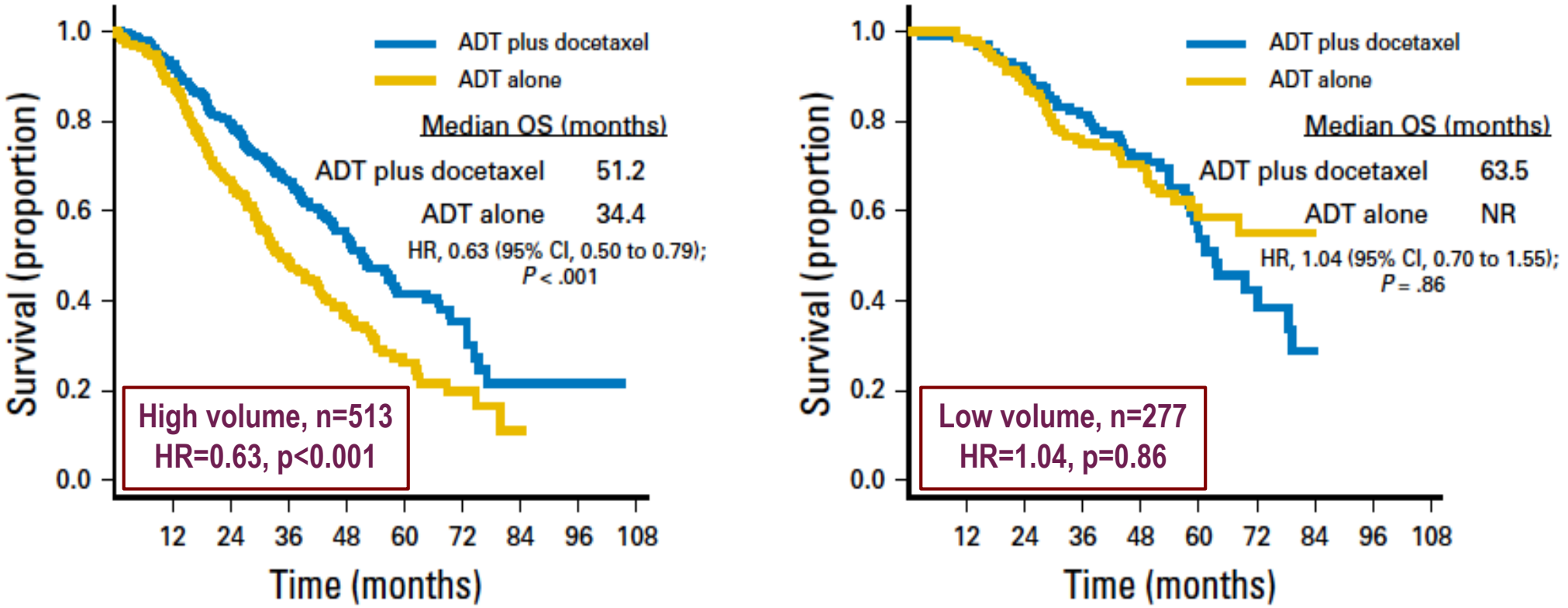
- 70–90% had metastatic disease at diagnosis
- Median age = 64 years
- ~67% with high volume metastases
- ~67% had Gleason 8–10

Men with lower-grade prostate cancer who develop metastases years after local therapy can still be treated with ADT alone

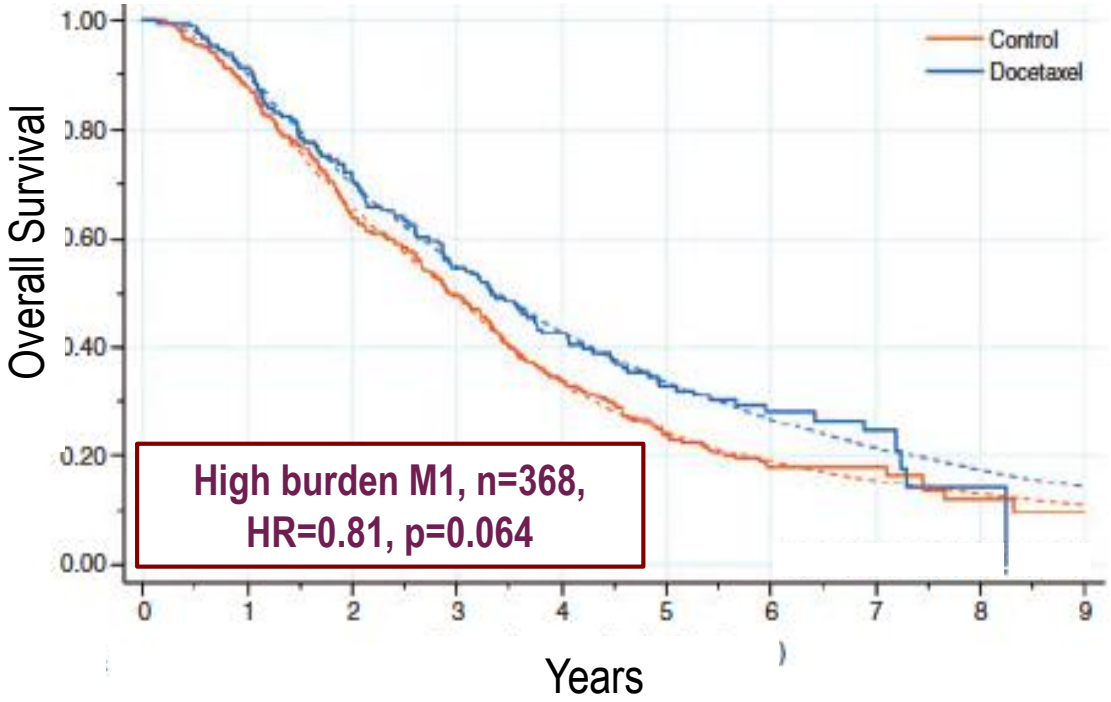
Should men with low-volume disease receive docetaxel + ADT?

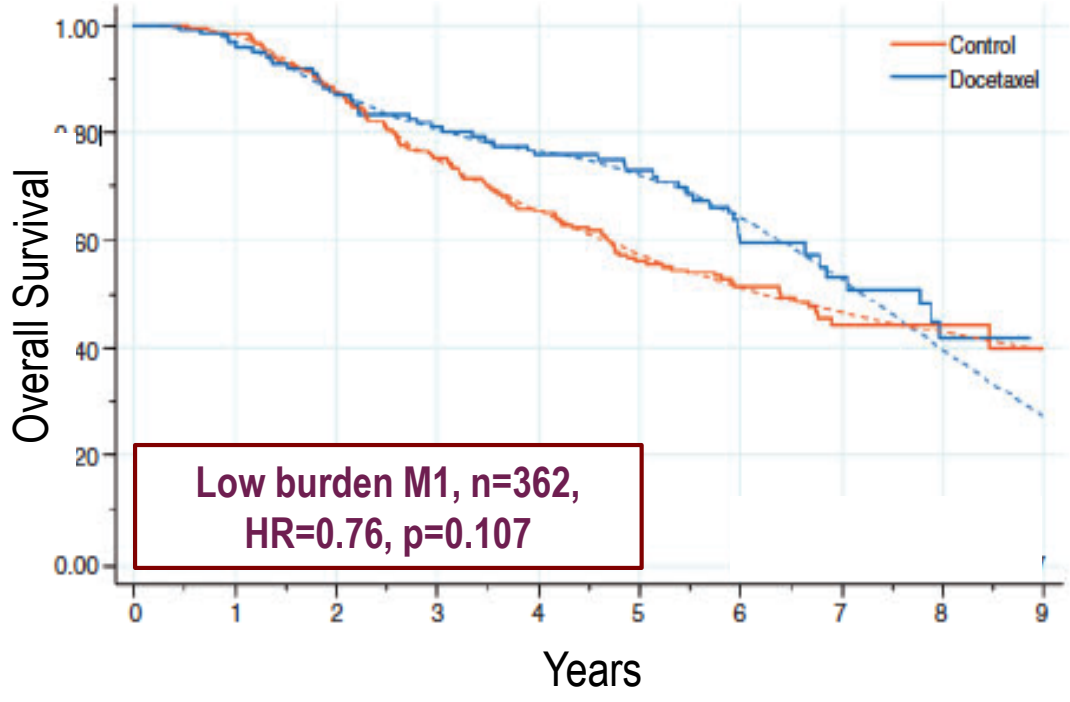
Chemohormonal Therapy in Metastatic Hormone-sensitive Prostate Cancer: Long-term Survival Analysis of the Randomised Phase III E3805 CHAARTED Trial

- This is a pre-planned but underpowered subgroup analysis



Addition of docetaxel to hormonal therapy In low- and high-burden metastatic hormone sensitive prostate cancer: Long-term survival results from the STAMPEDE trial





Should men with low-volume disease receive docetaxel + ADT?

Data from CHAARTED show no benefit

Data from STAMPEDE show a non-significant trend to benefit

Men with low volume disease should not receive docetaxel

TWO TRIALS SHOW BENEFIT OF ADDING ABIRATERONE TO ADT

For men with high risk advanced HSPC

High-risk criteria:

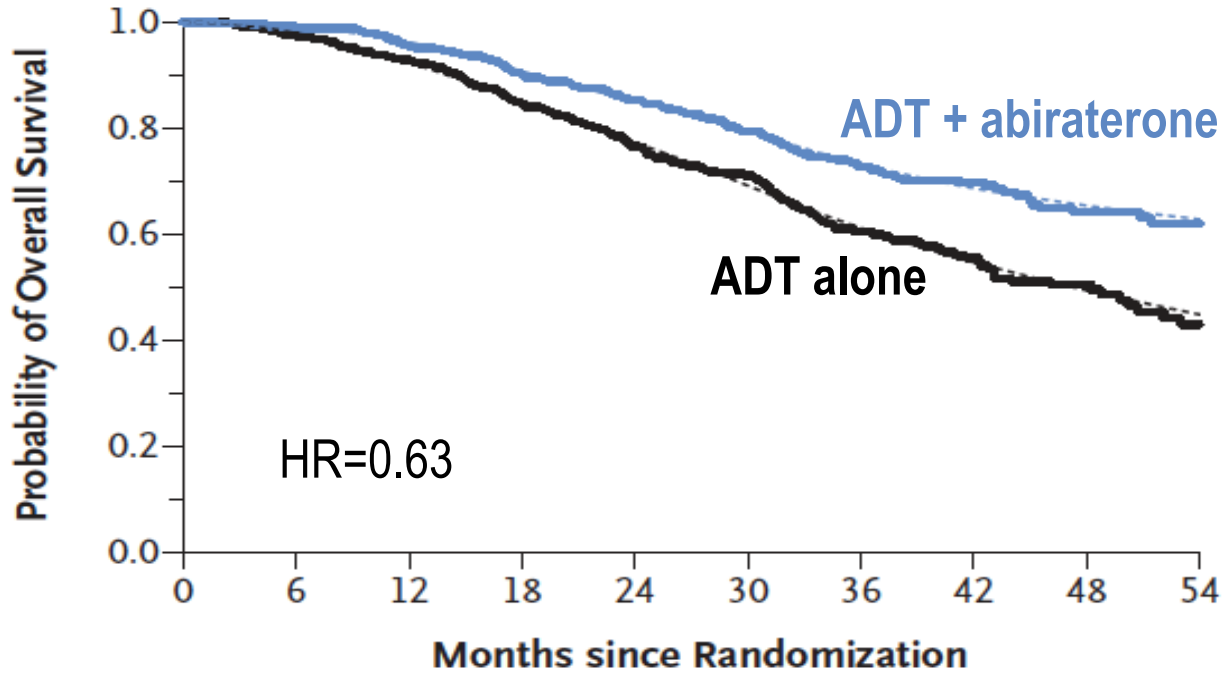
STAMPEDE (James ND, *et al,* NEJM 2017;377:338–51)

Newly diagnosed metastatic PC, or N+ or high-risk locally advanced disease, or relapse after surgery or RT with high-risk features

LATITUDE (Fizazi K, *et al,* NEJM 2017;377:352–60)

At least 2 of 3 of: Gleason ≥8, ≥3 bone lesions, visceral metastasis

OVERALL SURVIVAL IN PATIENTS WITH METASTATIC DISEASE



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

Data shown for STAMPEDE; OS-curves for LATITUDE are similar

ENZALUTAMIDE OR APALUTAMIDE FOR MEN WITH HORMONE-SENSITIVE PC

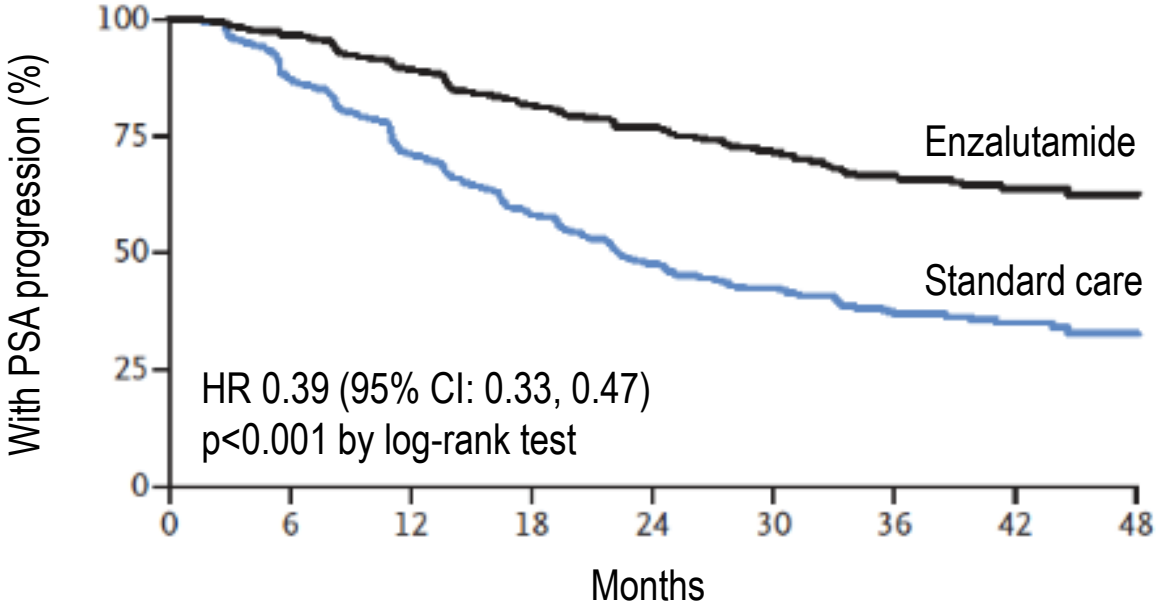
Apalutamide for Metastatic, Castration-sensitive Prostate Cancer
Chi KN, Agarwal N, Bjartell A, *et al.* N Engl J Med 2019;381:13–24

Enzalutamide with Standard First-line Therapy in Metastatic Prostate Cancer
Davis ID, Martin AJ, Stockler MR, *et al.* N Engl J Med 2019;381:121–31

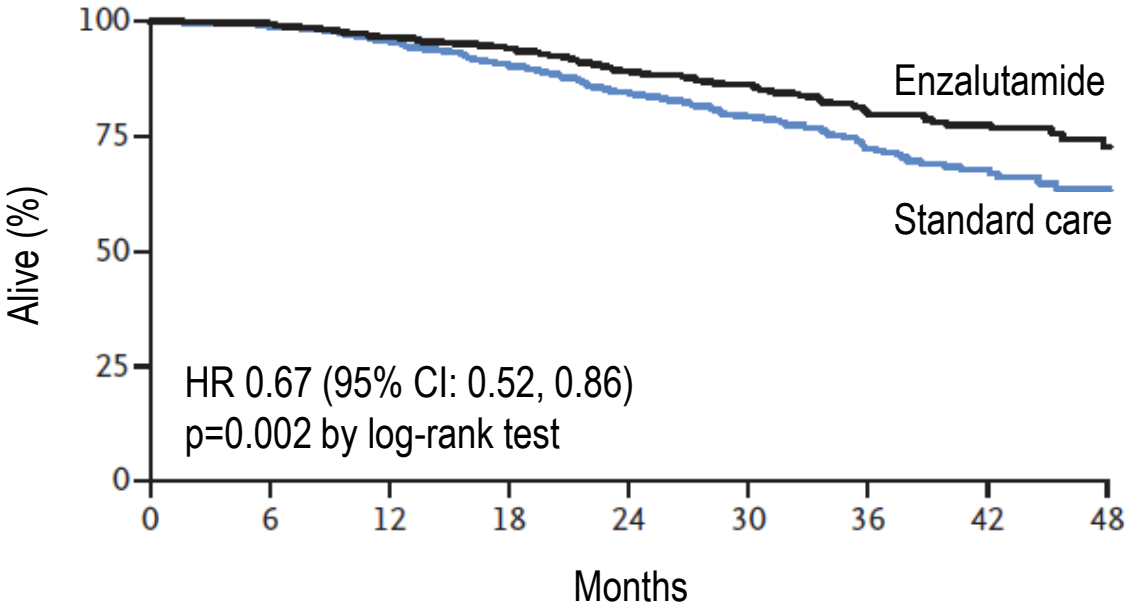
ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-sensitive Prostate Cancer
Armstrong AJ, Szmulewitz RZ, Petrylak DP, *et al.* J Clin Oncol 2019;37:2974–86

Enzalutamide with standard first-line therapy in metastatic prostate cancer

PSA progression-free survival



Overall survival



IF YOU ADD AN AGENT TO CLASSICAL ADT, WHICH SHOULD YOU USE?

Adding abiraterone, enzalutamide or apalutamide to ADT conveys a similar OS benefit (HR≈0.65)

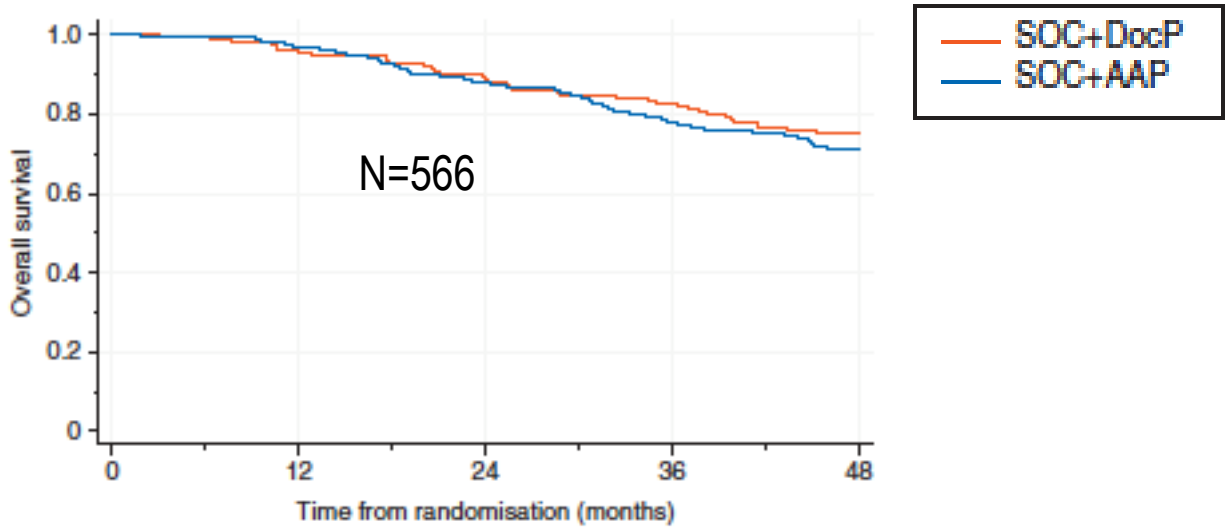
Adding docetaxel was also beneficial, but there are no data showing a difference in mean OS or QoL compared with AR targeted agents (see next slide)

6 cycles of docetaxel can lead to myelosuppression and neuropathy

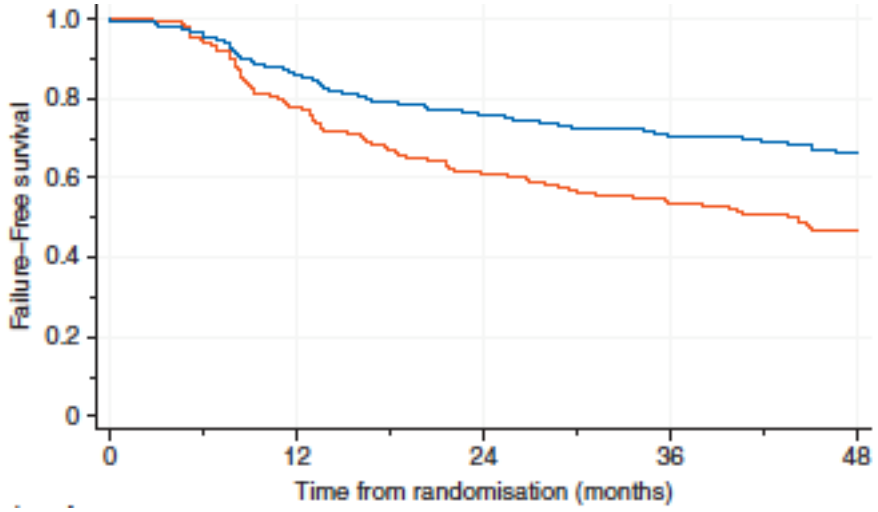
Hormonal agents are continued until disease progression; they result in milder, yet chronic, side effects and may cost more

Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol

Overall survival



Failure-free survival



On basis of FFS, abiraterone is favoured over docetaxel for most men

No evidence (yet) to support using both

DO ALL PATIENTS NEED CONCURRENT TREATMENT WITH A NEW HORMONAL AGENT (NHA) IN ADDITION TO ADT?

Is concurrent ADT + NHA better than sequential treatment?

- **Probably YES for those who met entry criteria to the trials**
- No trial compared ADT + NHA *vs.* ADT ➔ NHA (at progression)
- **BUT** survival gain and delay in progression/symptoms support concurrent treatment

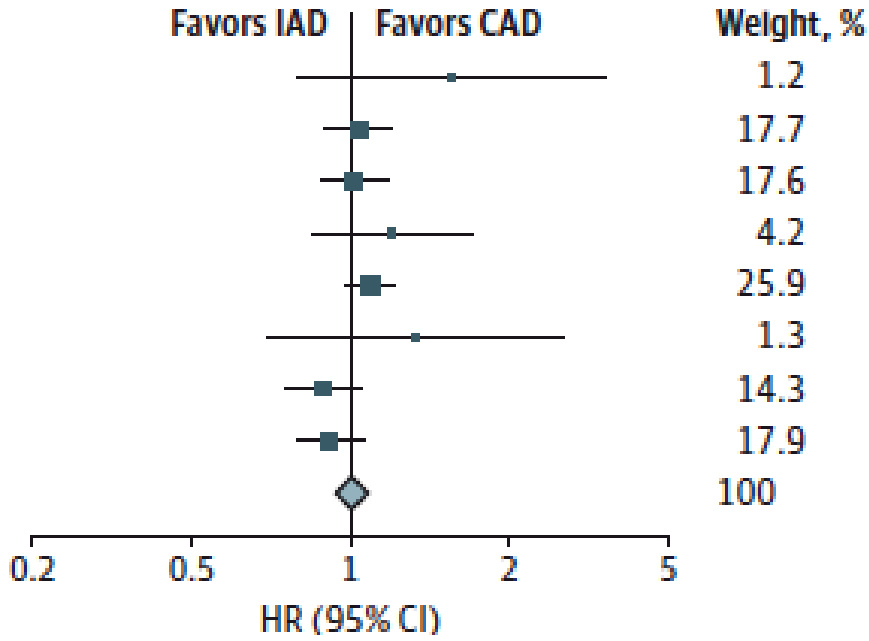
Participants in key trials were mainly those with high-risk disease

- Benefit of combined treatment in men with slow progression, low volume, Gleason ≤7 disease is uncertain.
- **These men can continue to receive ADT alone….**
  - …. including the option of intermittent ADT, if there is low-risk metastatic disease and good initial PSA response to 6 months ADT

Intermittent *vs.* Continuous Androgen Deprivation Therapy for Prostate Cancer: A Systemic Review and Meta-analysis

Overall survival

Source	Log HR (SE)	HR (95% CI)
Irani et al,[31] 2008	0.5128 (0.3950)	1.67 (0.77-3.62)
Calais da Silva et al,[27] 2009	0.0392 (0.0870)	1.04 (0.88-1.23)
Crook et al,[13] 2012	0.0198 (0.0871)	1.02 (0.86-1.21)
Mottet et al,[36] 2012	0.2070 (0.2069)	1.23 (0.82-1.85)
Hussain et al,[14] 2013	0.0953 (0.0641)	1.10 (0.97-1.25)
Organ et al,[37] 2012	0.3293 (0.3800)	1.39 (0.66-2.93)
Salonen et al,[38,39] 2008	-0.1393 (0.1008)	0.87 (0.71-1.06)
Calais da Silva et al,[15] 2013	-0.1054 (0.0863)	0.90 (0.76-1.07)
Total		1.02 (0.93-1.11)



Meta-analysis of trials shows no difference in overall survival between intermittent and continuous ADT

Which toxicities are expected with early and long-term use of new hormonal agents?

Risk and timing of cardiovascular disease after androgen-deprivation therapy In men with prostate cancer

Based on data from Swedish National Health Care Registers

Group	n	HR for risk of CV disease	Confidence interval
Age-matched Controls	187,785		
PC on GnRH analogues	26,959	1.21	1.18, 1.25
PC with orchidectomy	3,747	1.16	1.08, 1.25
PC on anti-androgens	10,656	0.87	0.82, 0.91

Substantial increase in risk for all types of ADT with prior history of CV disease

Other studies show consistent results

O'Farrell S, *et al.* J Clin Oncol 2015;33:1243–51.

TOXICITY OF ABIRATERONE AND ENZALUTAMIDE

Toxicity profile characteristics of novel androgen-deprivation therapy agents in patients with prostate cancer: a meta-analysis
Zhu J, Liao R, Su C, *et al.* Expert Rev Anticancer Ther 2018;18(2):193–8

The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer
Iacovelli R, Ciccarese C, Bria E, *et al.* Clin Genitourin Cancer 2018;16(3):e645–e653

Most toxicity is mild and rare (but increased CV effects):

- Abiraterone + prednisone: hypertension, hypokalaemia
- Enzalutamide: fatigue, hypertension, rare seizures,
- Apalutamide: rash, hypothyroidism

Participants in trials are selected with good PS and low comorbidity. CV toxicity may occur more often in the real world

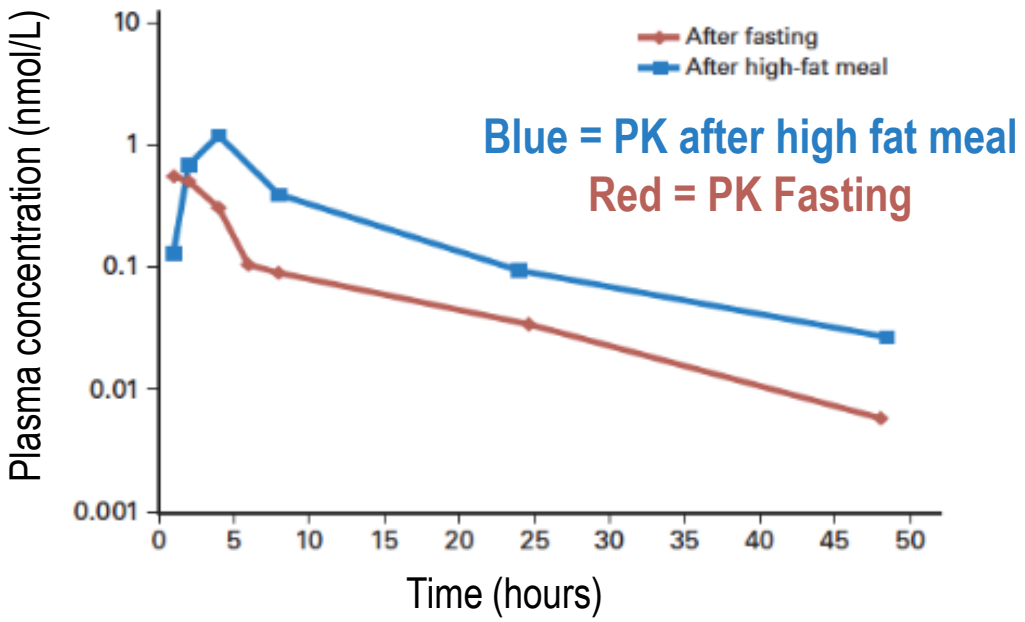
TOXICITY WILL INCREASE WITH LONG-TERM TREATMENT

… and financial toxicity will be extreme

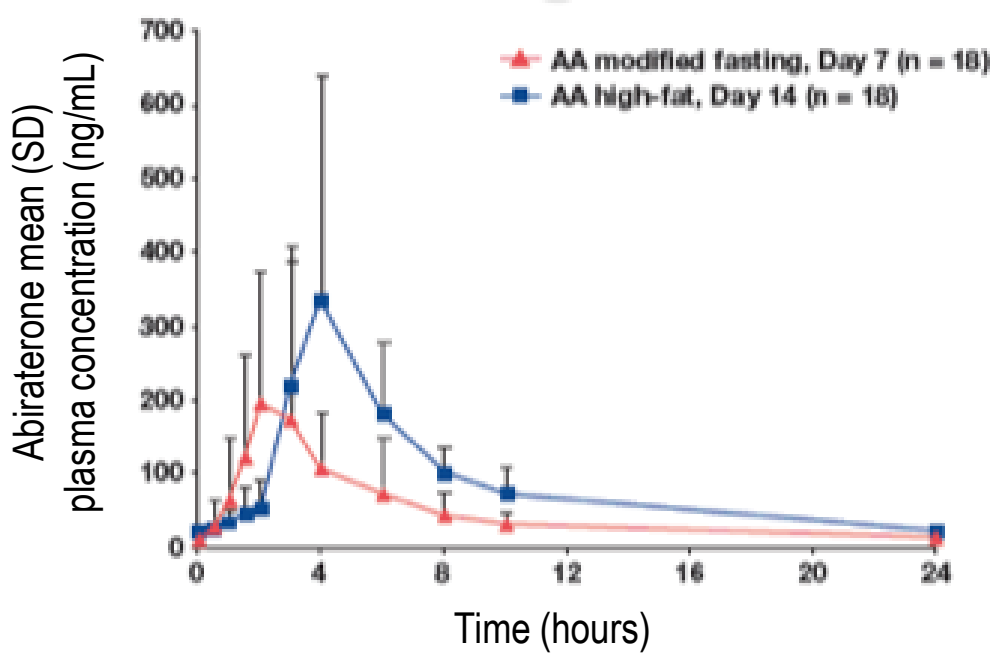
HOW TO MAKE ABIRATERONE CHEAPER?

Standard dose is 1000 mg/day (4 pills) on an empty stomach. Cost in USA is ~$10,000/month (but decreasing)

250 mg after a fatty meal gives similar drug concentration



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



Chi KN, *et al.* Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. J Clin Pharmacol 2015;55(12):1406–14, with permission of John Wiley and Sons, © 2015, The American College of Clinical Pharmacology

Prospective International Randomised Phase II Study of Low-dose Abiraterone With Food *vs*. Standard Dose Abiraterone in Castration-resistant Prostate Cancer

72 men randomised to abiraterone 1000 mg/d on empty stomach (STANDARD) or 250 mg/day after low fat breakfast (LOW)

Primary endpoint: change in PSA at 12 weeks

- No sig diff. with a trend to greater fall in PSA in LOW arm
- Time to PSA progression ~14 months in both arms (p=0.56)

Similar PK with less variability in LOW arm

Similar PD effects to decrease target adrenal androgen

NCCN now include low dose abiraterone with food (as an option) in their guidelines

Szmulewitz RZ,, *et al.* J Clin Oncol 2018;36(14):1389–95.

Low-dose Abiraterone in Metastatic Prostate Cancer: Is it Practice Changing? Facts and Facets

Survey of Indian oncologists

Most now aware of NCCN guideline

91% would change practice to use low-dose abiraterone with food

Estimated:

- Mean saving per patient = $US 3,640
- Annual saving to Indian health service = $US 182 million

Patel A, *et al.* JCO Global Oncol 2020;6:382–6.

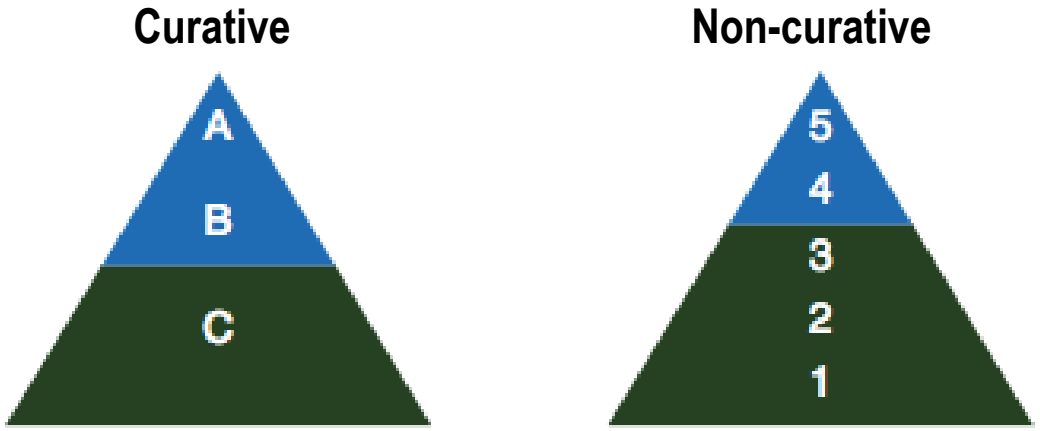
Improving Treatment for Advanced Prostate Cancer

"Until enzalutamide (and related drugs such as apalutamide and darolutamide) are marketed at similar prices, their routine use in the management of any stage of prostate cancer cannot be justified, since the annual cost would be approximately $120,000 per patient, as compared with approximately $8,400 for low-dose abiraterone."

Tannock IF, *et al.* N Engl J Med 2019;381(2):176–7.

ESMO CLINICAL VALUE SCALE

ESMO MCBS evaluation



Curative-Evaluation form 1: for new approached to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative

Based on criteria for:

Improved OS

Improved surrogate for OS

Improved DFS or PFS

Living better

Improved QoL

Reduced toxicity

SO HOW SHOULD WE TREAT HORMONE-SENSITIVE PROSTATE CANCER?

With ESMO Magnitude of Clinical Benefit Score (MCBS)

If slowly progressive, low-volume, Gleason ≤7

- ADT alone, consider intermittent ADT

(No MCBS for equivalence)

If rising PSA with doubling time <10 months OR any of: *de novo* presentation of metastases, high-volume disease, Gleason ≥8, rapid progression, visceral metastases

- ADT + abiraterone preferred for most men (ADT + enzalutamide as alternative) **MCBS-5**
- ADT + docetaxel **MCBS-4**

  (docetaxel may be given prior to adding abiraterone or enzalutamide but no proof of added benefit)

TREATMENT AT PROGRESSION

With ESMO Magnitude of Clinical Benefit Score (MCBS)

If men have had ADT alone, or ADT + docetaxel

- Add abiraterone (or enzalutamide) to ADT MCBS-5

If men have received ADT + abiraterone or enzalutamide

- Response rate to alternative agent is low, but worth trying in those with slowly progressing disease
- If rapid progression, or short duration of hormonal response, give docetaxel (or cabazitaxel if already received docetaxel)
  - if fit enough to receive chemotherapy MCBS-4
- Radium-223 is alternative for bone-dominant disease MCBS-4

Give a bone protecting agent (e.g., zoledronate every 3 months)

- See Tombal, *et al*. ASCO, 2019

Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone In metastatic castration-resistant prostate cancer: A multicenter, randomised, open-label, phase 2 crossover trial

RCT (N=202) found 36% PSA response rate for enzalutamide after abiraterone;
4% for abiraterone after enzalutamide

Other studies have shown lower response rates for 2nd line treatment in either order

No benefit of abiraterone + enzalutamide compared with enzalutamide alone for CRPC
(Morris, *et al.* ASCO 2019)

STAMPEDE is studying this for hormone-sensitive disease

Khalaf DJ, *et al.* Lancet Oncol 2019;20:1730–9.

Informing patients about expected outcomes: The efficacy-effectiveness gap

Patients are highly selected to take part in clinical trials (younger, high PS, comorbidity excluded)

Efficacy = Benefit of a new treatment in clinical trials

Effectiveness = Benefit of a new treatment in real world

Patients in the real world have less benefit and more toxicity than those in clinical trials

Example: Men receiving docetaxel for CRPC

TAX327 trial: median OS = 19.3 mos and 3% septic neutropenia

Routine practice at PMH: median OS = 13.6 mos with 9.6% septic neutropenia

ADJUST YOUR EXPECTATIONS!

Templeton AJ, *et al.* J Clin Oncol 2020; 38(15):1651–4.

Randomised controlled trials and population-based observational research: Partners in the evolution of medical evidence

RCTs	Population-based studies
Precise measures of efficacy under ideal conditions	Difficulty in eliminating bias and confounders of effect
Poor measure of effectiveness under real-life conditions	**Can estimate effectiveness in the general population**
Limited information on toxicity	**Assess toxicity under real-life conditions**
Applicability to clinical practice can be limited	**Evaluate uptake of treatment in general population**

Booth CM, Tannock IF. Br J Cancer 2014;110:551–5.

UHN Princess Margaret Cancer Centre

ESMO

“THE OPINION OF EXPERTS IS RESPONSIBLE FOR ALL OF THE ERRORS THROUGHOUT MEDICAL HISTORY”

…but you can find expert opinions here:

Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019

Gillessen S, Attard G, Beer TM, *et al.* Eur Urol 2020;7:508–47

EPILOGUE: CHANGING STATISTICS

Prostate cancer statistics

More than 1.1 million cases of prostate cancer were recorded in 2012, accounting for around 8% of all new cases and 15% in men

Two thirds of cases of prostate cancer are diagnosed in more developed regions of the world

This is misleading and changing because:

1. A substantial proportion of “Western” prostate cancers are screen-detected – many of them non-lethal
2. Men in developing countries are living longer, so the incidence of prostate cancer is increasing

Most lethal prostate cancer will be in lower and middle-income countries. Cost-effective treatments are essential

World Cancer Research Fund International

ESMO

THANK YOU!