Systemic Treatment of metastatic prostate cancer

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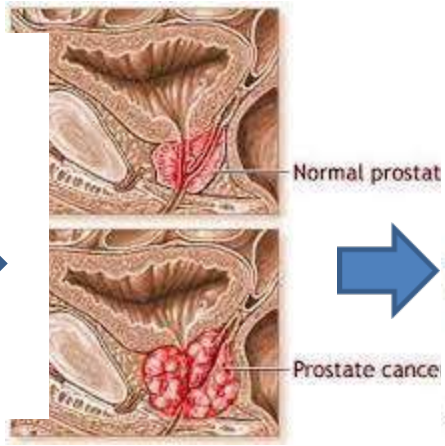
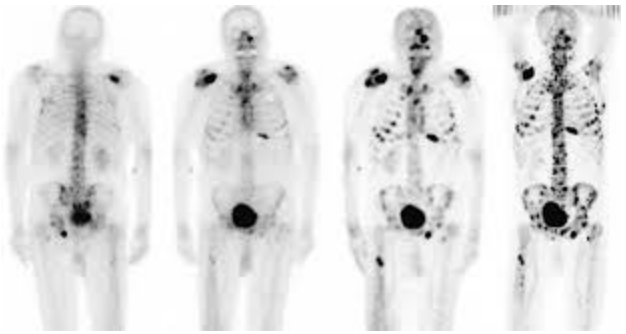
Past-Present-Future

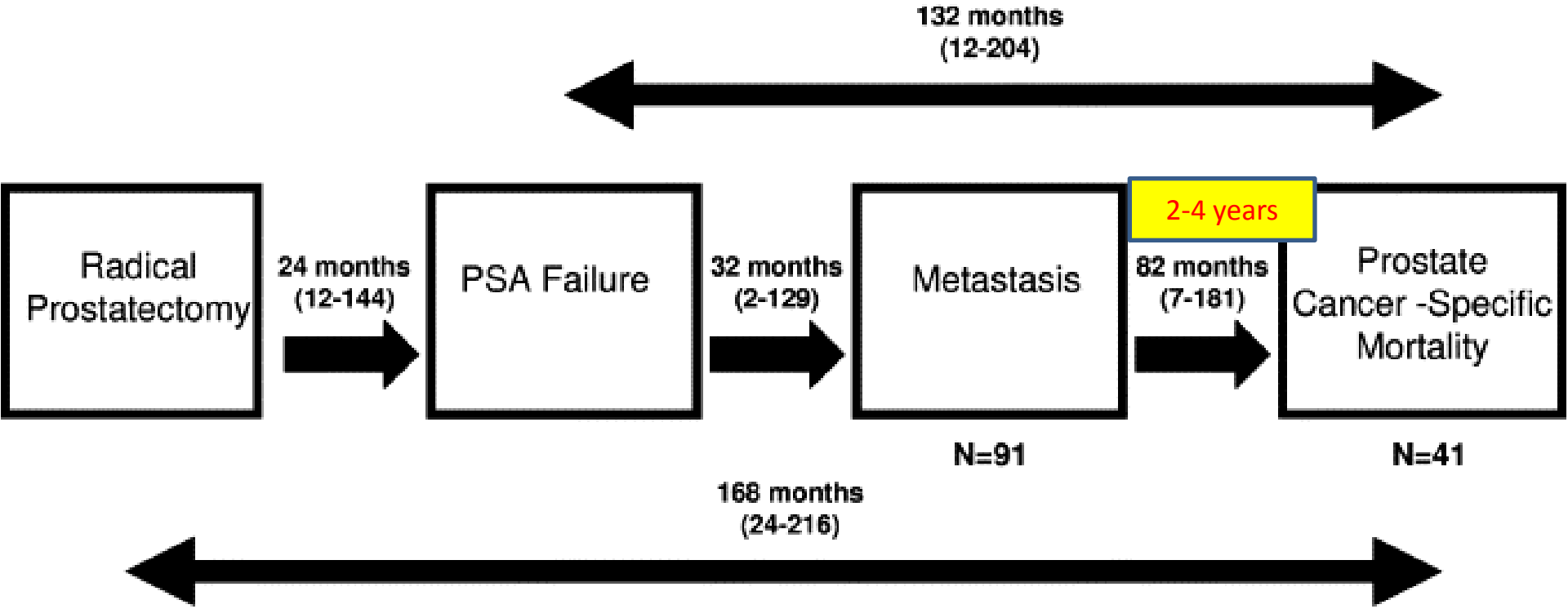
- HSPC vs CRPC
- Treatment for CRPC
- Treatment for HSPC
- What we learned in 2016
- What is new knowledge in 2017



PSA

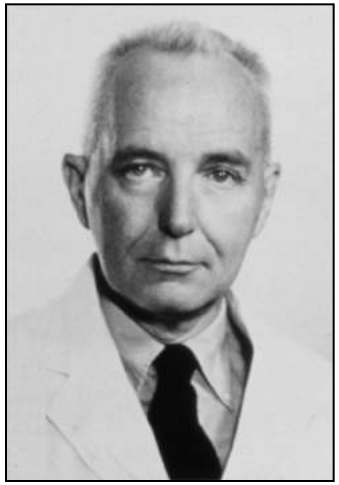


Treatment for Prostate cancer



Makarov, et al; J Urol:179:156, 2008

Charles Huggins, Nobel lecture, 13 décembre 1966



Following orchiectomy, the prostate shrinks, the oxidative phase of carbohydrate metabolism declines, and secretion stops. (…) The prostatic cell does not die in the absence of testosterone, it merely shrivels.

HSPC vs CRPC

- **Castration (hormonal) -sensitive: disease controlled by androgen suppression**
  - **Median OS may reach 69 months**
    - **HussainNEJM2013**

Castration-resistant:

- **Median OS may reach 34 months (asymptomatic or low-symptomatic patients)**

Ryan Lancet Oncol 2015, Beer NEJM2014

Castration-Resistant Prostate Cancer (CRPC): Definition

Castrate serum testosterone

<50 ng/mL or 1.7 nmol/L

+ either

Biochemical progression

3 consecutive increases in PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL

OR

Radiological progression

The appearance of ≥2 bone lesions on a bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

PSA: prostate-specific antigen

EAU guidelines on prostate cancer (2014 update) – www.uroweb.org

Identify right diagnosis with criteria “CRPC”

Serum testosterone

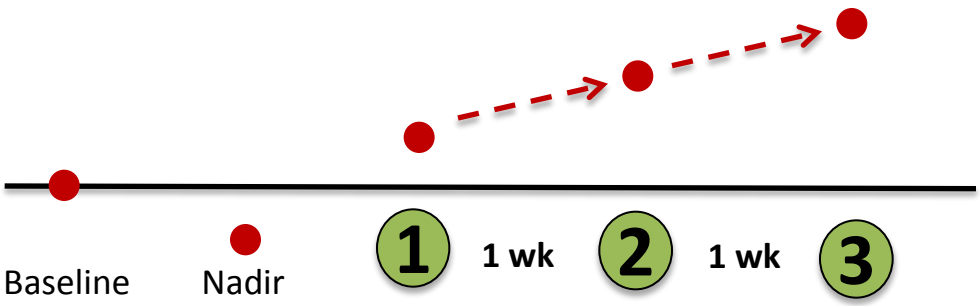
< 50 ng/dL (1.7 nmol/L)

By using Androgen Deprivation Therapy

One or any in combination

Biochemical progression

Three consecutive rises in PSA



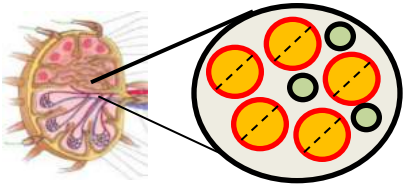
PSA increases ≥ 50% and ≥ 2 ng/mL above nadir

PSA increases ≥ 50% and ≥ 2 ng/mL above nadir

Confirm the trend of PSA increase

Radiological progression

Or



Presence ≥ 2 bone lesions

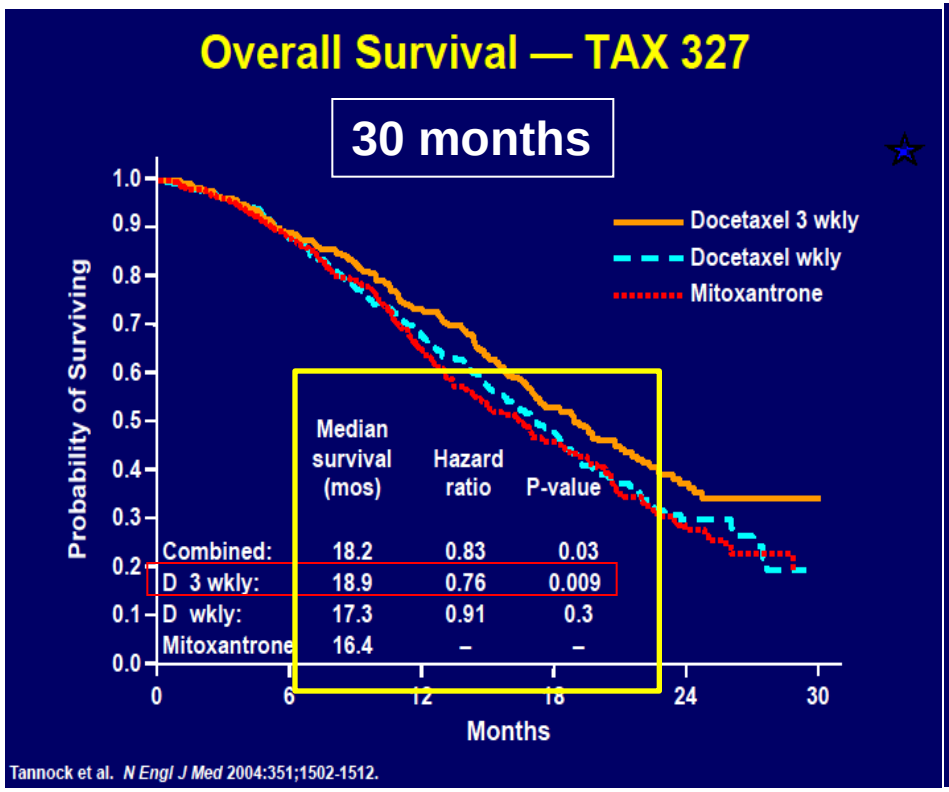
Presence soft tissue lesions with nodes >2 cm in diameter

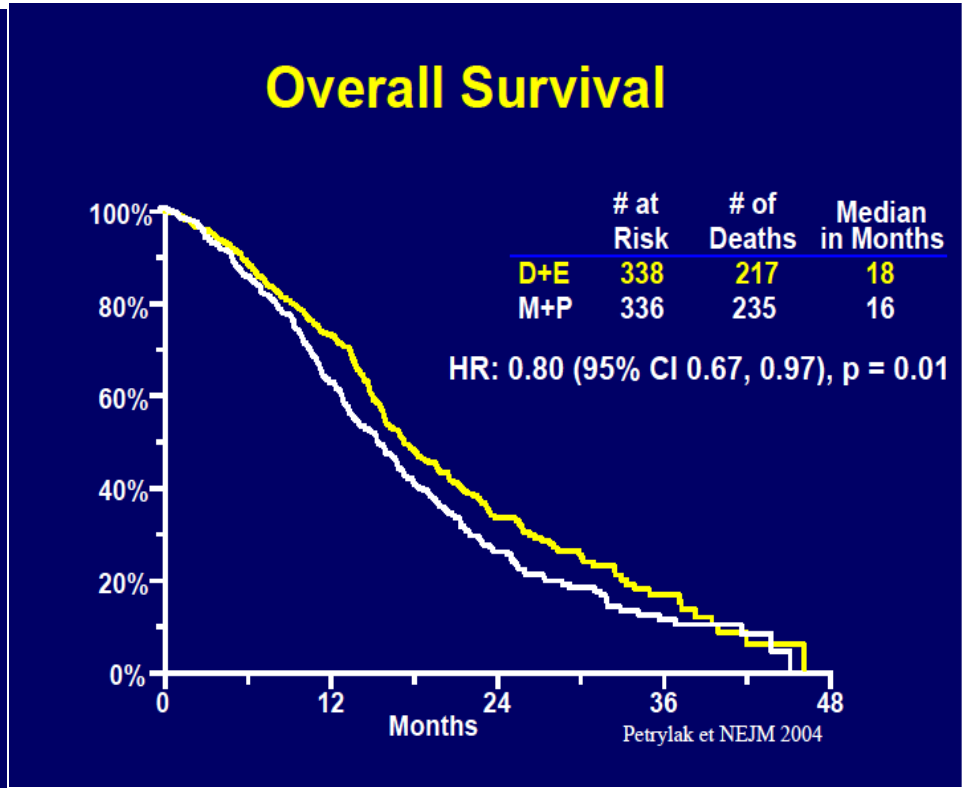
EAU guideline 2015; PCWG2; RECIST 1.1

TAX 327: 3 arms

- 5 mg prednisolone BID
- Mitoxantrone 12 mg / m2 q 3 wk
- Docetaxel 75 mg /m2 q 3 wk 10 cycle
- Docetaxel 30 mg / m2 wkly for 6 wk 5 cycle

Two randomised phase 3 trials have demonstrated a significant improvement in overall survival (OS) for docetaxel- based chemotherapy, compared with the mitoxantrone-prednisone combination





Tannock IF et al NEJM 2004; 351: 1502–12

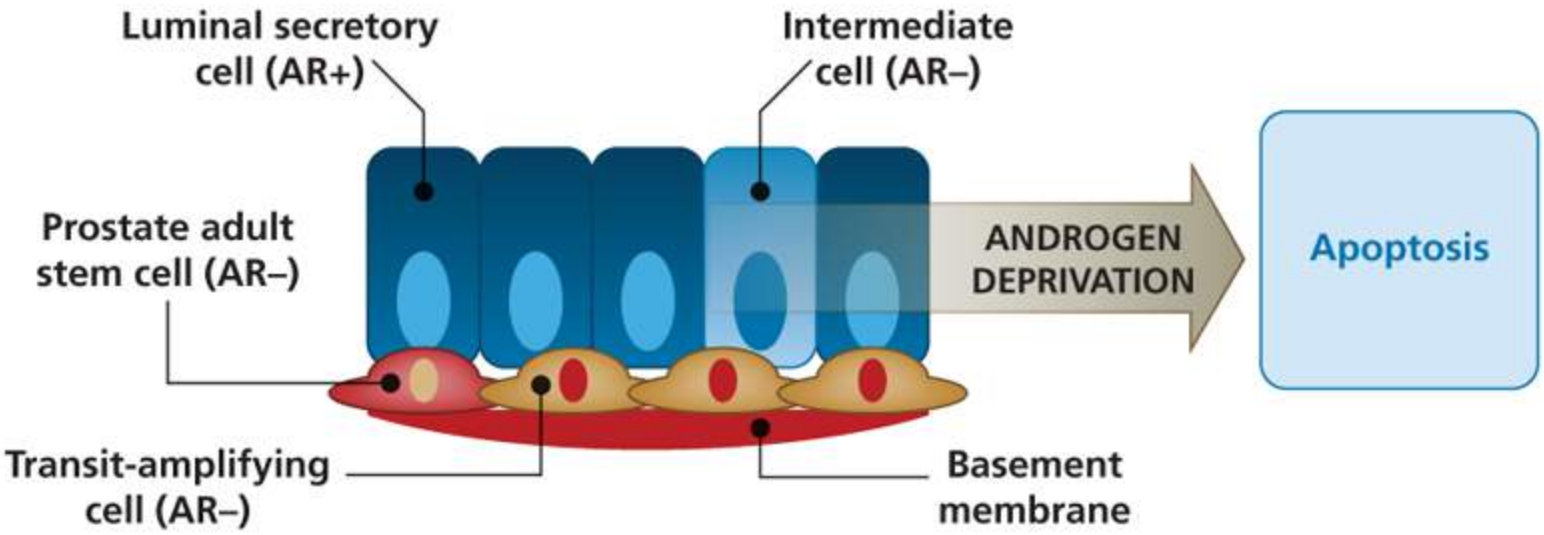
Petrylak DP et al NEJM 2004; 351: 1513–20.

Docetaxel given at the dose of 75 mg/m2 every 21 d is the sole regimen approved by the FDA and EMA for the treatment of mCRPC

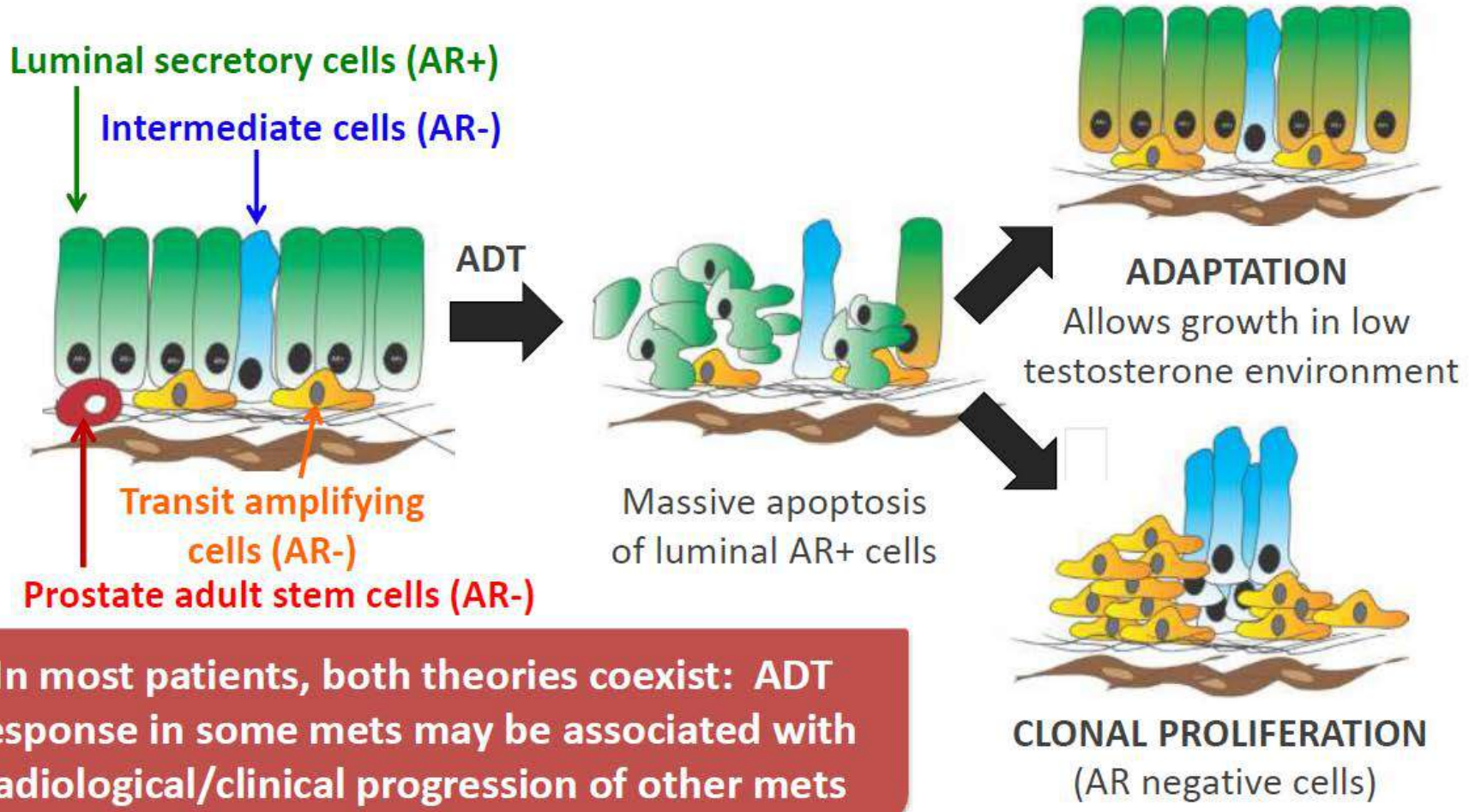
CRPC is not truly CRPC

- Transit-amplifying cells and intermediate cells (both AR–)
- Luminal secretory cells (AR+)

- Deprived of circulating androgen, the AR+ luminal cells will induce apoptosis



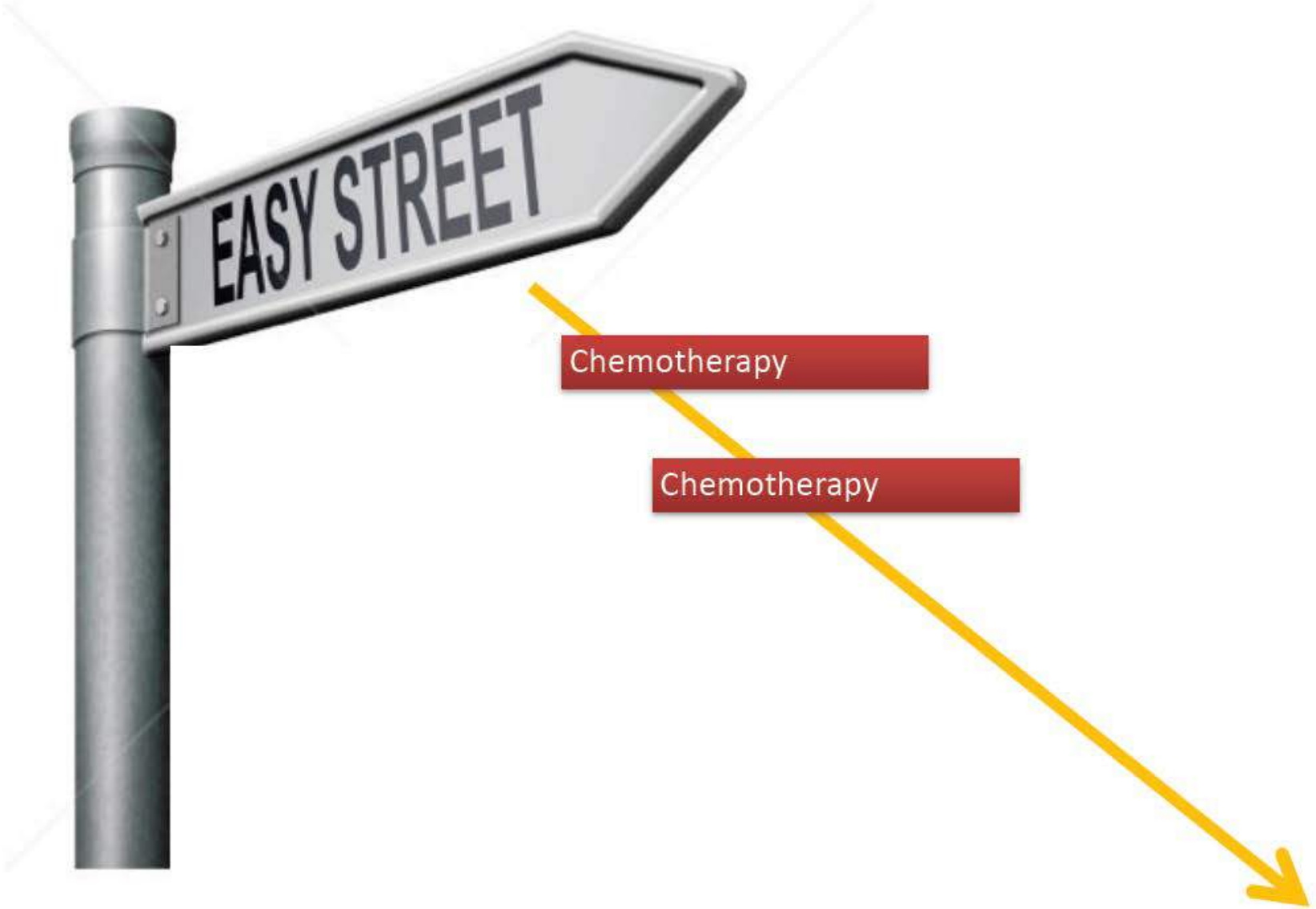
PCa progression in low testosterone environment: 2 leading theories



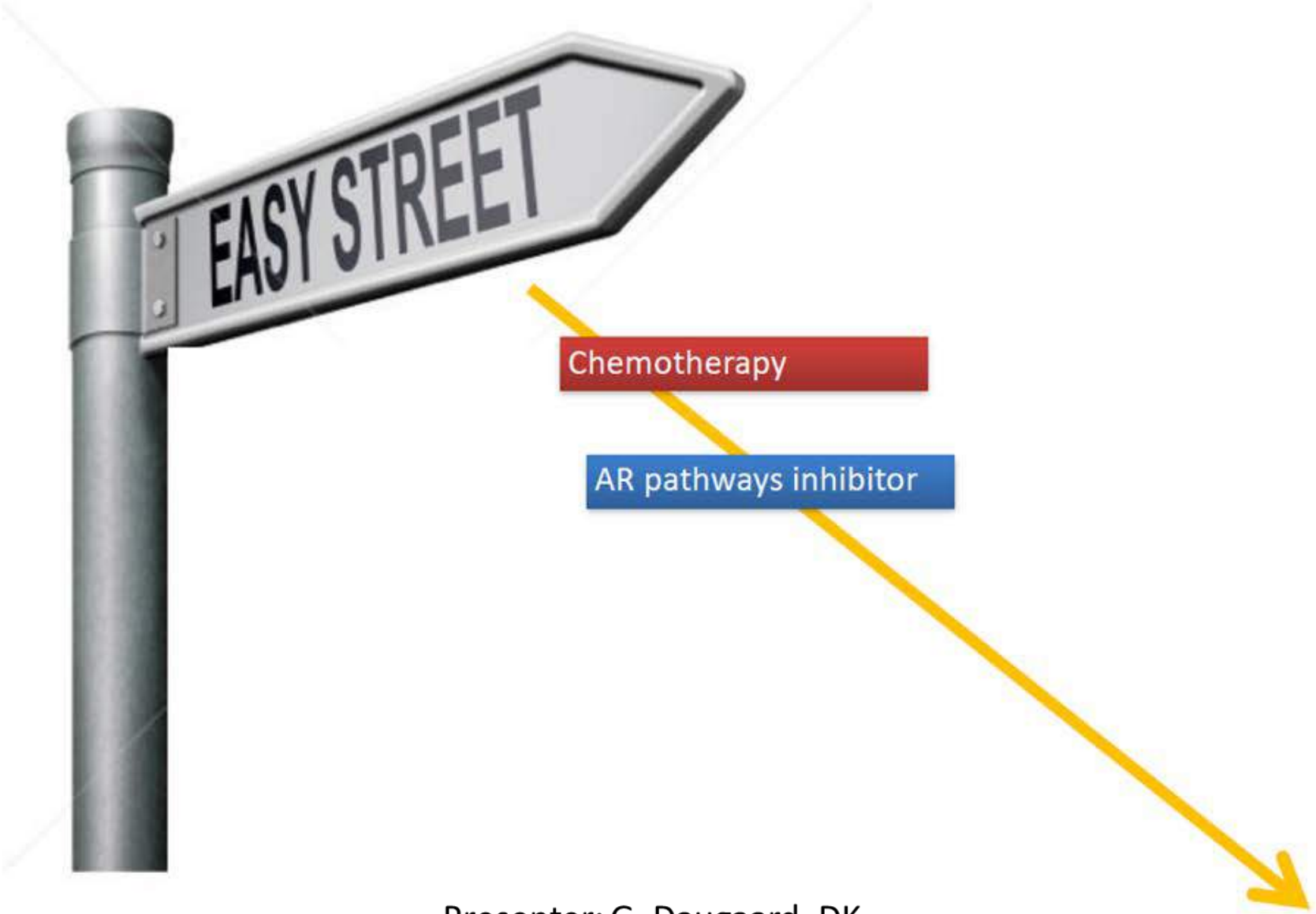
In most patients, both theories coexist: ADT response in some mets may be associated with radiological/clinical progression of other mets

Tombal B. *Eur J Cancer.* 2011;47:S179–188.

AR: androgen receptor; ADT: androgen deprivation therapy; mets: metastases

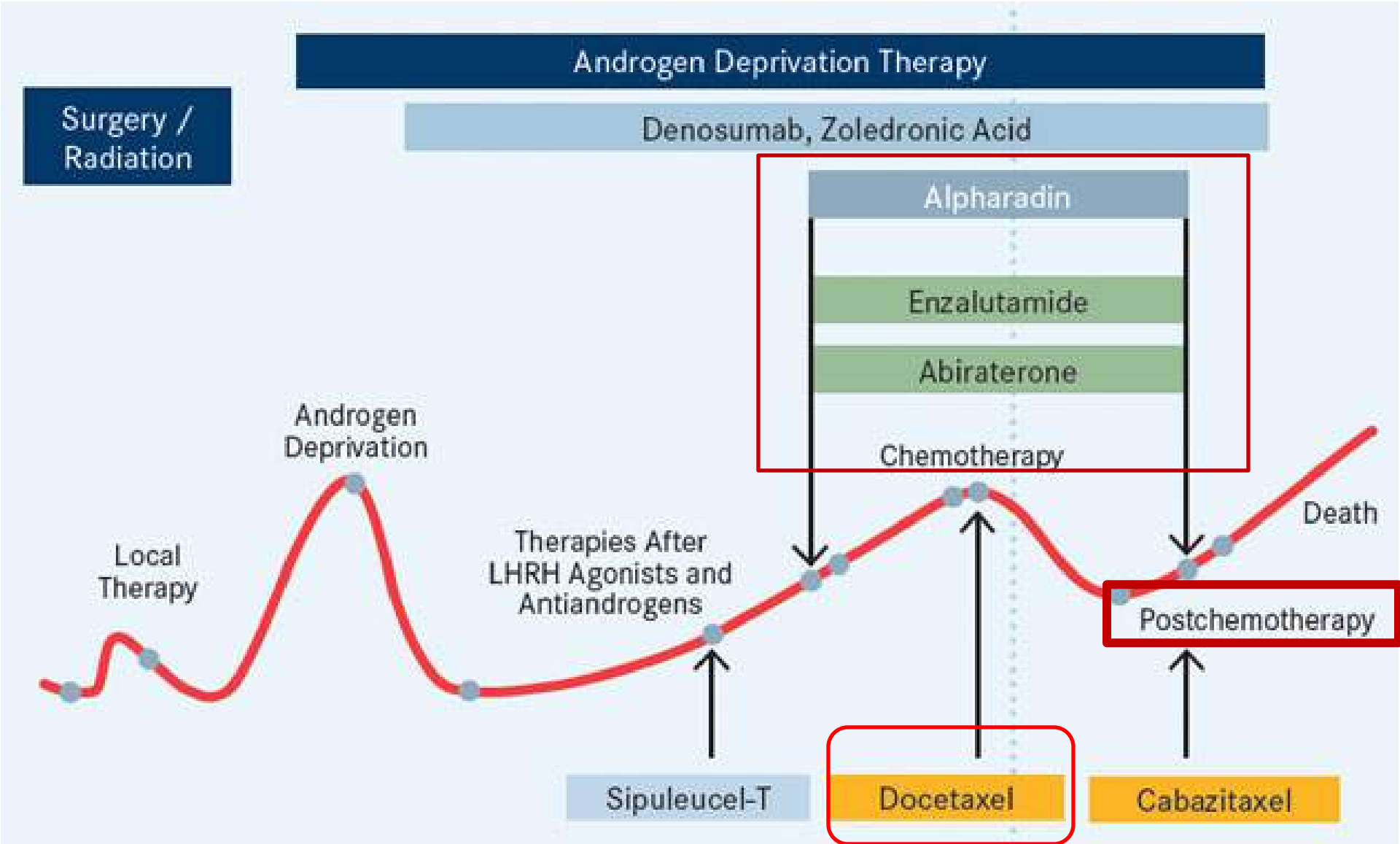


Presenter: G. Daugaard, DK
ESMO 2015

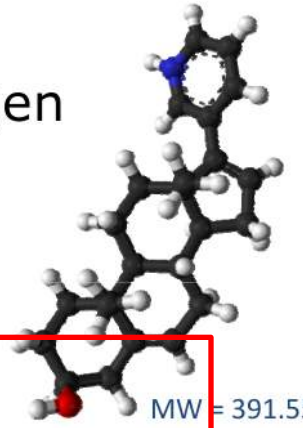


Presenter: G. Daugaard, DK
ESMO 2015

Treatment landscape of prostate cancer: post-chemotherapy era

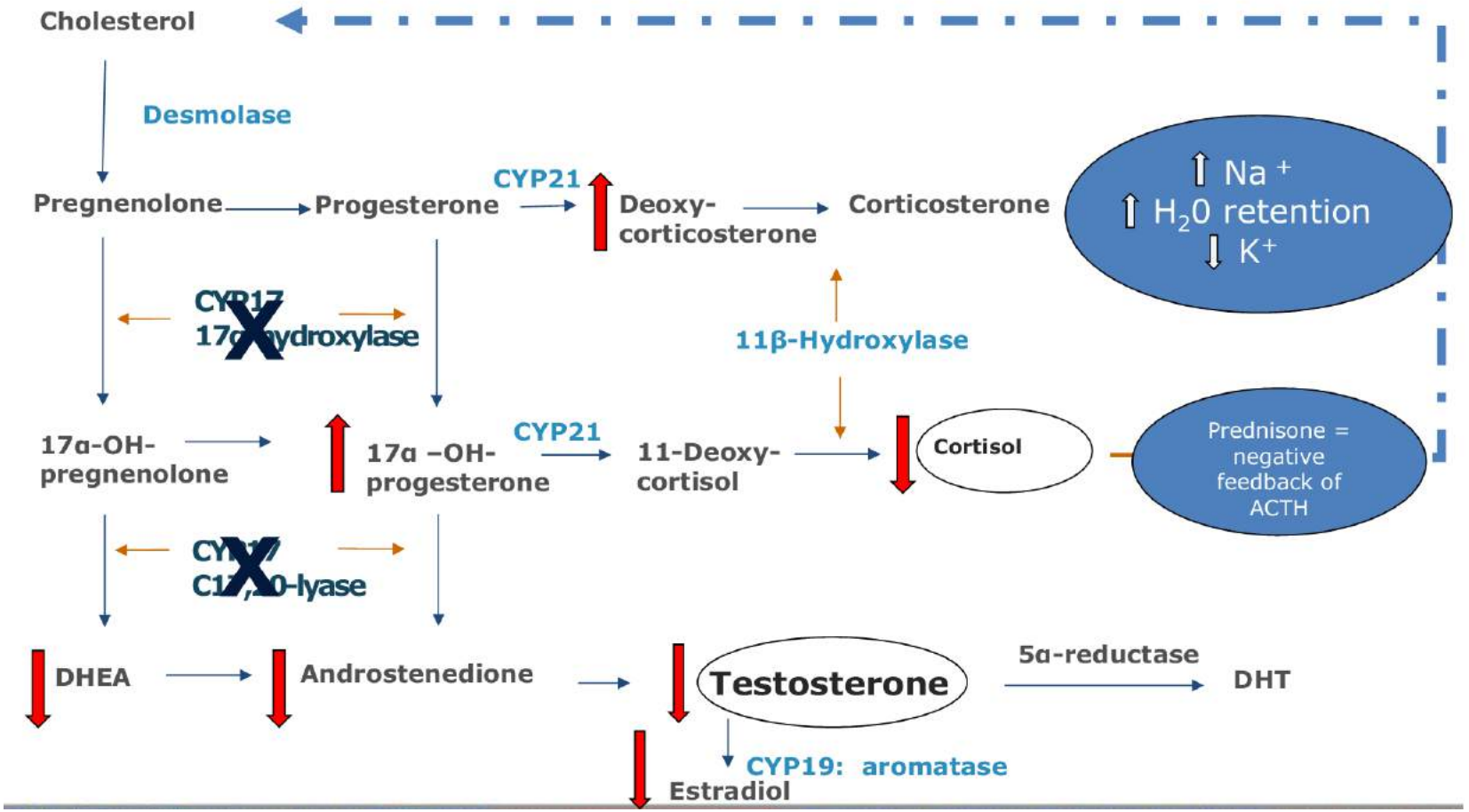


Zytiga (Abiraterone acetate) overview



- Prostate cancer still sensitive to blockade of androgen signaling after castration-resistance
- Abiraterone unique mechanism of action
  - Oral irreversible inhibitor of CYP-17
  - Mineralocorticoid excess manageable with prednisone/prednisolone
- FDA approved Zytiga (abiraterone acetate) for the treatment of men with metastatic castration-resistant prostate cancer after docetaxel failure

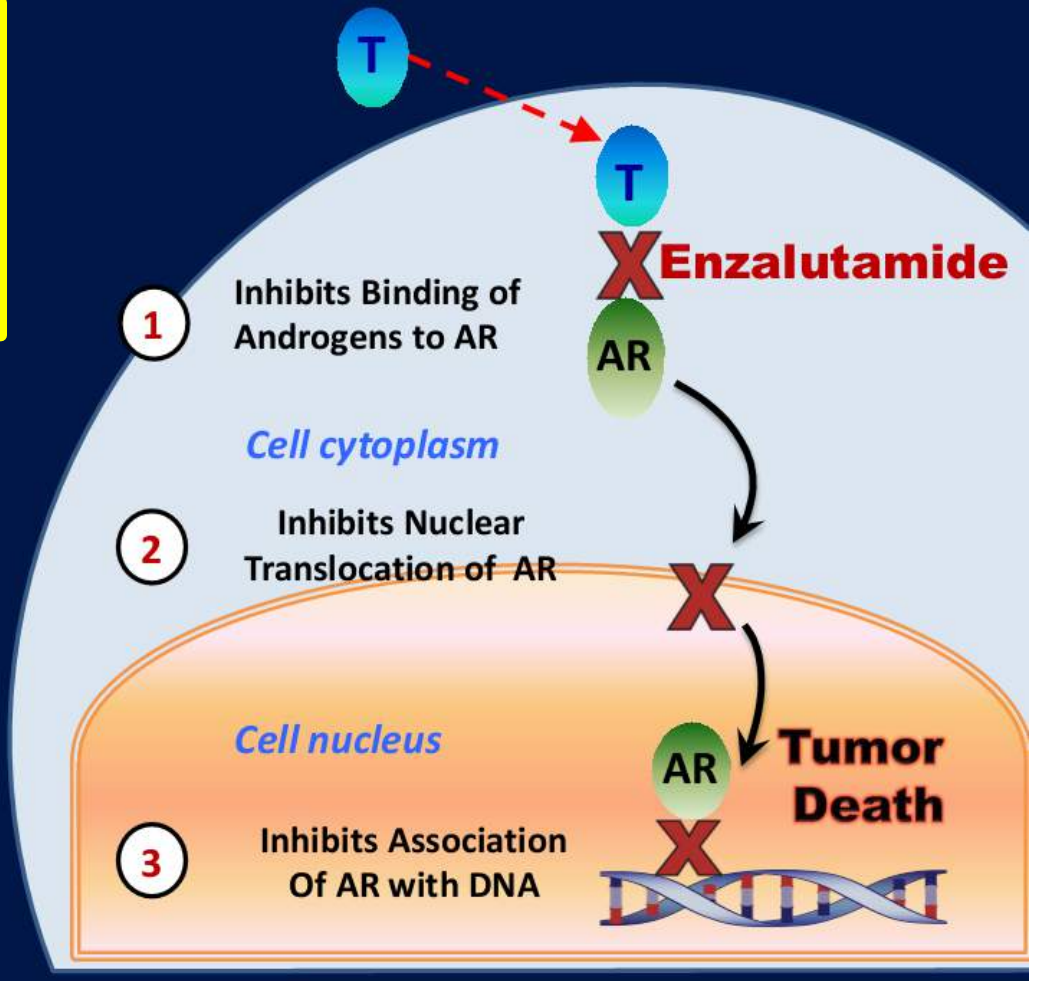
Steroid Synthesis Pathway
MOA of Abiraterone Acetate & Related Side Effects



Attard, et al, J. Clin. Oncol. 2008

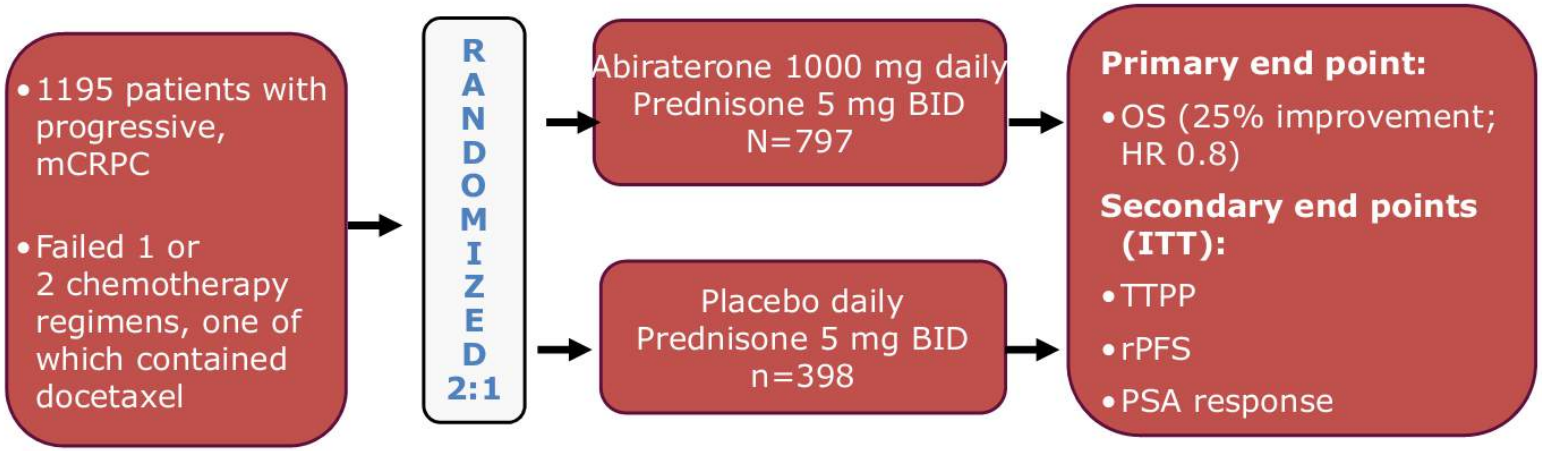
Enzalutamide (MDV3100)

- Oral investigational drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.
- No demonstrated agonist effects in pre-clinical models.



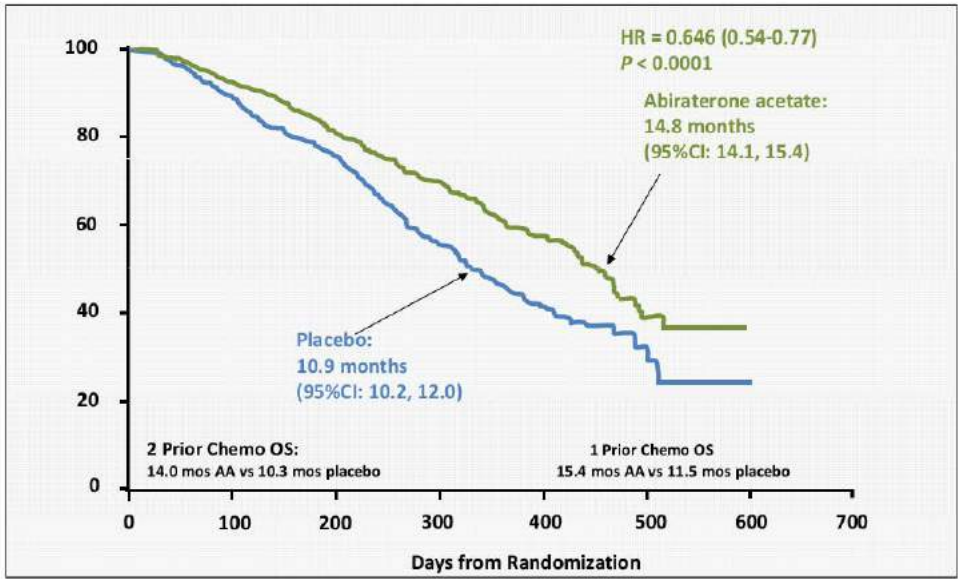
Tran et al. Science 2009;324:787–90.
Charles Sawyers & Michael Jung

COU-AA-301 Study Design

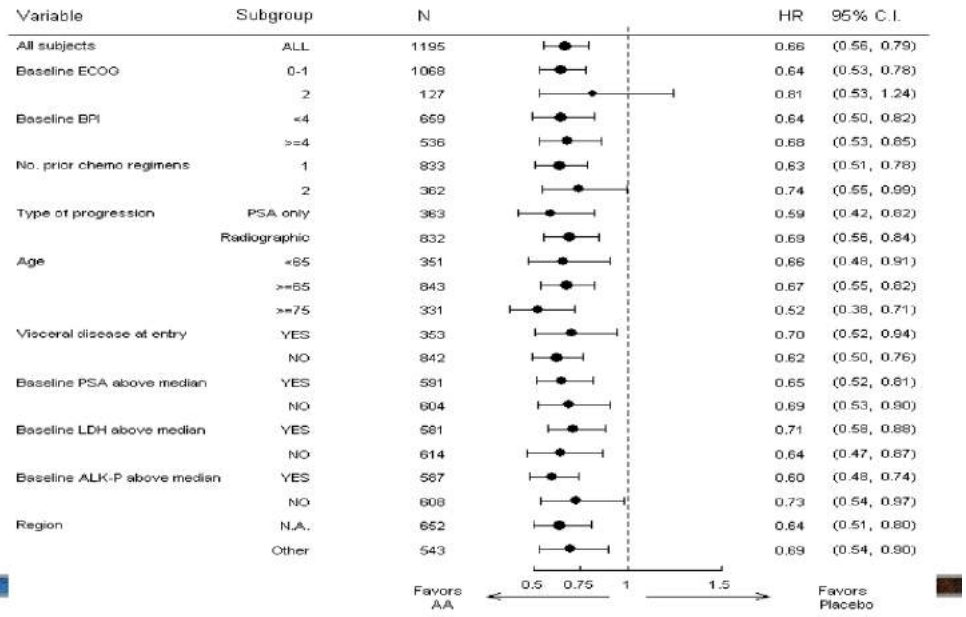


- Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)
- Stratification according to:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)

COU-AA-301: Abiraterone Acetate Improves OS in mCRPC

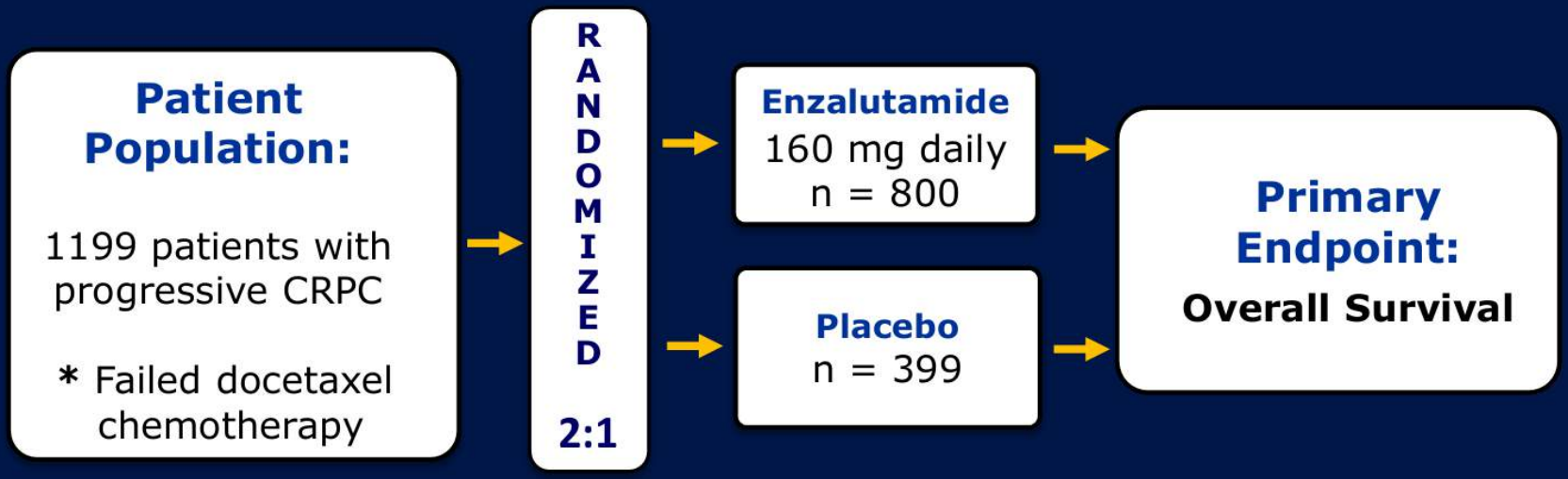


OS 14.8 mo VS 10.9 mo



POST-DOC

AFFIRM Trial Design



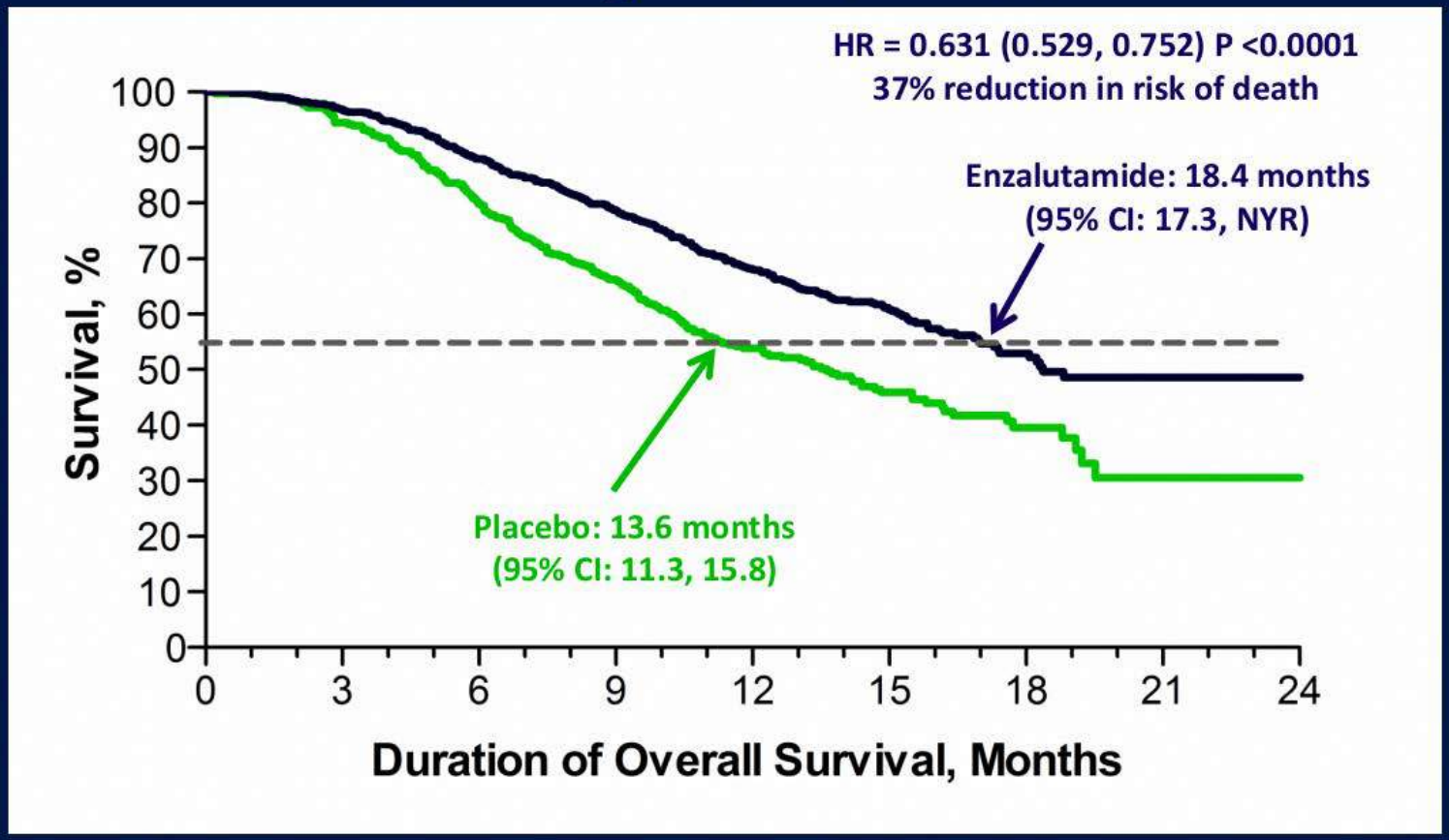
Glucocorticoids were not required but allowed.

PCWG2 criteria used (continue therapy through minor PSA changes; confirm bone scan 'progression'; focus on benefit not response).*

Recruitment in 156 centers from 15 countries and 5 continents.
Enrollment between September 2009 and November 2010.

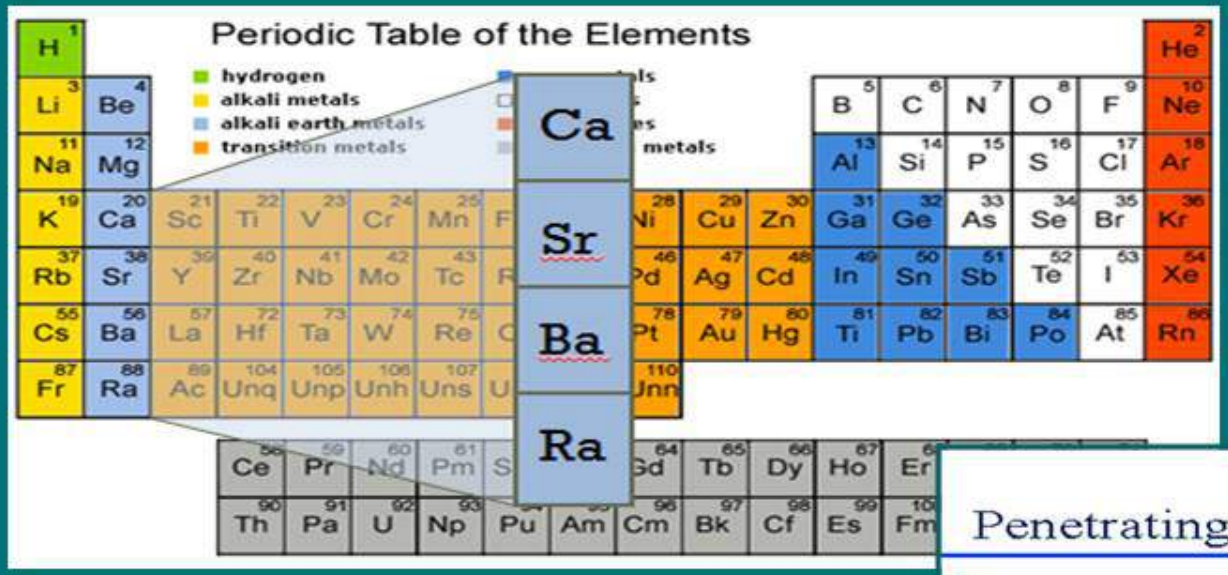
** Scher et al, 2008*

Enzalutamide Prolonged Survival, Reducing Risk of Death

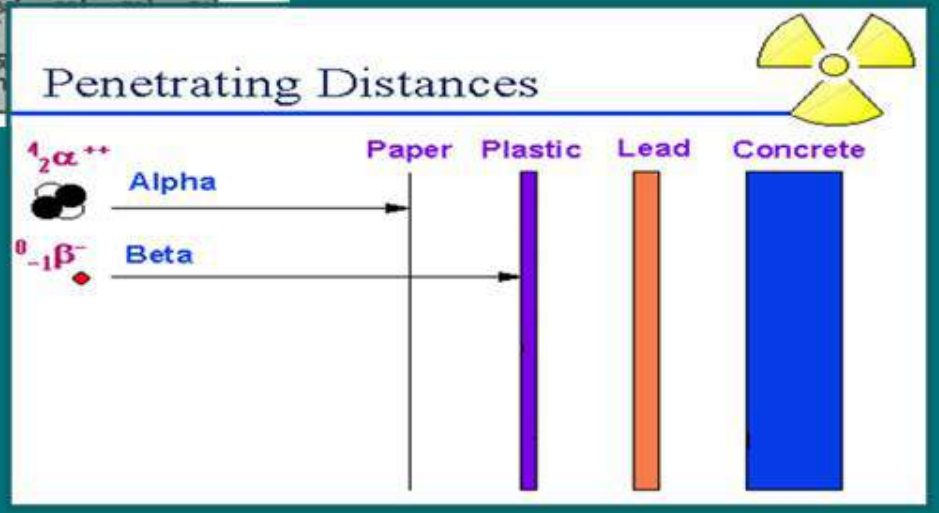


Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

Radium-223 (alpharadin)



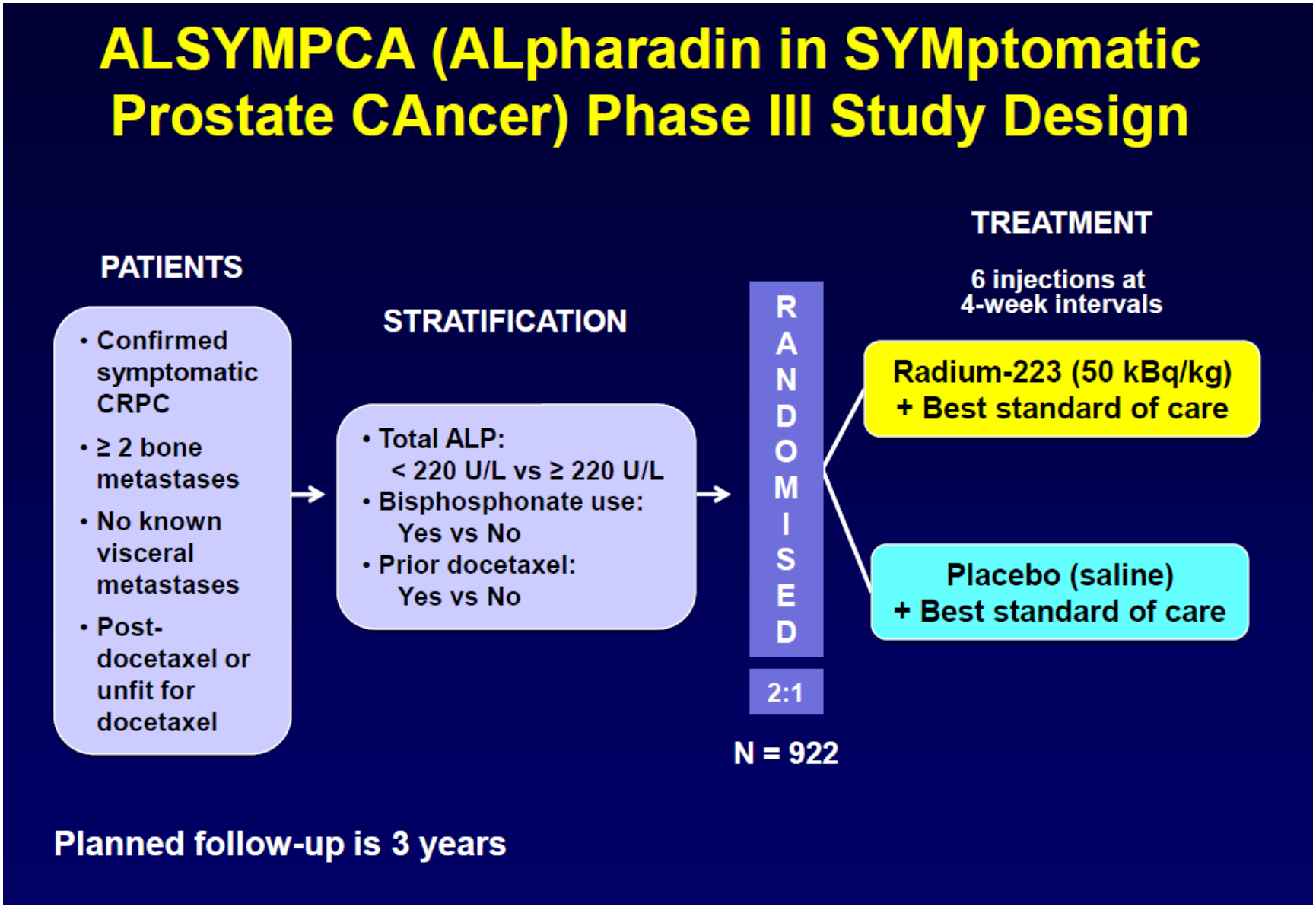
Radium223: an alpha-emitting calcium-mimetic



PRESENTED AT: ASCO Annual '15 Meeting

Presented By Tanya Dorff at 2015 ASCO Annual Meeting

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design

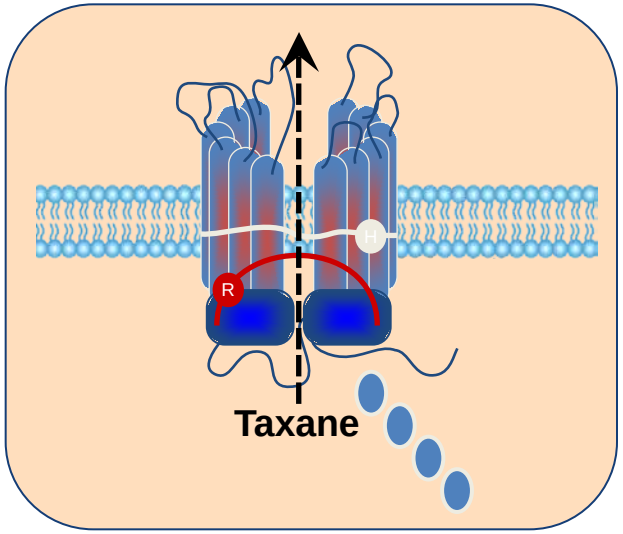


Primary endpoint: OS

Park C, ESMO 2011, oral presentation

Cabazitaxel: selected to overcome taxane resistance

- **Cabazitaxel:**
  - **Poor affinity for the PgP efflux pump**
  - **greater penetration of the blood brain barrier compared with docetaxel and paclitaxel**
  - **Active in vitro and in vivo on tumors resistant to Docetaxel**



- Docetaxel and paclitaxel have a strong affinity for the PgP pump
- If the PgP pump is surexpressed, it drives drug out of tumour cell

Mita AC et al, Clin Cancer Res. 2009, 15, 723-730

TROPIC: Phase III registration study
146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors

ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)

mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily

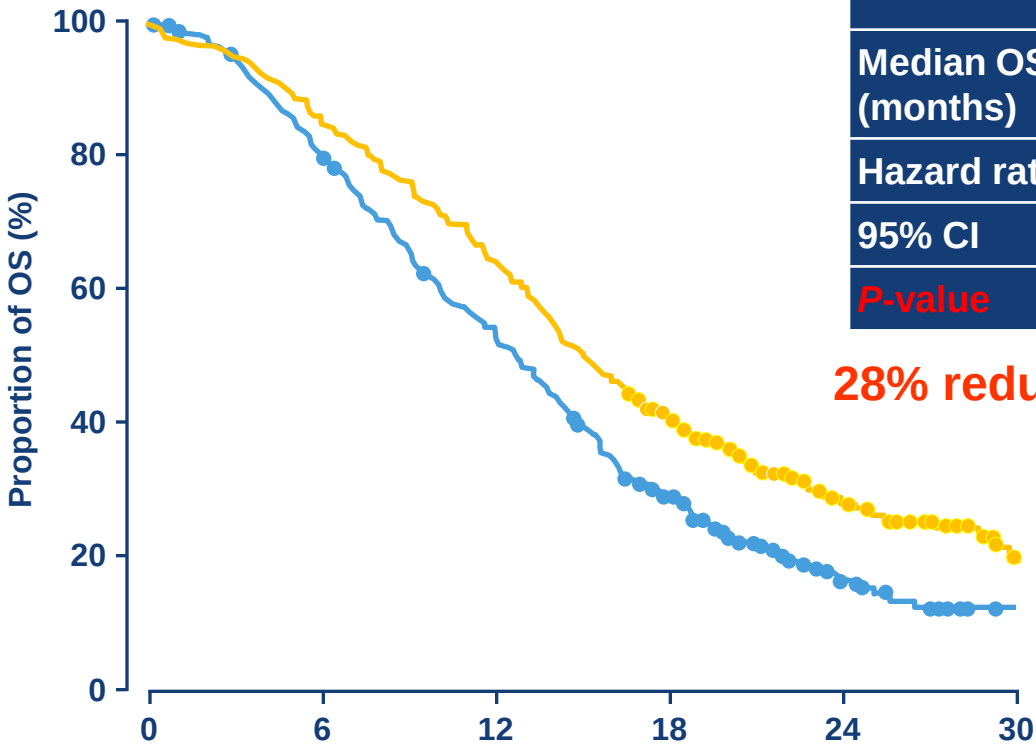
Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54

Primary endpoint: TROPIC
Overall survival (updated ITT analysis*)



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.72	
95% CI	0.61–0.84	
P-value	<.0001	

28% reduction in risk of death

Censored
MP
CBZP

Combined median follow-up: 13.7 months

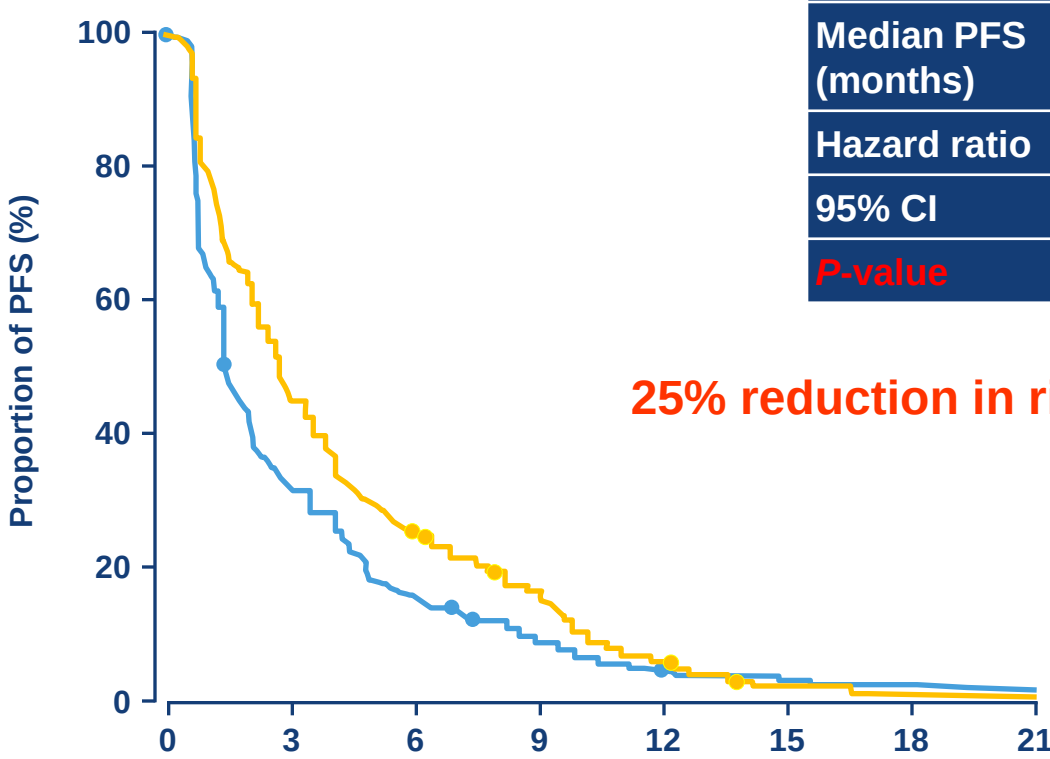
Number at Risk							
	MP	377	299	195	94	31	9
	CBZP	378	321	241	137	60	19

* Data cut-off 3/10/2010

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54

TROPIC Progression-free survival

	MP	CBZP
Median PFS (months)	1.4	2.8
Hazard ratio	0.75	
95% CI	0.65–0.87	
P-value	0.0002	



25% reduction in risk of progression

Censored
MP
CBZP

Combined median follow-up: 13.7 months

Number at Risk									
	MP	377	117	55	30	12	9	6	4
	CBZP	378	168	92	55	18	6	1	1

* Data cut-off 3/10/2010

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54

TROPIC : Hematological Results

	MP (n=371)		CBZP (n=371)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Hematology				
Anemia	81.4	4.9	97.3	10.5
Leukopenia	92.5	42.3	95.7	68.2
Neutropenia*	87.6	**58.0**	93.5	**81.7**
Thrombocytopenia	43.1	1.6	47.4	4.0

*Prophylactic use of G-CSF was permitted except for cycle 1 of treatment at the discretion of the investigator.

- **Higher rate of grade ≥ 3 neutropenia than in TAX 327 but patients enrolled in TROPIC had more advanced disease, were heavily pretreated and had weekly hematological testing**

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010
De Bono JS et al Lancet 2010; 376: 1147–54

New therapeutic agents in last decade

Trial	Regimen	Pts	HR	N	Survival (months)	Delta (months)
IMPACT[1]	Sipuleucel-T	CRPC	0.78	512	25.8 vs 21.7	4.1
TAX 327[2]	Docetaxel+Prednisone vs Mitoxantrone+Prednisone	CRPC Chemonaive	0.76	1006	18.9 vs 16.5	2.4
TROPIC[3]	Cabazitaxel+Prednisone vs Mitoxantrone+Prednisone	CRPC Post-docetaxel	0.70	755	15.1 vs 12.7	2.4
COU-AA-301[4]	Abiraterone +Prednisone vs Prednisone	CRPC Post-docetaxel	0.74	1195	15.8 vs 11.2	4.6
ALSYMCA[5]	Alpharadin vs Placebo	CRPC	0.695	809	14.0 vs 11.2	3.6
AFFIRM[6]	MDV3100 vs Placebo	CRPC Post-docetaxel	0.63	1199	18.4 vs 13.6	4.8

However, survival prolongation on average 3.5 months!

1. Kantoff PW et al. N Engl J Med 2010;363:411-22.
2. Tannock IF et al. N Engl J Med 2004;351:1502-12.
3. de Bono JS et al. Lancet 2010;376:1147-54.
4. Fizazi K et al. Lancet Oncol 2012.
5. Parker C et al. ASCO 2012 (LBA 4512).
6. Scher H et al. N Engl J Med 2012;367:1187-97.

Year 2012

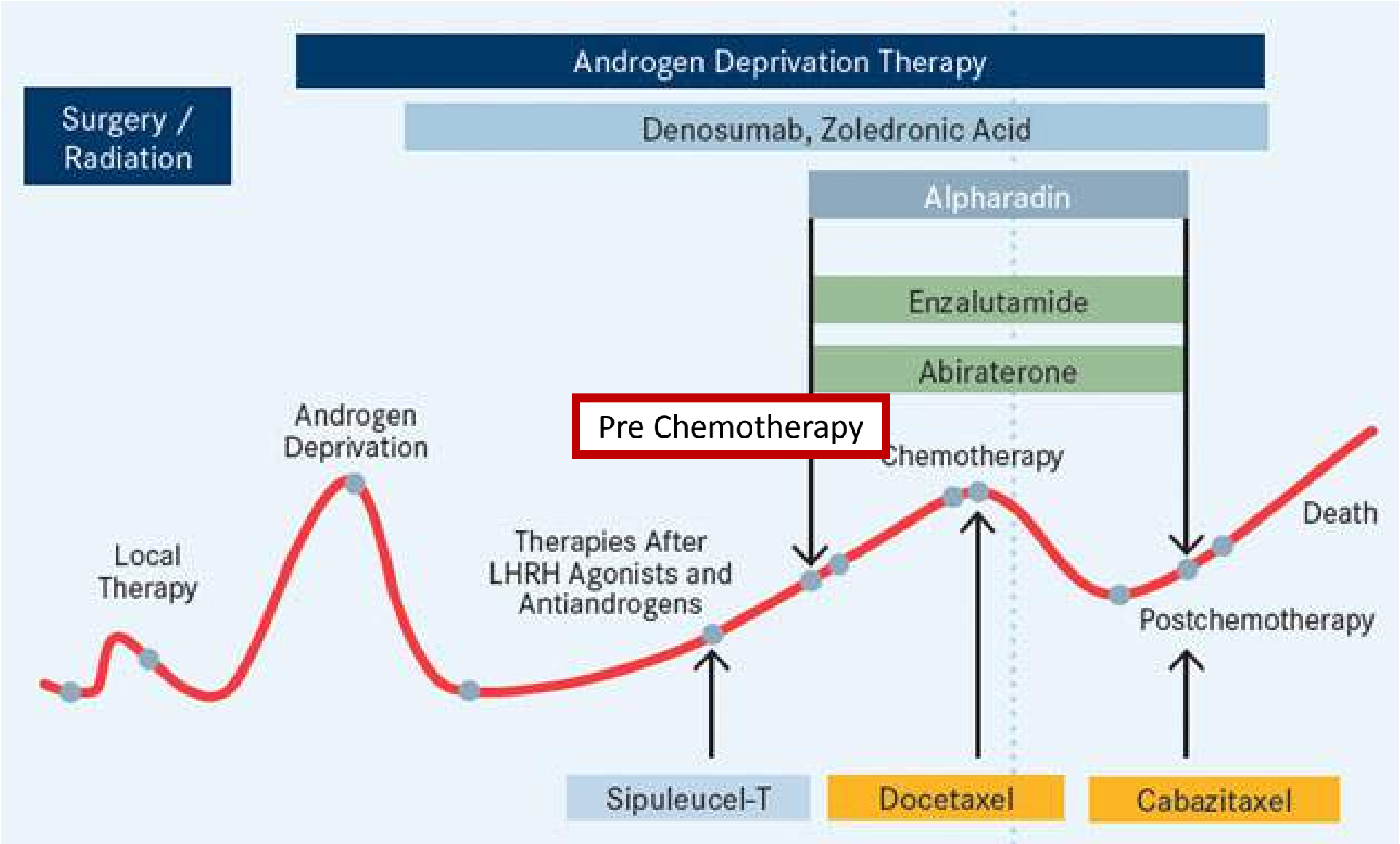
Short response to AA
ARV-7

Post-chemotherapy era

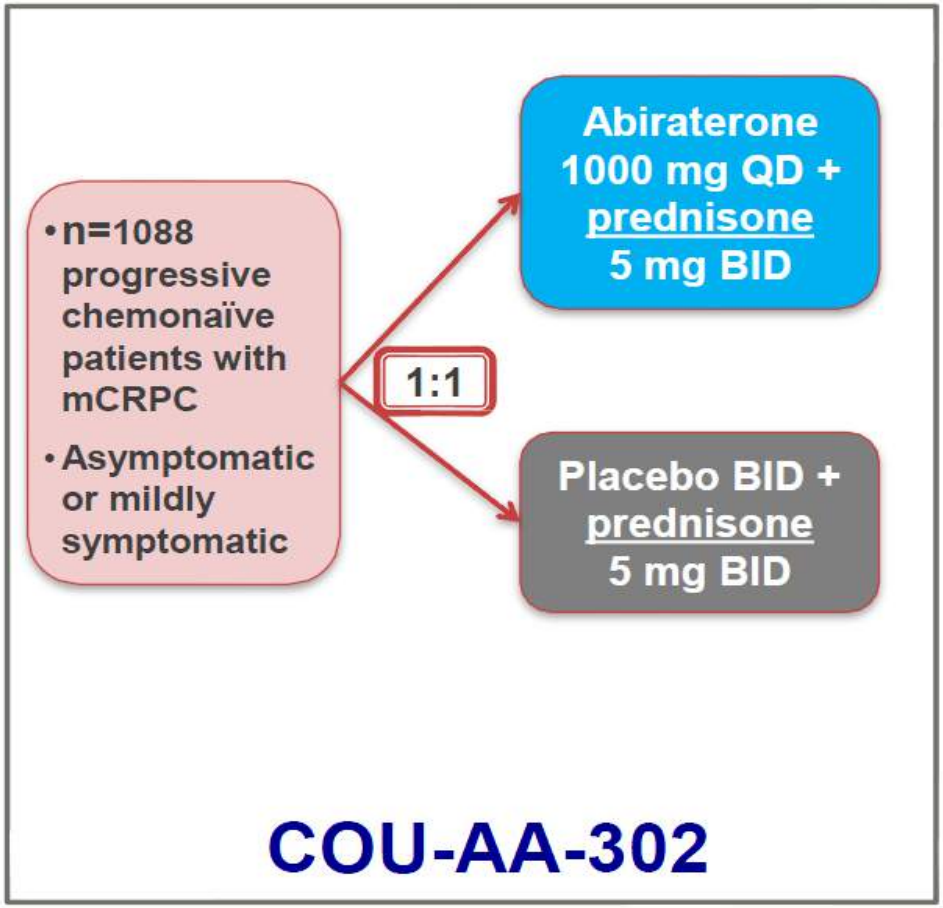
No Biomarker to choose agents

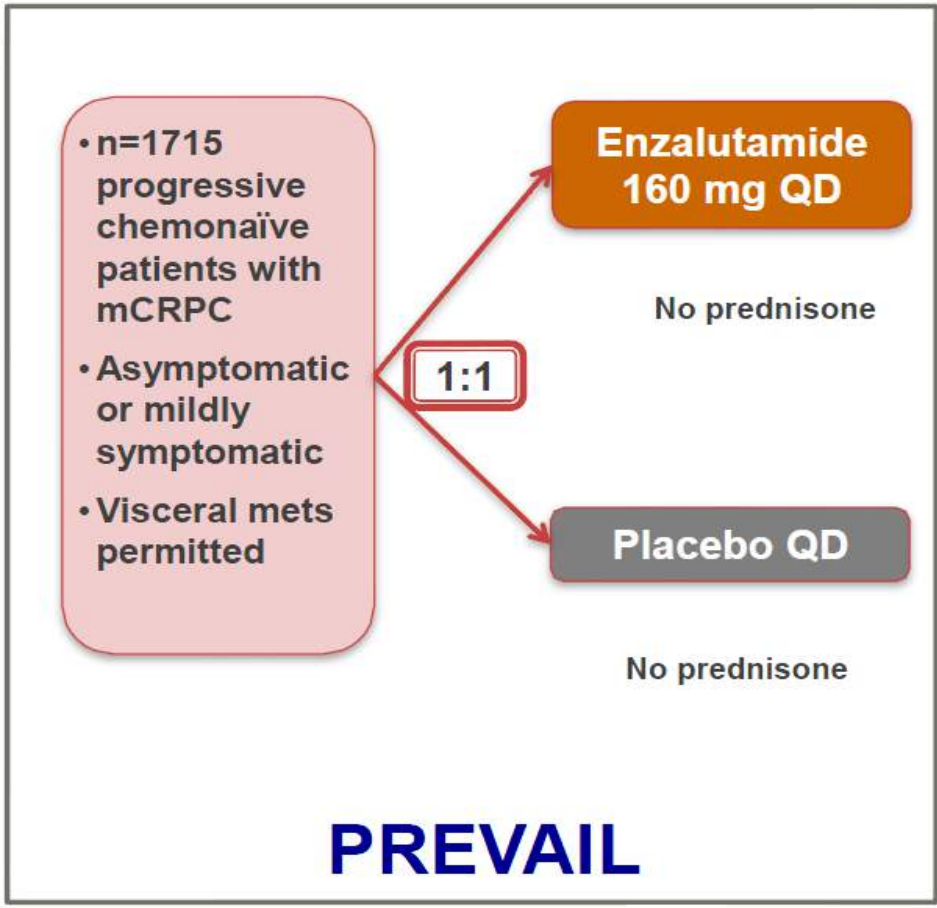
More treatment options are available for mCRPC patients!

Treatment landscape of prostate cancer: pre-chemotherapy era



Abiraterone and Enzalutamide in mCRPC Phase III Studies Pre-docetaxel (Primary Endpoint: rPFS and OS)





Summary of pre-chemo studies

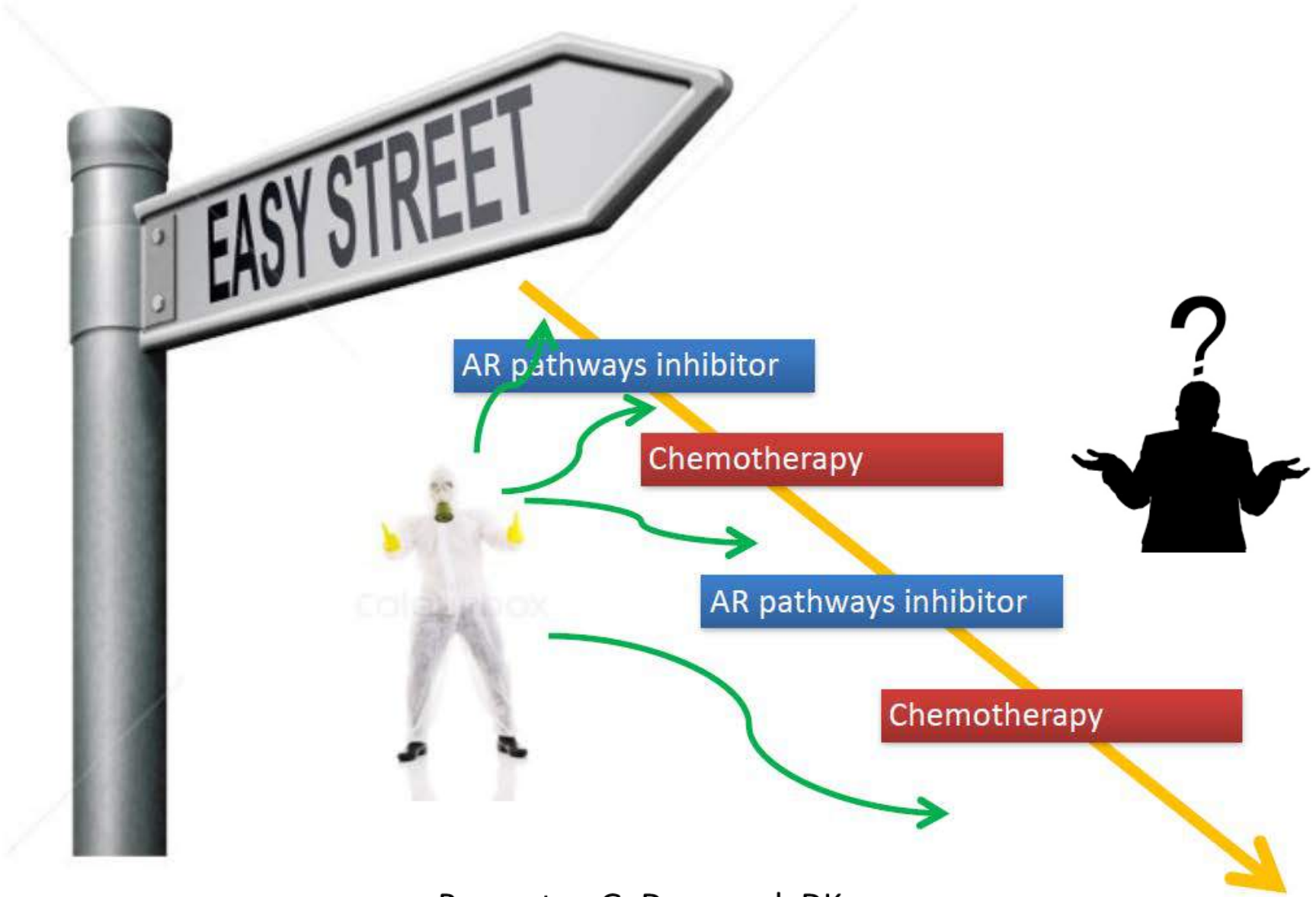
Study	Treatment	Time of f/u (months)	OS (months)	rPFS (months)	Time to opiate use (months)	Time to initiate use of chemo (months)	Time to PSA progression (months)	Time to ECOG deterioration (months)	PSA response
COU-AA-302[1-2]	Abiraterone acetate 1000 mg + Prednisone	49.2	34.7	16.5	33.4	26.5	11.1	12.3	68%
	Prednisone		30.3	8.2	23.4	16.8	5.6	10.9	29%
PREVAIL[3]	Enzalutamide 160 mg	22	NR	-	-	28.0	11.2	-	78%
	Placebo		30.2	-	-	10.8	2.8	-	3%

1. Ryan et al. Lancet Oncology 16 (2015) : 152-160.; 2. Rathkopf et al. European Urology 66 (2014) : 815-825. 3. Beer et al. New England Journal- of Medicine 371 (2014) : 424-433. 4. Nilsson et al. The New England Journal of Medicine 369 (2013) : 213-223. 5. Tannock et al. New England Journal of Medicine 351 (2004) : 1502-1512. 6. Berthold et al. Journal of Clinical Oncology 26 (2008) : 242-245.

Year 2013

Pre-chemotherapy era

More treatment options are available for mCRPC patients!



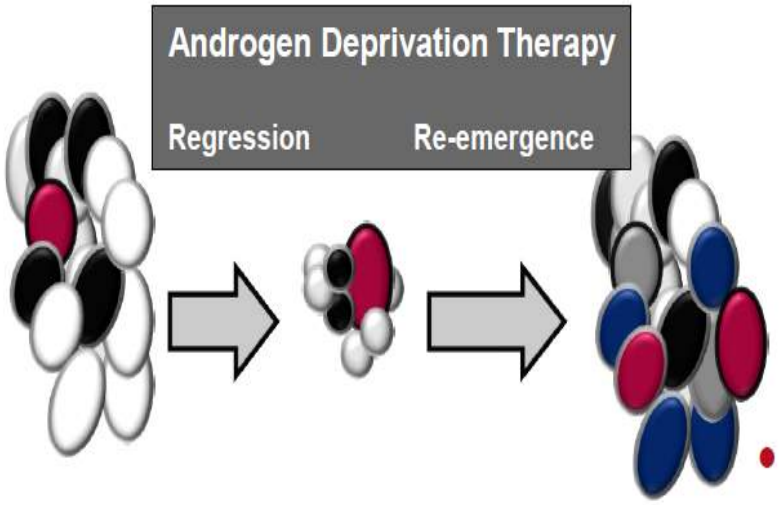
Presenter: G. Daugaard, DK
ESMO 2015

The Art of Sequencing

- Based on the concept that more treatments = increased survival
- No head to head study to compare efficacy.

HSPC

Early Chemo+ADT: A debate in one slide – a need for a 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 chemo

Chemotherapy in HSPC

Chemohormonal upfront therapy has a role in high volume hormone-sensitive prostate cancer

Negative result

1 Study

"GETUG-AFU15"

Positive result

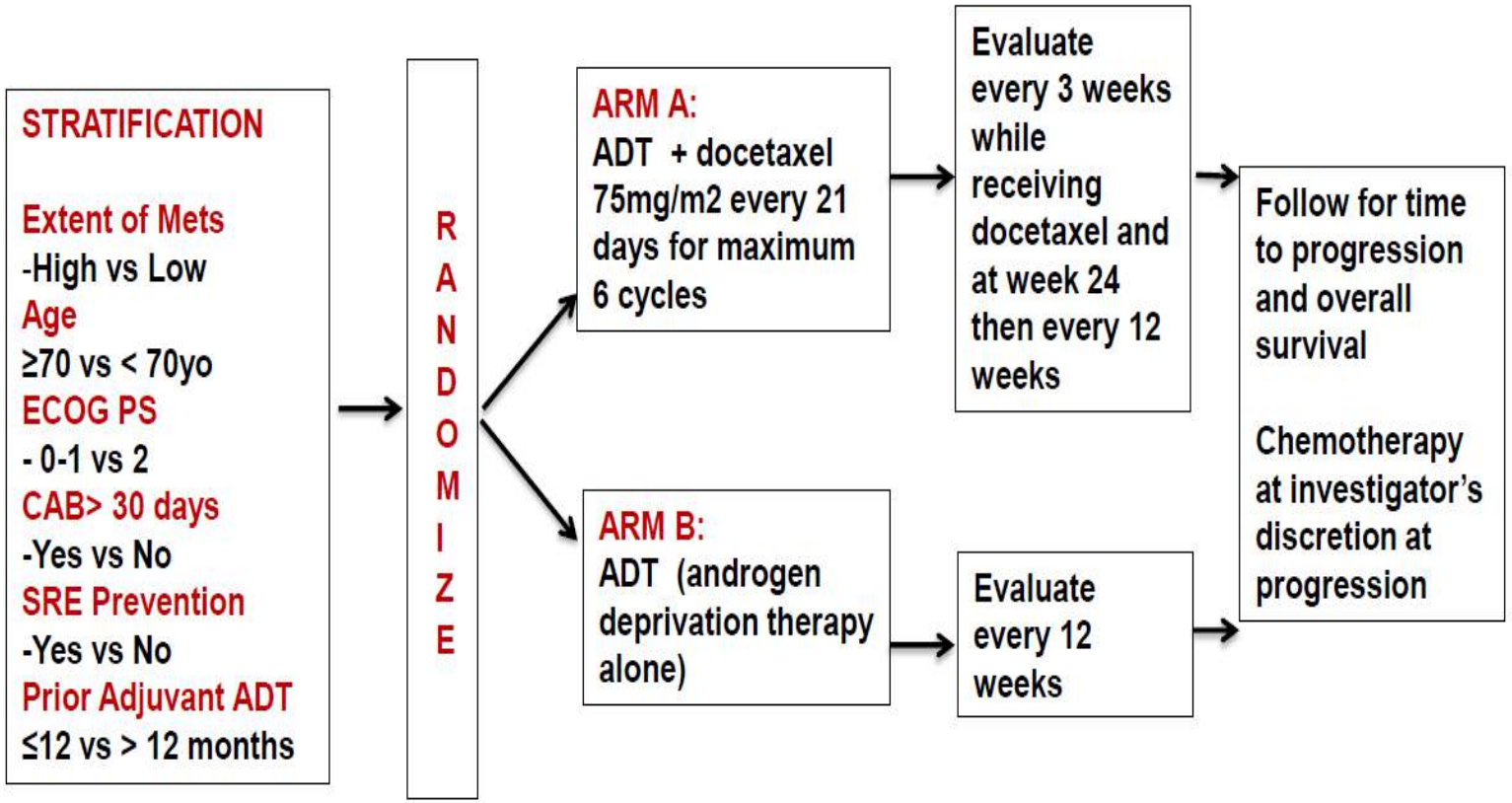
2 Studies

"STAMPEDE" and *"CHAARTED"*

STAMPEDE

CHAARTED

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

MADRID 2014 ESMO congress

Different Definitions of High Volume Disease

- **SWOG: S8894: *NEJM* 1998: Orchiectomy +/- Flutamide**[1]

  Extensive disease: included appendicular skeletal involvement (with or without axial skeletal involvement), visceral (lung or liver) metastasis or both

  Median OS = 27 months

- **MDACC: *J Clin Oncol* 2008; ADT +/KAVE**[2]

  High volume: 3 or more bone mets and / or visceral mets

  Median OS = 37 months

[1]Eisenberger et al *NEJM*, 1998;

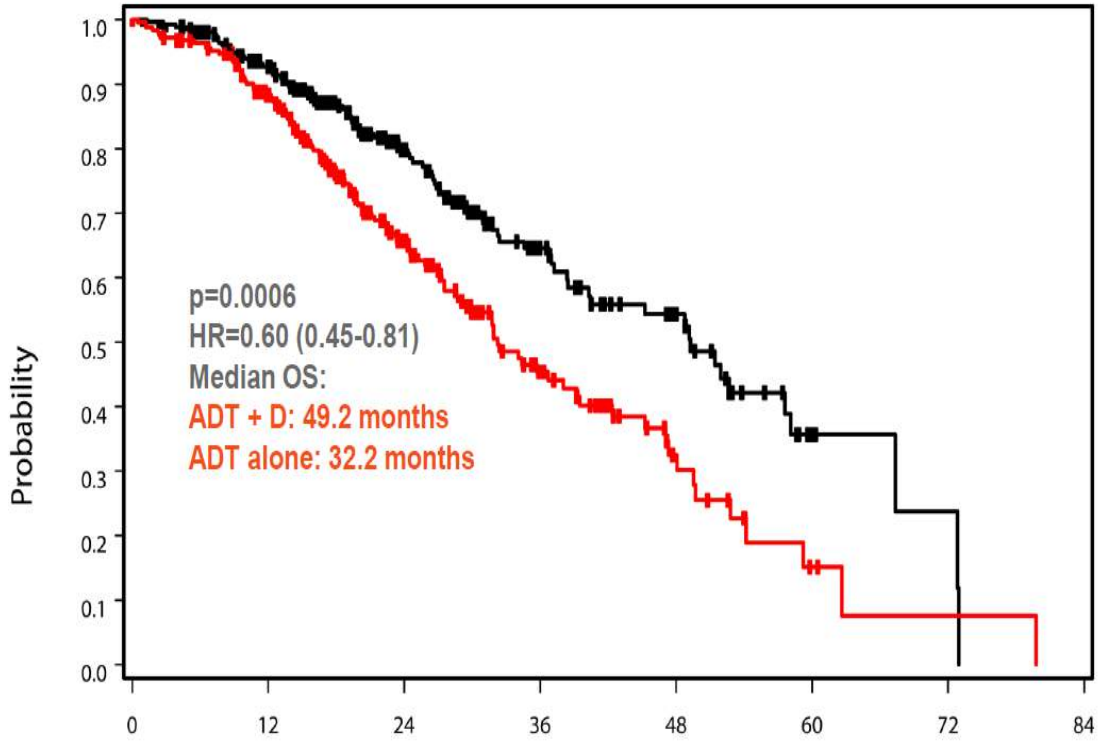
[2]Millikan et al *J Clin Oncol*, 2008.

E3805 Definition of High Volume

- **High volume:**
  - visceral metastases

  and/or
  - 4 or more bone metastases with at least 1 beyond pelvis and vertebral column
- At inception, only patients with high volume disease were to be accrued

OS for Patients with High Volume Metastatic Disease at Start of ADT



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 SWOG 9346 team.

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

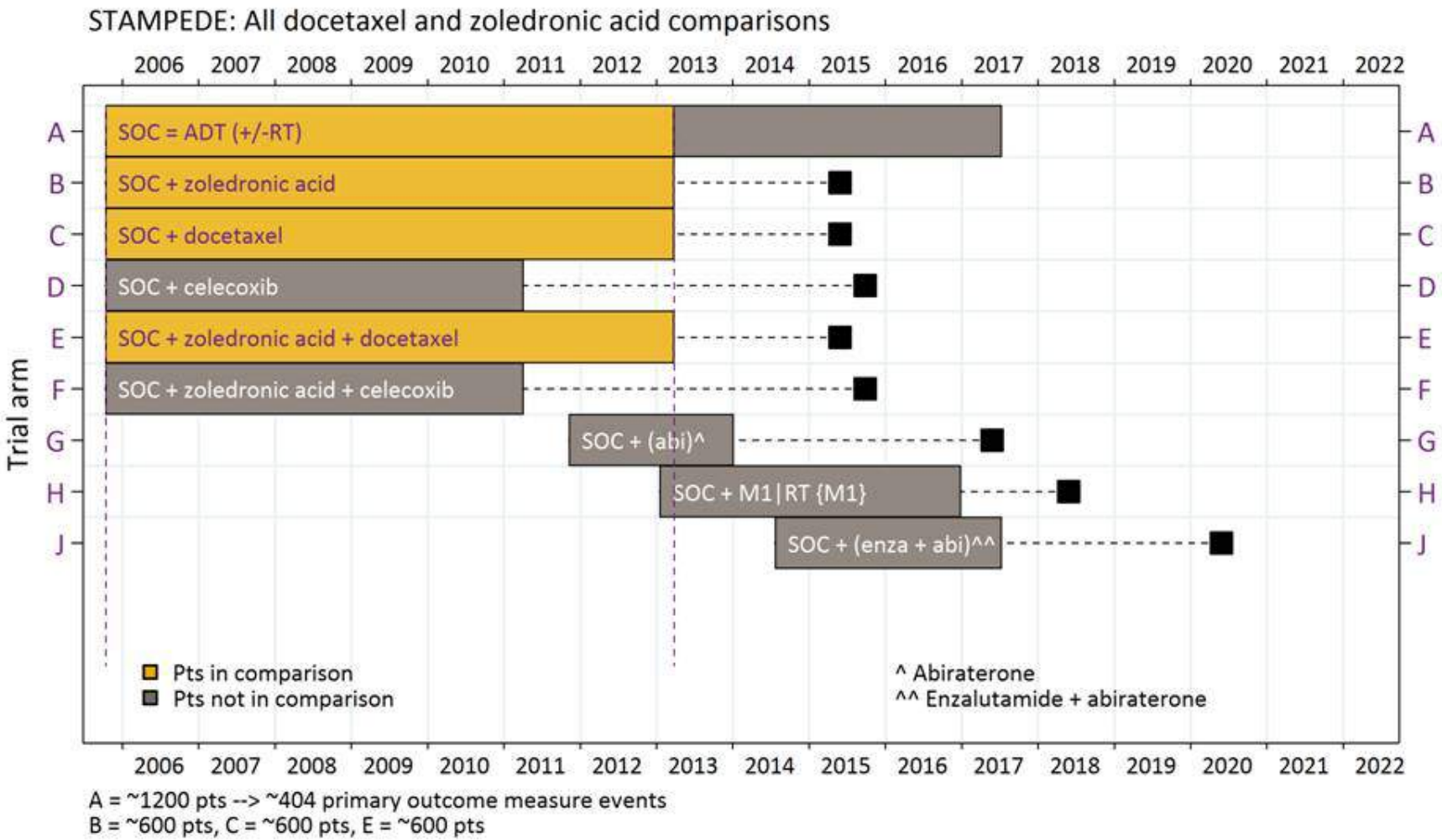
Fit for follow-up

WHO performance status 0-2

Written informed consent

Full criteria

www.stampedetrial.org

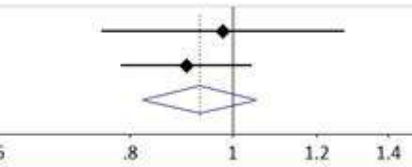

STAMPEDE: All docetaxel and zoledronic acid comparisons
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Trial arm
A
B
C
D
E
F
G
H
J
SOC = ADT (+/-RT)
SOC + zoledronic acid
SOC + docetaxel
SOC + celecoxib
SOC + zoledronic acid + docetaxel
SOC + zoledronic acid + celecoxib
SOC + (abi)^
SOC + M1|RT {M1}
SOC + (enza + abi)^^
Pts in comparison
Pts not in comparison
^ Abiraterone
^^ Enzalutamide + abiraterone
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
A = ~1200 pts --> ~404 primary outcome measure events
B = ~600 pts, C = ~600 pts, E = ~600 pts

Treatment effect by metastatic status: FFS

Pre-planned analysis

+ZA

Mets status	FFS events	No. pts	Haz. Ratio (95% CI)
M0	255	686	0.98 (0.75, 1.28)
M1	866	1091	0.90 (0.78, 1.04)
Overall	1121	1777	0.93 (0.82, 1.05)



+Doc

Mets status	FFS events	No. pts	Haz. Ratio (95% CI)
M0	229	689	0.57 (0.42, 0.76)
M1	832	1087	0.62 (0.54, 0.73)
Overall	1061	1776	0.62 (0.54, 0.70)

+ZA+Doc

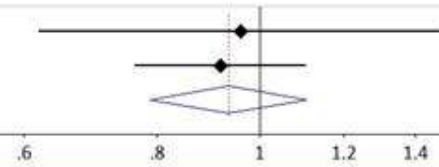
Mets status	FFS events	No. pts	Haz. Ratio (95% CI)
M0	232	687	0.70 (0.52, 0.94)
M1	832	1090	0.60 (0.52, 0.70)
Overall	1064	1777	0.62 (0.54, 0.71)

Treatment effect by metastatic status: Overall survival

Pre-planned analysis

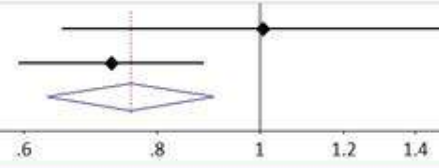
+ZA

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	93	686	0.96 (0.62, 1.48)
M1	509	1091	0.92 (0.76, 1.11)
Overall	602	1777	0.93 (0.79, 1.11)



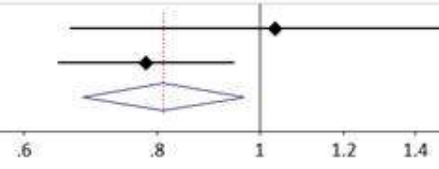
+Doc

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	93	689	1.01 (0.65, 1.56)
M1	477	1087	0.73 (0.59, 0.89)
Overall	570	1776	0.76 (0.63, 0.91)

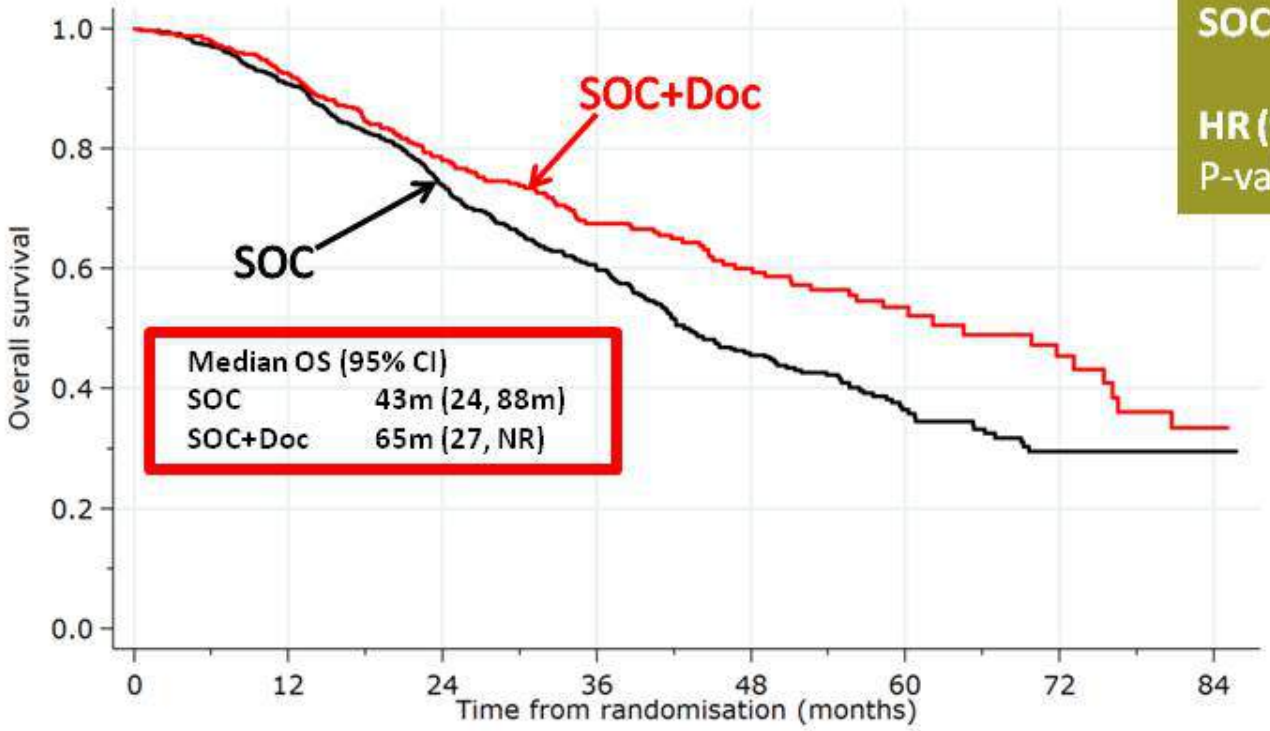


+ZA+Doc

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	91	687	1.03 (0.66, 1.61)
M1	495	1090	0.78 (0.65, 0.95)
Overall	586	1777	0.81 (0.68, 0.97)



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

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

Restricted mean OS time

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

Conclusions

- Docetaxel improves survival for hormone-naive prostate cancer
- Zoledronic acid does not improve survival
- Adding both improves survival but offers no obvious benefit over adding just docetaxel
- Multi-arm, multi-stage trials are practicable and efficient
- Docetaxel should be:

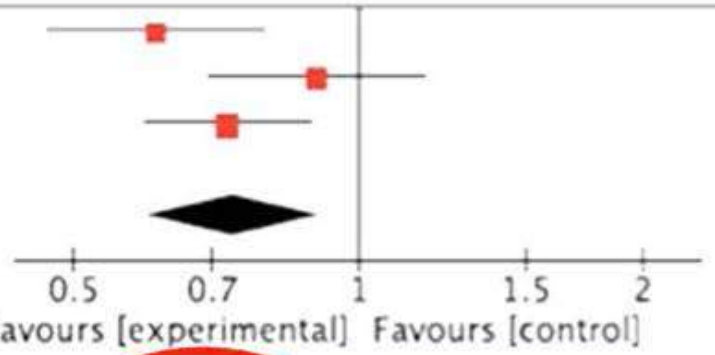
  → Considered for routine practice in suitable men with newly-diagnosed metastatic disease

  → Considered for selected men with high-risk non-metastatic disease in view of substantial prolongation of failure-free survival

Forest plot of overall survival for the 3 studies

(thanks to Dr Eitan Amir)

Study or Subgroup	Weight*	Hazard Ratio IV, Random, 95% CI
CHAARTED	30.3%	0.61 [0.47, 0.80]
GETUG-15	30.8%	0.90 [0.70, 1.18]
STAMPEDE	38.9%	0.73 [0.59, 0.89]
Total (95% CI)	**100.0%**	**0.74 [0.60, 0.90]**



Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.26$, df = 2 (P = 0.12)

Test for overall effect: Z = 2.92 (P = 0.003)

* weight by inverse variance

UHN Princess Margaret Cancer Centre

Presented By Ian Tannock at 2015 ASCO Annual Meeting

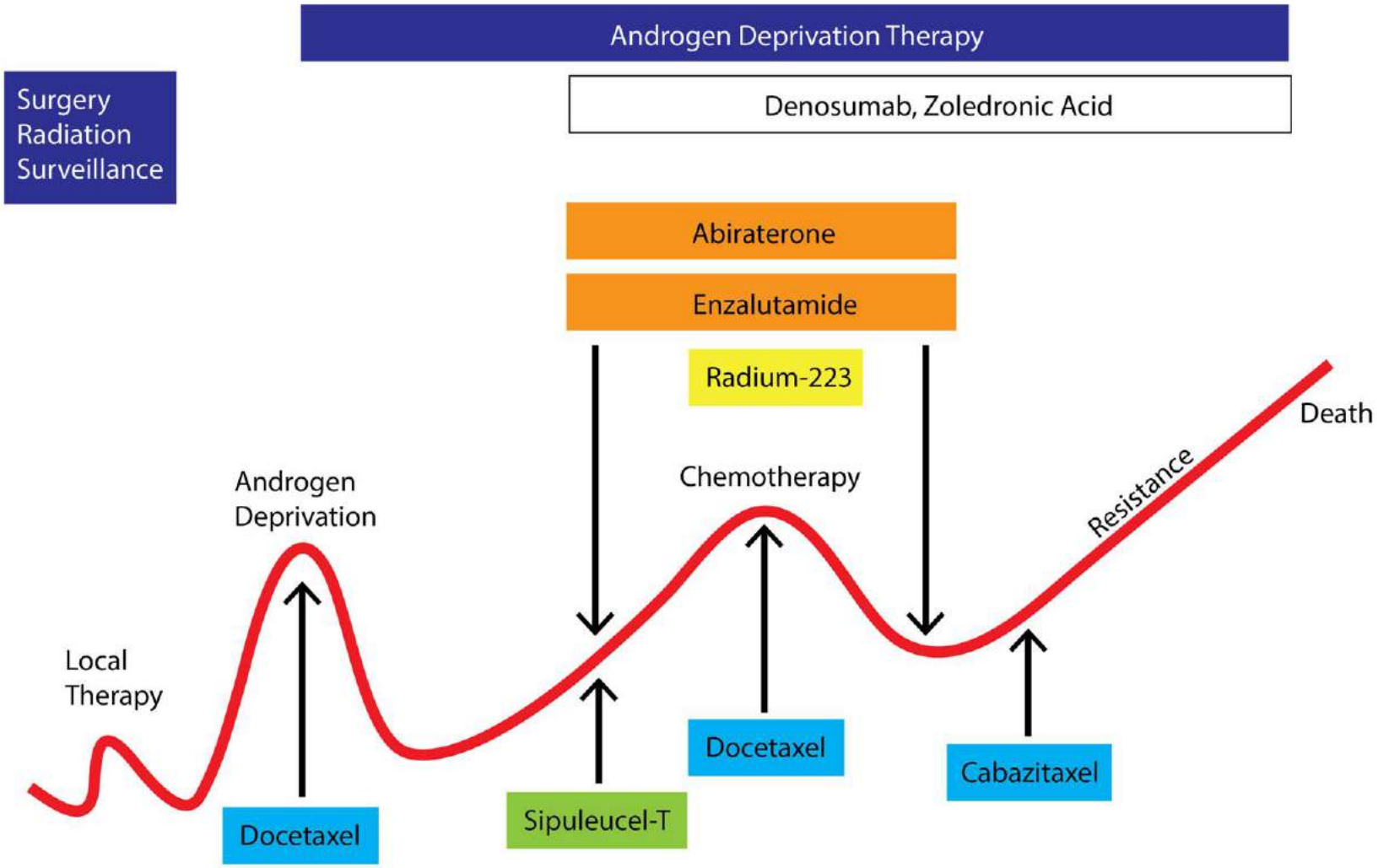
RECOMMENDATION #1

Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

- Summary
  - 6 cycles of docetaxel in addition to ADT represents the standard of care for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy
  - The benefit in patients with a high volume of metastases is clear and justifies the treatment burden
  - In non-metastatic or low volume metastatic disease a case by case discussion is required

31/05/2015

Presented By Ian Tannock at 2015 ASCO Annual Meeting

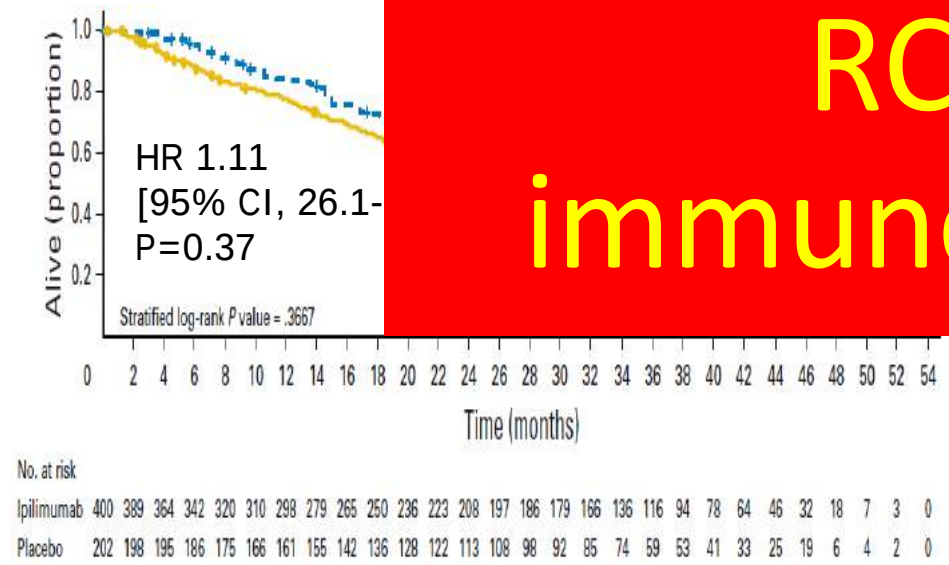


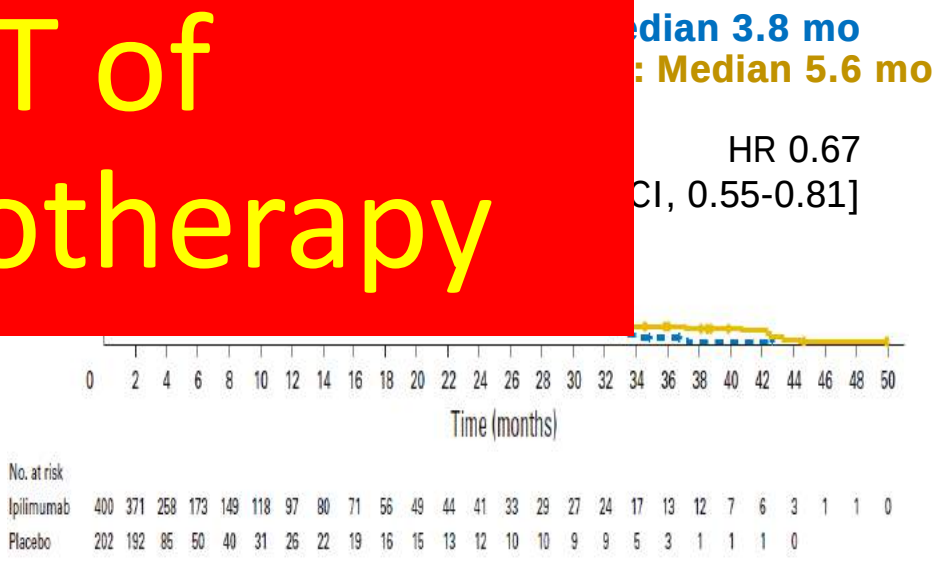
Presented By Himisha Beltran at 2016 ASCO Annual Meeting

What did We Learned in 2016?

Randomized Phase III Trial of Ipilimumab vs Placebo in Chemonaive mCRPC

No positive phase 3 RCT of immunotherapy





602 chemonaive mCRPC patients with no or mild symptoms randomized to ipilimumab (n=400) or placebo (n=202); Primary end-point: OS; Secondary end-point: PFS and safety

mCRPC: metastatic castrate-resistant prostate cancer; OS: overall survival; PFS: progression-free survival

Beer TM et al. J Clin Oncol 2016; 35; 40-47

2 Randomise Phase III Trials of Cabazitaxel

- FIRSTANA
- PROSELICA

FIRSTANA: Randomized, Open-Label Phase III Trial of CABA (25 or 20 mg/m²) vs DOC in Chemo-naive mCRPC

159 centers worldwide

mCRPC pts who have not previously received chemotherapy

N=1,168

RANDOMIZE

- CABA 25 mg/m² q3w + P (10 mg/d); N=388
- CABA 20 mg/m² q3w + P (10 mg/d); N=389
- DOC 75 mg/m² q3w + P (10 mg/d); N=391

- **Primary endpoint: OS**
- Secondary: safety, PFS, tumor response, PSA response, pain response, QoL, time to SREs

- Prophylactic G-CSF **NOT** allowed at cycle 1
- Statistics: superiority trial (HR 0.75)

What is the best first regimen?

G-CSF: granulocyte colony stimulating factor; q3w: every 3 weeks; PFS: progression-free survival; SREs: skeletal related events; P: prednisone or prednisolone

Sartor AO et al. J Clin Oncol 2016;34(suppl):abstract 5006 - ClinicalTrials.gov NCT01308567

FIRSTANA – Key Results

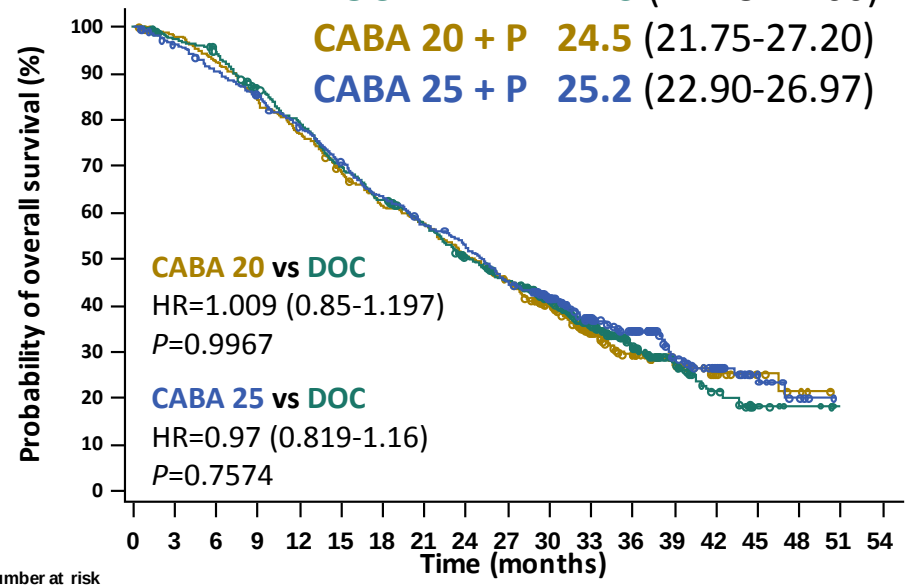
OS (primary endpoint)

Median OS, mo (95% CI)

DOC + P **24.3** (22.18-27.60)

CABA 20 + P **24.5** (21.75-27.20)

CABA 25 + P **25.2** (22.90-26.97)



CABA 20 vs DOC
HR=1.009 (0.85-1.197)
P=0.9967

CABA 25 vs DOC
HR=0.97 (0.819-1.16)
P=0.7574

Number at risk

DOC + P	391	366	336	307	243	192	133	57	18	3	0
CABA 20 + P	389	356	319	296	234	192	133	49	19	3	0
CABA 25 + P	388	345	325	296	239	197	138	70	28	5	0

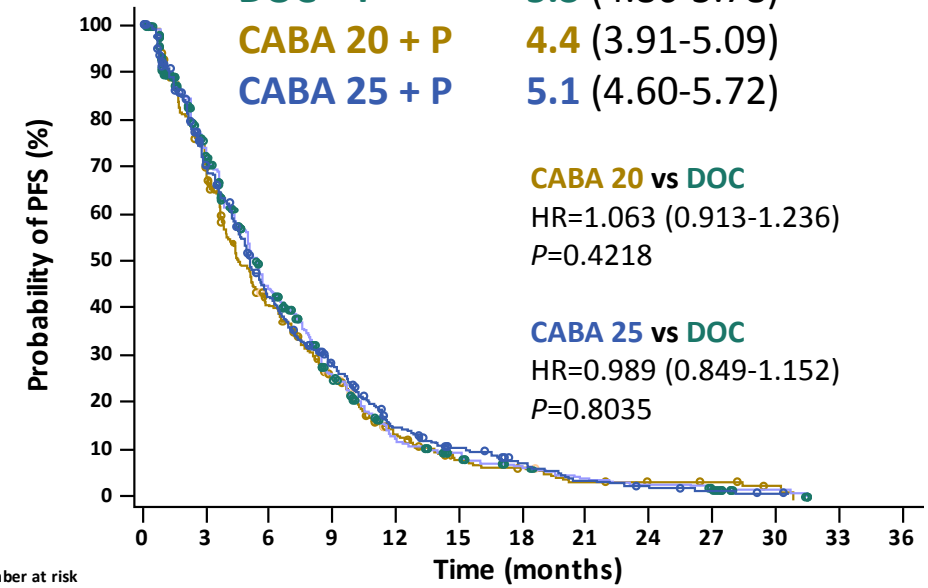
PFS (composite)*

Median PFS, mo (95% CI)

DOC + P **5.3** (4.86-5.78)

CABA 20 + P **4.4** (3.91-5.09)

CABA 25 + P **5.1** (4.60-5.72)



CABA 20 vs DOC
HR=1.063 (0.913-1.236)
P=0.4218

CABA 25 vs DOC
HR=0.989 (0.849-1.152)
P=0.8035

Number at risk

DOC + P	391	152	83	37	16	8	3	0
CABA 20 + P	389	145	83	39	15	6	2	0
CABA 25 + P	388	149	94	48	19	5	1	0

**PFS: progression-free survival defined as tumor progression or PSA progression or pain progression or death*

Sartor AO et al. J Clin Oncol 2016;34(suppl):abstract 5006 - ClinicalTrials.gov NCT01308567

FIRSTANA - Selected Adverse Events

	DOC + P N=387		CABA 20 + P N=369		CABA 25 + P N=391	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Febrile neutropenia	8.3	8.3	2.4	2.4	12.0	**12.0**
Neutropenic infection	4.9	4.1	1.6	1.4	6.1	**5.9**
Diarrhea	37.0	2.3	32.5	3.5	**49.9**	**5.6**
Peripheral sensory neuropathy	**25.1**	**2.1**	11.7	0.3	12.3	0
Edema peripheral	**20.4**	1.6	9.8	0	7.7	0.3
Stomatitis	**13.7**	0.8	4.9	0	6.6	0.3
Nail disorder	**9.0**	0.3	0.3	0	0.8	0
Hematuria	3.6	0.3	20.3	3.5	**25.1**	**3.6**
Urinary tract infection	2.3	0.8	**10.8**	3.3	9.5	2.0
Alopecia	**39.0**	0	8.9	0	13.0	0

Sartor AO et al. J Clin Oncol 2016;34(suppl):abstract 5006 - ClinicalTrials.gov NCT01308567

PROSELICA: Randomized, Open-label, Non-inferiority Phase III Trial Comparing 2 Doses of CABA Post-DOC

172 centers worldwide

mCRPC pts progressing during or after treatment with a DOC-based regimen
N=1,200

RANDOMIZE

CABA 25 mg/m² q3w
+ P (10 mg/d) for 10 cycles
N=598

CABA 20 mg/m² q3w
+ P (10 mg/d) for 10 cycles
N=602

- Primary endpoint: OS
- Secondary: safety, PFS, tumor response, PSA response, pain, QoL

- Prophylactic G-CSF **NOT** allowed at cycle 1
- Statistics: **non-inferiority trial design** (CABA 20 maintains **at least 50%** of the OS benefit of CABA 25 vs mito in TROPIC)

What is the proper dose in 2nd line?

de Bono J et al. J Clin Oncol 2016;34(suppl):abstract 5008 - ClinicalTrials.gov NCT01308580

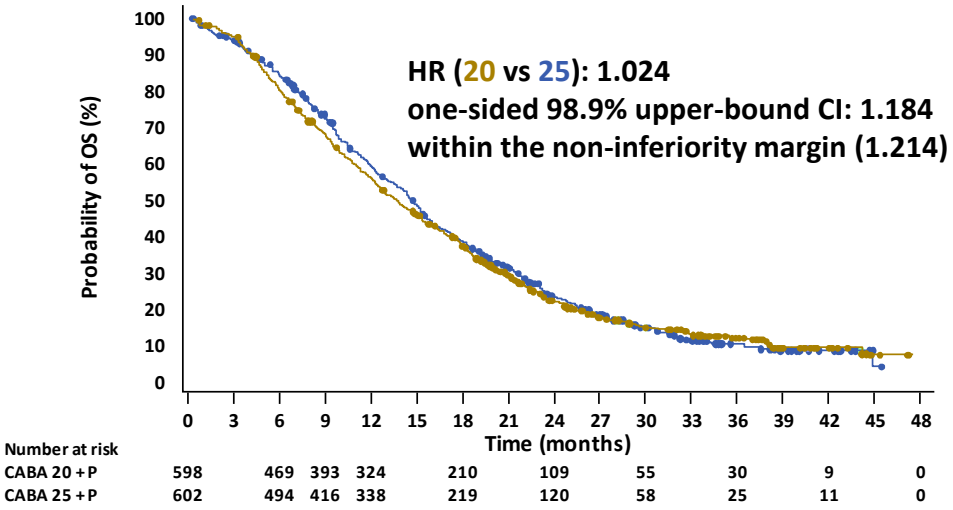
PROSELICA – Key Results

OS (primary endpoint)

Median OS, months (95% CI)

CABA 20 + P **13.4 (12.19-14.88)**

CABA 25 + P **14.5 (13.47-15.28)**

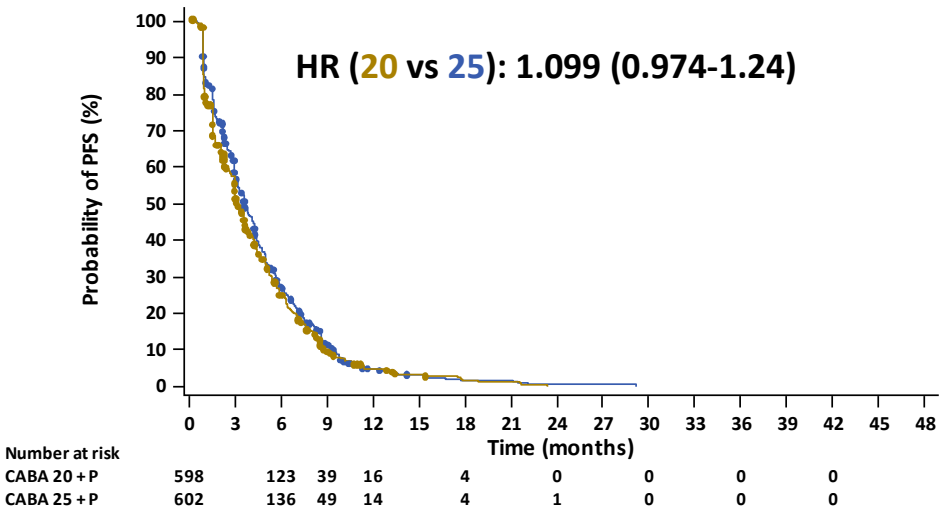


PFS (composite)*

Median PFS, months (95% CI)

CABA 20 + P **2.9 (2.79-3.45)**

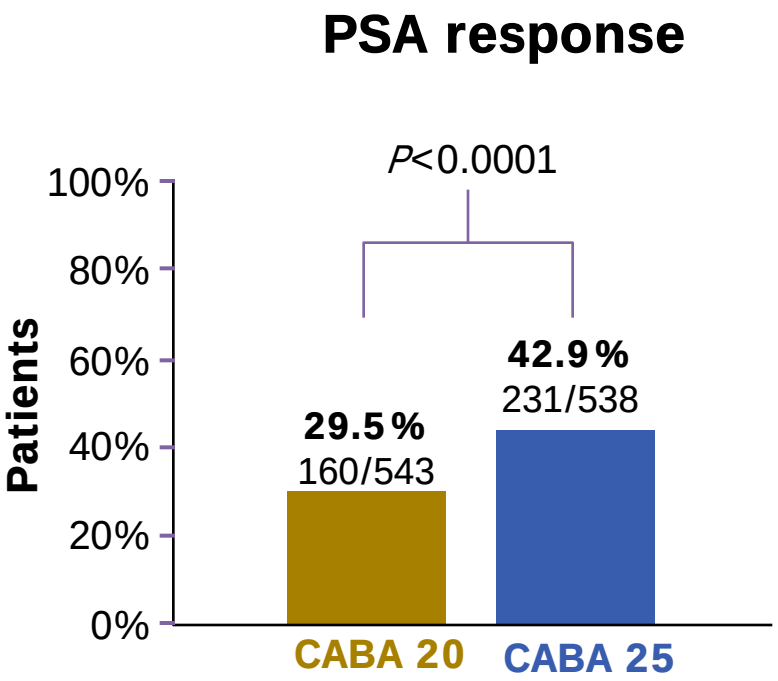
CABA 25 + P **3.5 (3.12-3.94)**



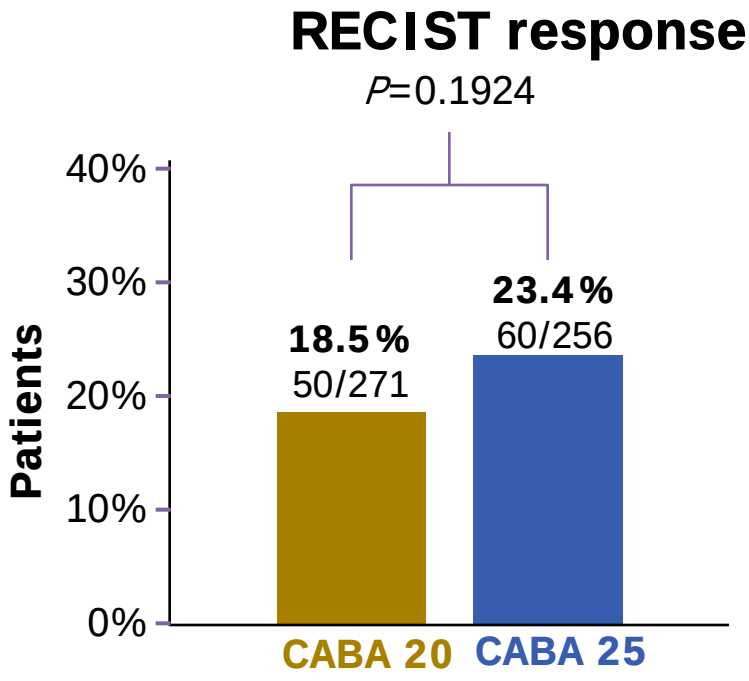
**PFS: progression-free survival defined as tumor progression or PSA progression or pain progression or death*

de Bono J et al. J Clin Oncol 2016;34(suppl):abstract 5008 - ClinicalTrials.gov NCT01308580

PROSELICA – PSA and Tumor Responses



Assessed in evaluable patients: with baseline ≥10 ng/ml and at least on post-baseline measurement



Assessed in patients with measurable disease at baseline and evaluable data to meet the criteria for RECIST derivation

De Bono J et al. J Clin Oncol 2016;34(suppl):abstract 5008 - ClinicalTrials.gov NCT01308580

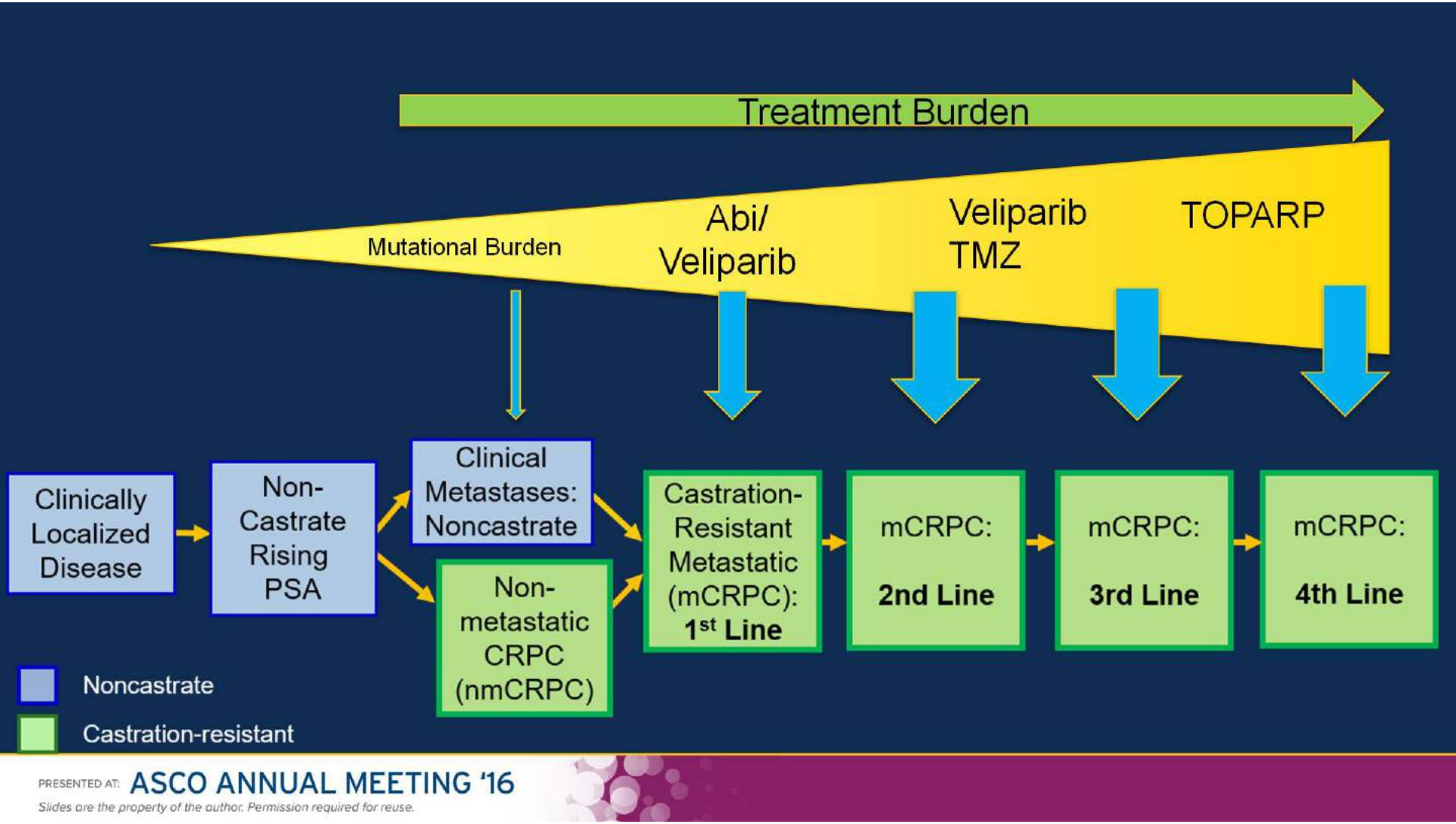
DNA Damage Repair Defects (DRD)
"Homozygous deletions/deleterious mutations"

N=22/87 (25%)

DNA Repair Gene	Frequency	%

"Personalize treatment for case of DRD "

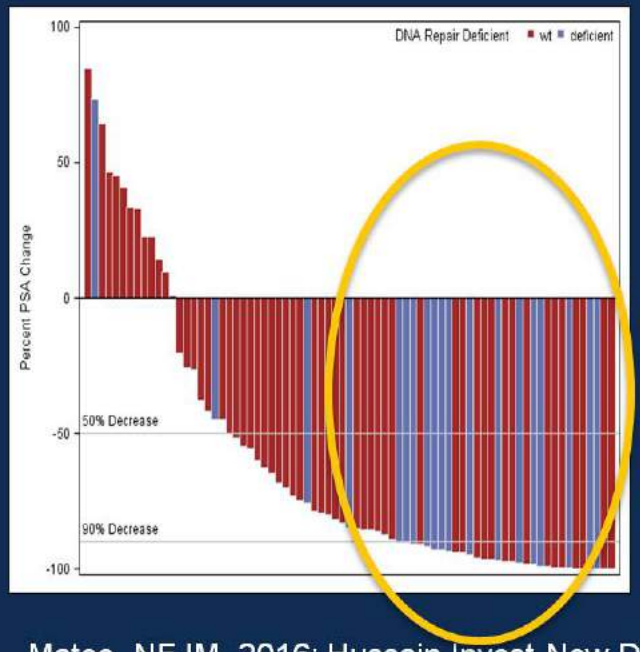
For Metastatic Castration-Resistant Prostate Cancer Patients (NCI9012). A University of Chicago Phase II Consortium Trial



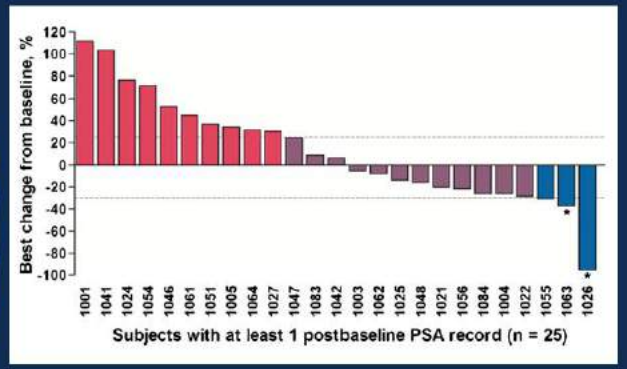
Presented By Michael Morris at 2016 ASCO Annual Meeting

Reported studies

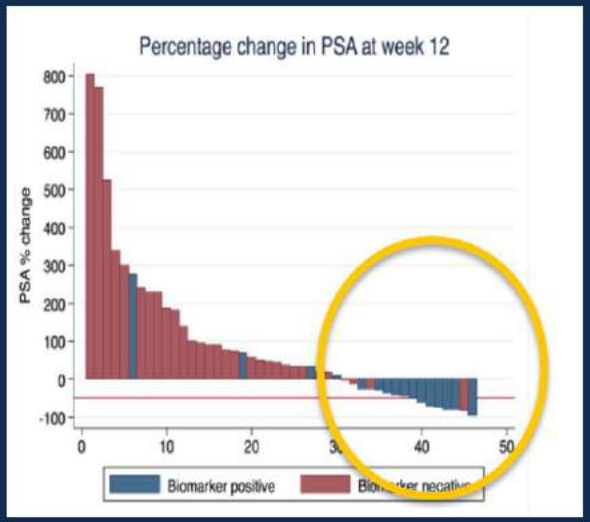
Abi + veliparib



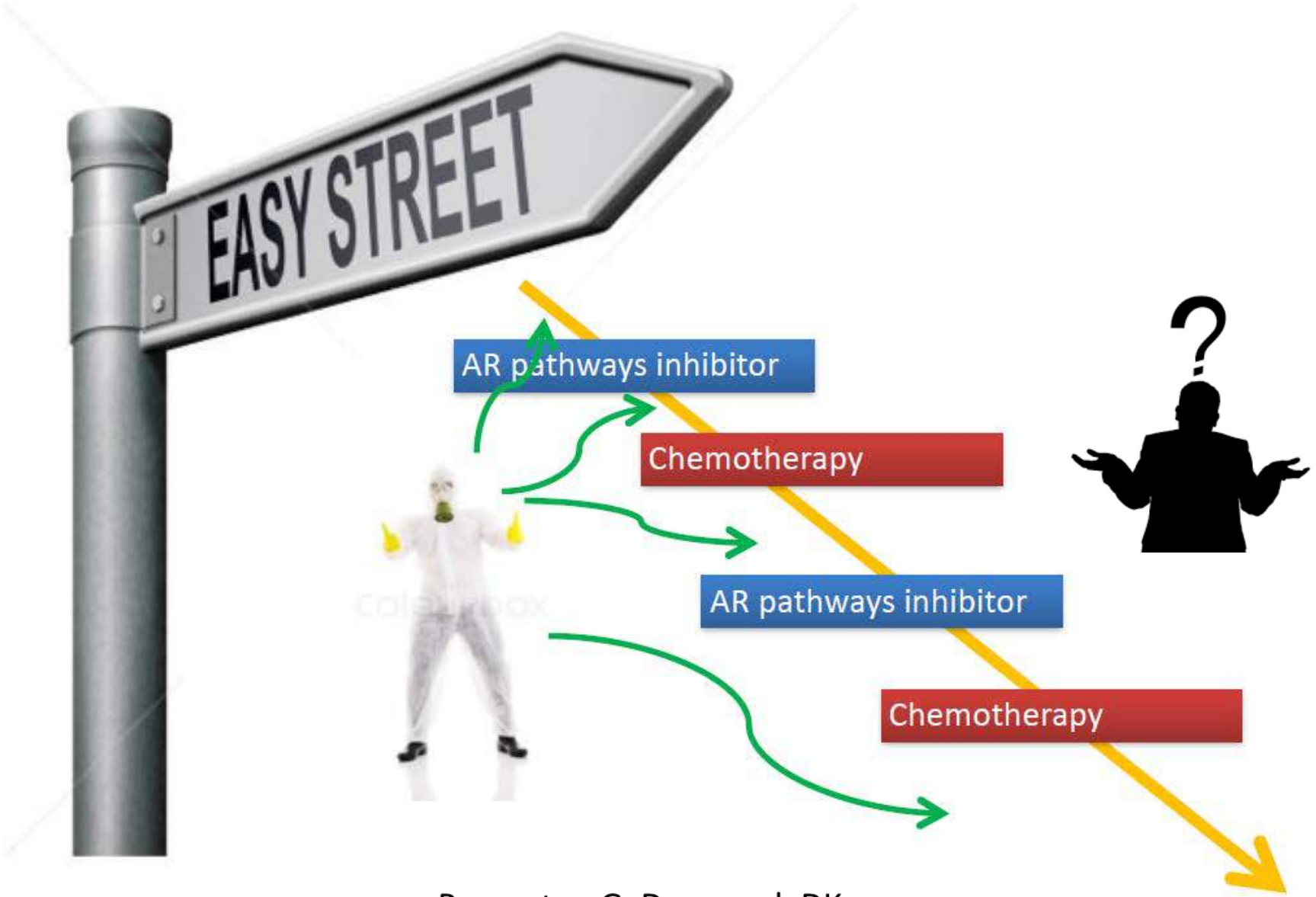
Veliparib + TMZ



TOPARP



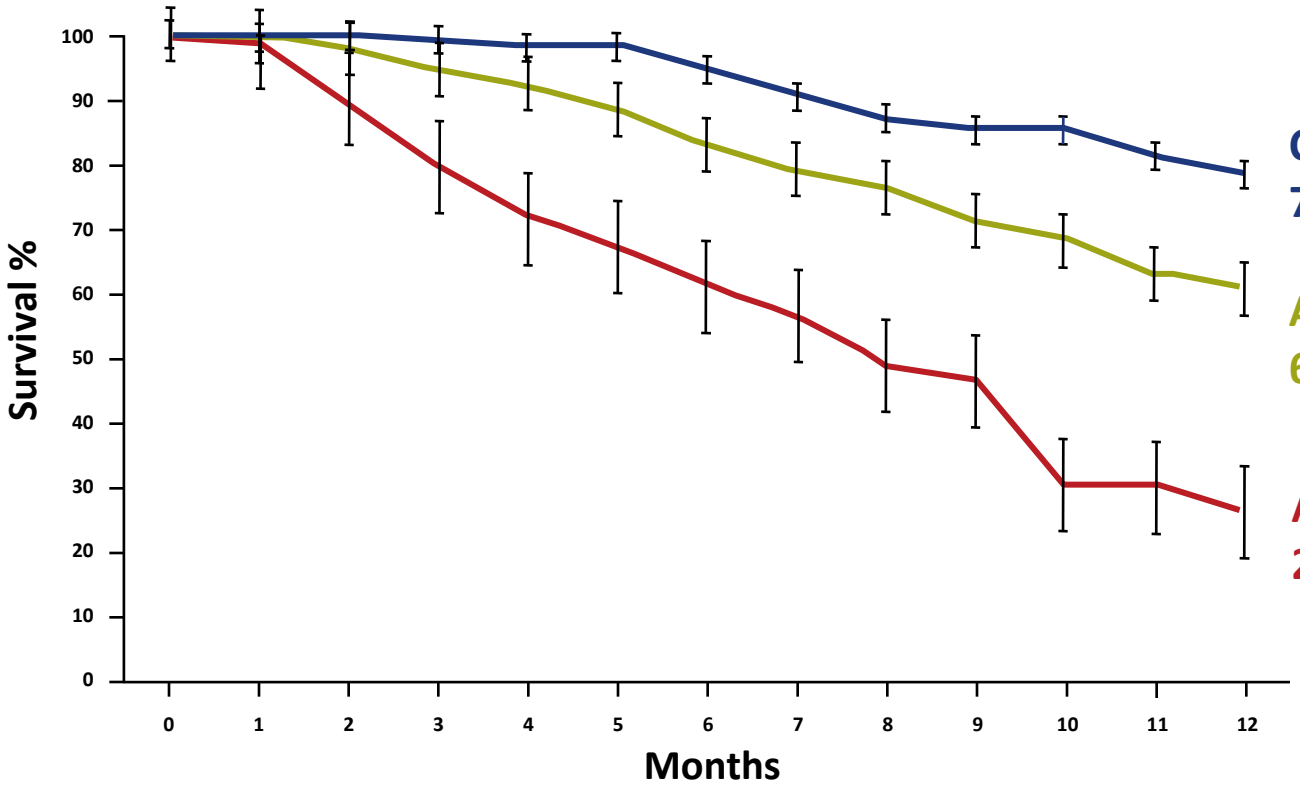
Mateo, NEJM, 2016; Hussain Invest New Drugs, 2014; Hussain, ASCO 2016



Presenter: G. Daugaard, DK
ESMO 2015

Systematic Review of 13 Published Retrospective Studies in mCRPC (N=1,016)

12-month cumulative OS rate by sequence (post-DOC)



%, [95% CI]

CABA→ART, n=229
76.4% [70.9-81.9]

ART→CABA, n=318
61.3% [56.0-66.7]

ART→ART, n=397
28.5% [24.1-32.9]

Poor outcome when novel AR-targeted agents are prescribed in sequence

ART: novel AR-targeted agent (abiraterone acetate or enzalutamide)

Maines F et al. Crit Rev Hematol Oncol 2015;96:498-506

FLAC International Database (HEGP)

- Retrospective analysis of 574 consecutive patients with mCRPC treated with **CABA (after DOC)** in 44 centers from 6 countries (France, Greece, Poland, Spain, Turkey, UK)

574 mCRPC pts treated with CABA

DOC → CABA →ART (N=124)

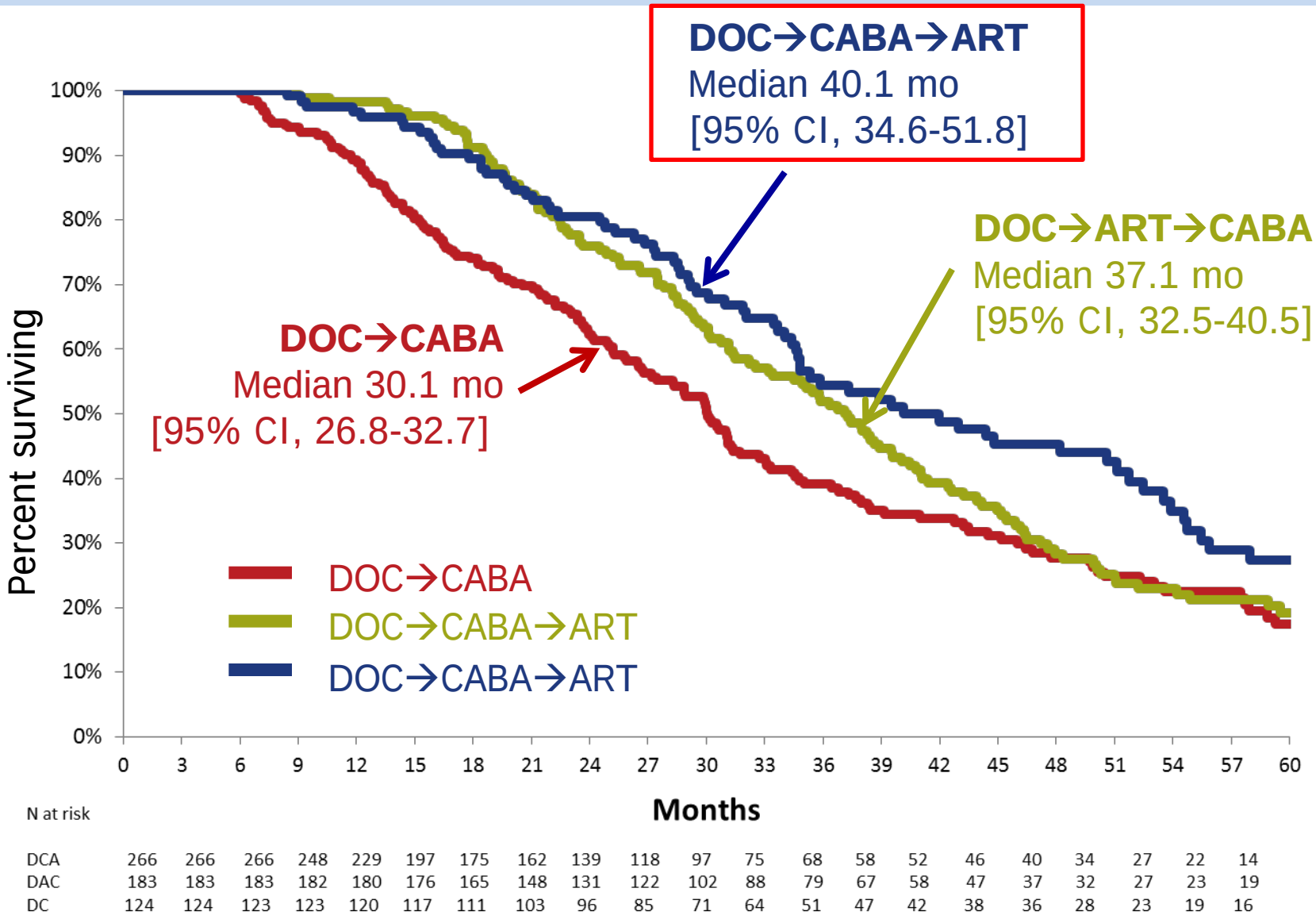
DOC → ART → CABA (N=183)

DOC → CABA (N=267)*

ART: novel AR-targeted agent (enzalutamide or abiraterone); HEGP: Hôpital Européen Georges-Pompidou
**Historical reference – First recruited patients (ART were not yet available)*

Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

FLAC - OS from First DOC Cycle



Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

CATS International Database (HEGP)

- Retrospective analysis of 560 consecutive patients treated with DOC, CABA and one ART in 31 centers in 7 countries (France, Austria, Greece, Italy, Israel, Spain, UK)

560 mCRPC pts treated with DOC, CABA and ART

DOC → CABA →ART (N=129)

DOC → ART → CABA (N=390)

ART → DOC → CABA (N=41)

Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS – OS from First Life-Extending T ce

Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

And, what is new knowledge in 2017

A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

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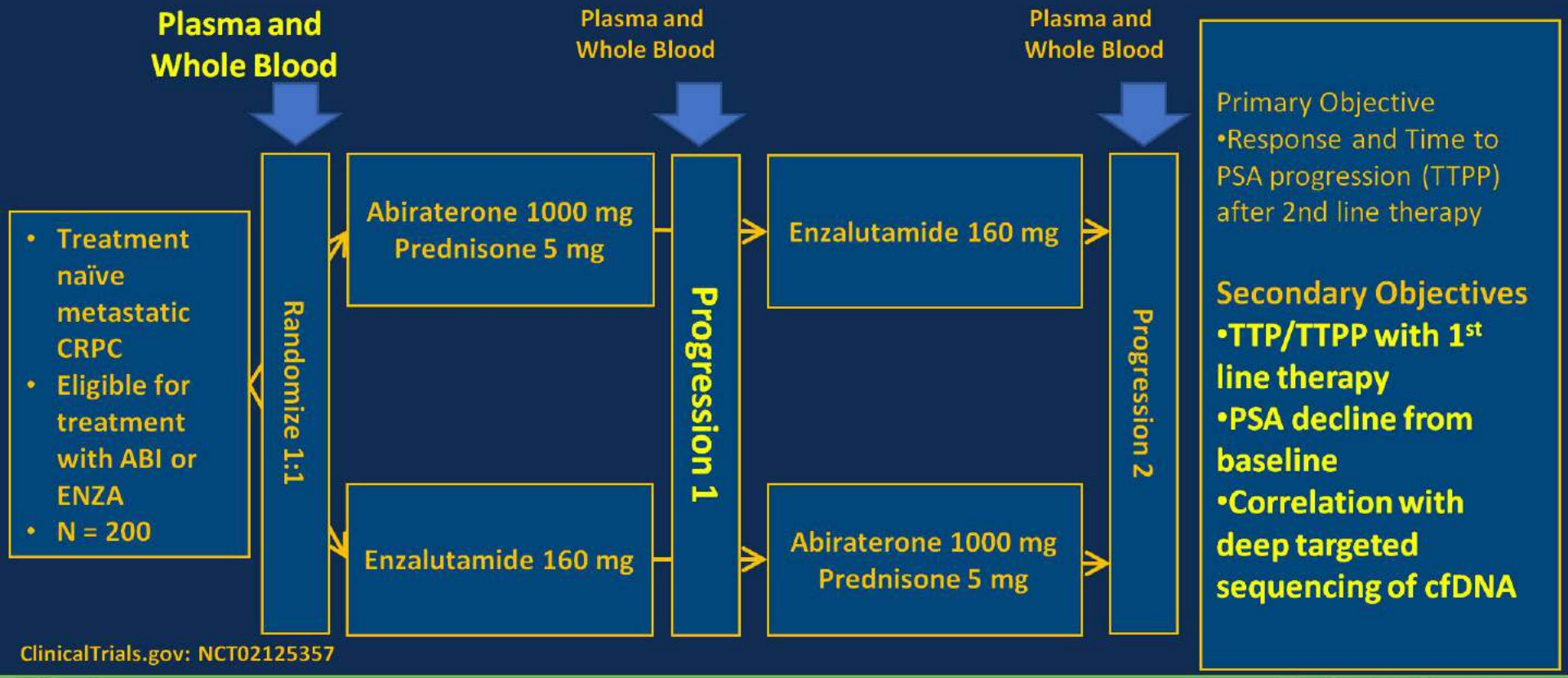
Study Schema



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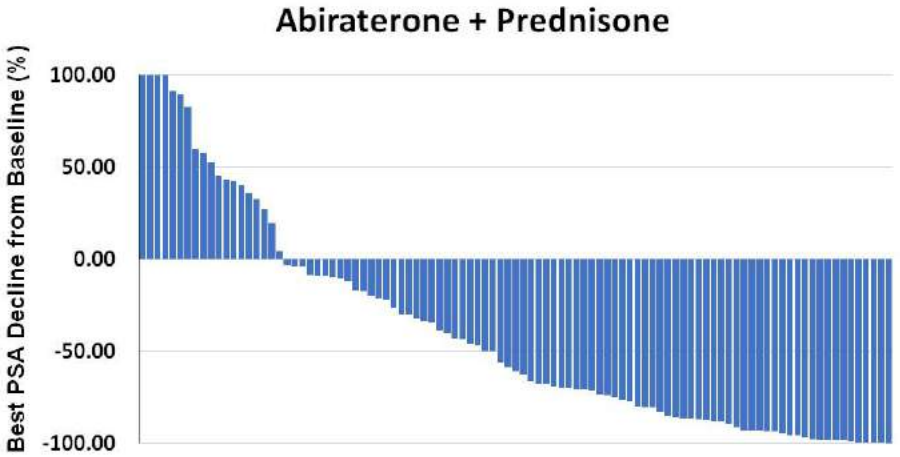
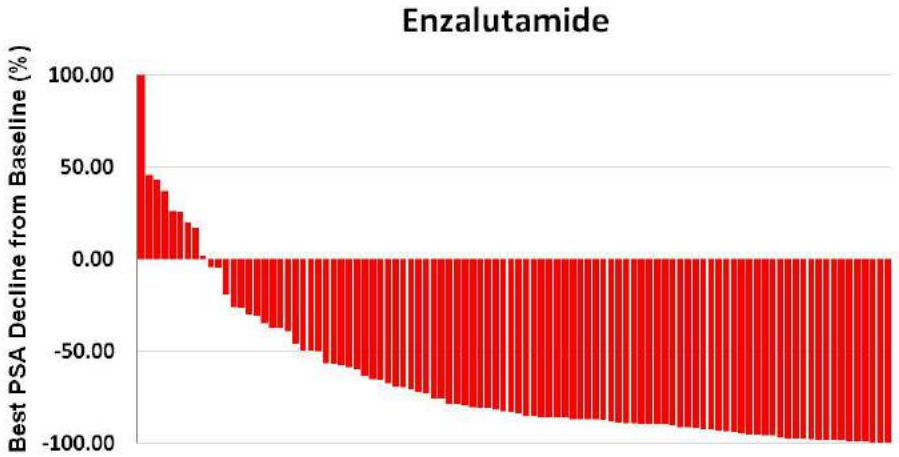
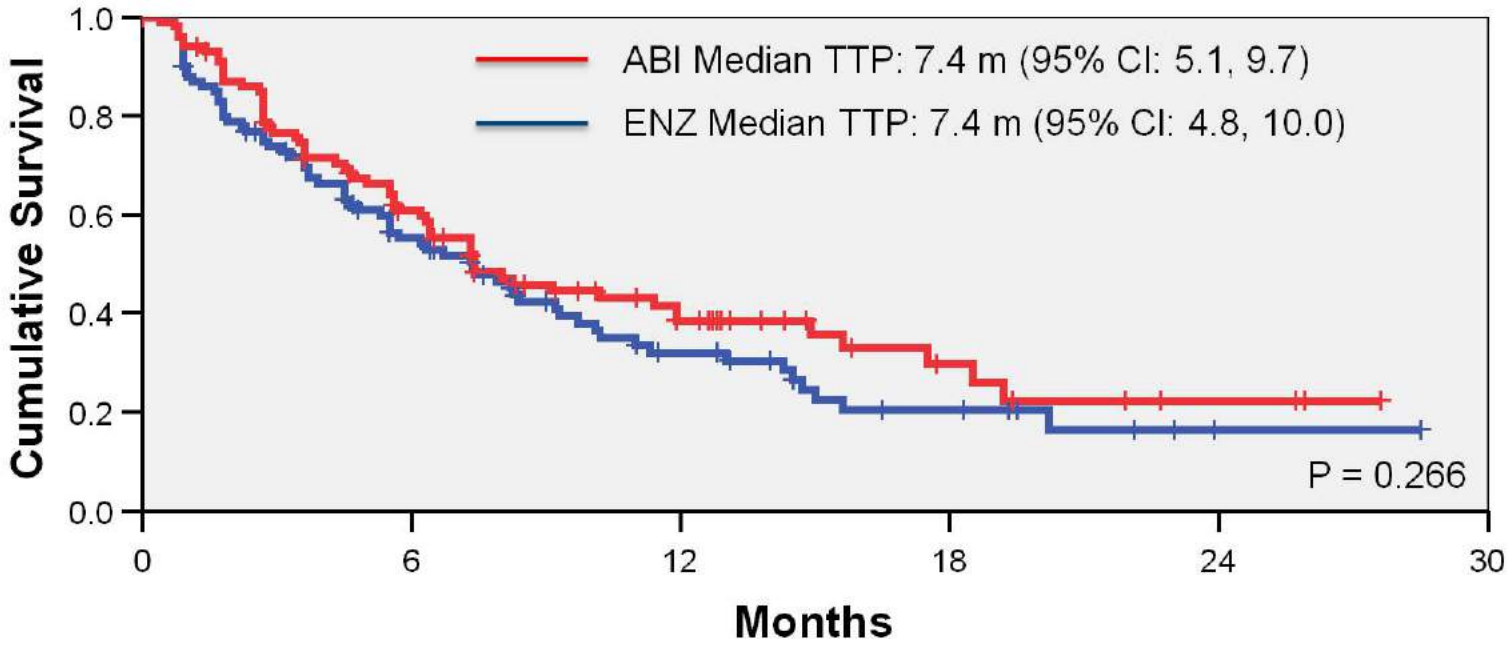
Best PSA decline: 12 weeks

	Abiraterone N=99	Enzalutamide N=98	P-value
PSA Decline ≥ 30%	64 (65%)	83 (85%)	0.0012
PSA Decline ≥ 50%	54 (55%)	75 (77%)	0.0012
No PSA Decline	20 (20%)	10 (10%)	0.0501





Time to Progression



*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease

Phase 2 : high response in Enz , but not different in time to PD

A Phase 4, Randomized, Double-Blind, Placebo-Controlled Study of Continued Enzalutamide Post Prostate-Specific Antigen Progression in Men With Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer

Gerhardt Attard,[1] Michael Borre,[2] Howard Gurney,[3] Yohann Loriot,[4] Corina Andresen-Daniil,[5] Ranjith Kalleda,[5] Trinh Pham,[5] Mary-Ellen Taplin[6]

[1]The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Macquarie University, Sydney, Australia; [4]Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [5]Medivation, Inc. (Medivation was acquired by Pfizer Inc in September 2016), San Francisco, CA; [6]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

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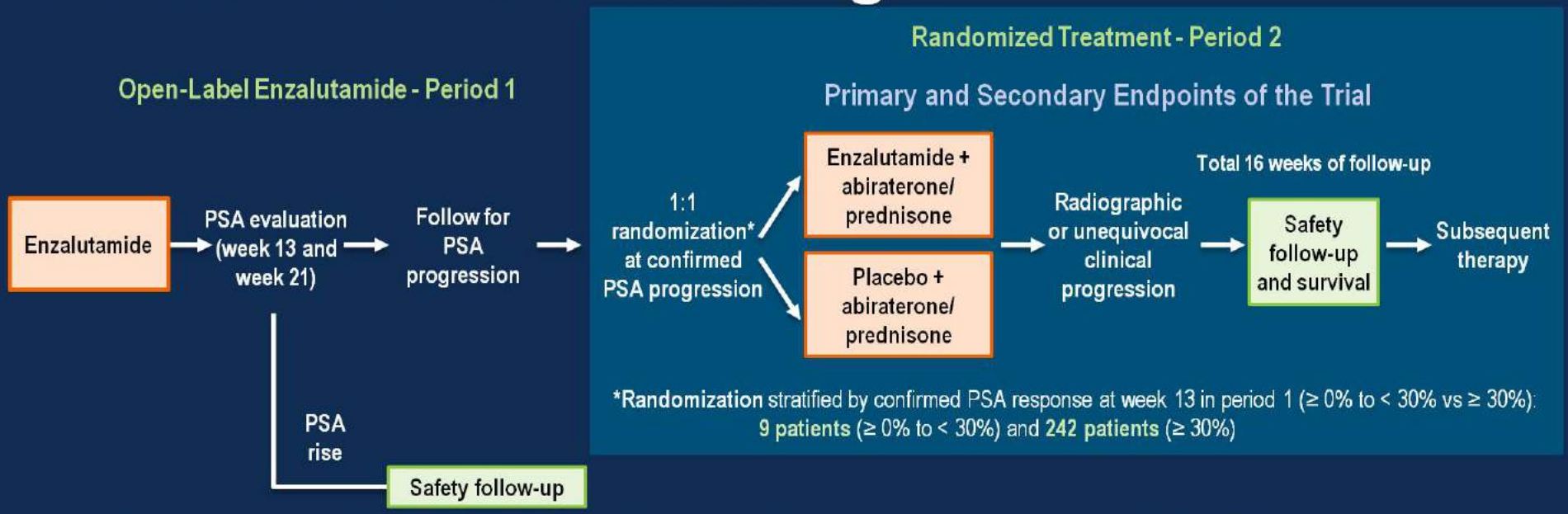
Adding AA beyond progression of enza

PLATO: Novel Trial Design



Enrolled n = 509 (Target n = 500) | **PSA Responders n = 412 (Target n = 415)** | **Randomized n = 251 (Target n = 250)** | **PFS Events n = 175 (Target n = 175)**

Period 1 results presented by Attard G et al, at the European Cancer Congress; September 25-29, 2015; Vienna, Austria.

Patients enrolled in 51 study centers in North America, Europe, and Australia.
Abbreviation: PFS, progression-free survival.
NCT01995513; https://clinicaltrials.gov/show/NCT01995513.

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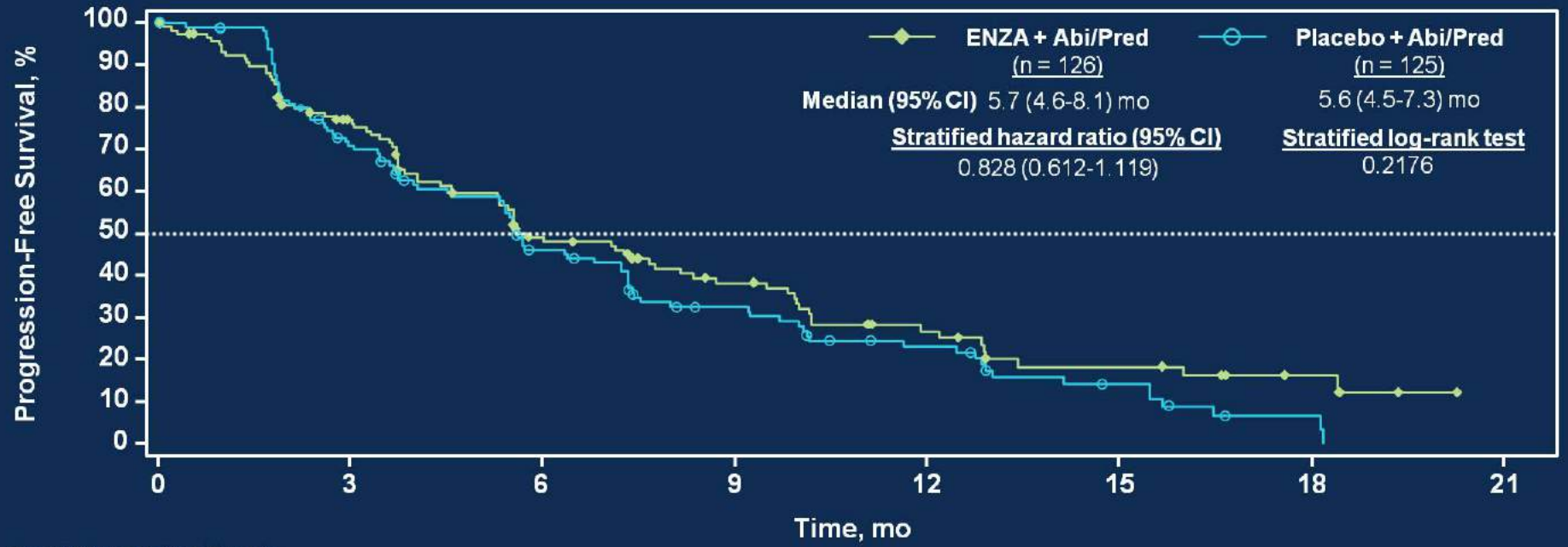
Primary Endpoint: PFS



Event/Cumulative Events

ENZA + Abi/Pred	27/27	30/57	10/67	9/76	5/81	1/82	1/83
Placebo + Abi/Pred	33/33	26/59	13/72	8/80	6/86	4/90	2/92

Abbreviations: CI, confidence interval; mo, months.

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Practice Changing?

- Suggests adding second AR targeted drug is not effective.
- Supports my ‘One shot on goal’ theory
- Await phase III study of Abi+Enz vs Enz alone

Abiraterone + Prednisone (Abi) +/- Veliparib (Vel) For Metastatic Castration-Resistant Prostate Cancer Patients (CRPC pts): NCI 9012 Updated Clinical and Genomics Data

Hussain M, Daignault S, Twardowski P, Albany C, Stein MN, Kunju LP, Robinson DR, Siddiqui J, Cooney KA, Montgomery RB, Antonarakis ES, Shevrin DH, Corn PG, Whang YE, Smith DC, Caram MV, Mehra R, Tomlins SA, Knudsen KE, Stadler WM, Feng FY, Chinnaiyan AM

Northwestern University Robert H. Lurie Comprehensive Cancer Center; Department of Biostatistics, University of Michigan; City of Hope Comprehensive Cancer Center; Indiana University Melvin and Bren Simon Cancer Center; Rutgers Cancer Institute of New Jersey; University of Michigan; University of Michigan Health System; University of Utah; University of Washington; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; NorthShore University Health System; The University of Texas MD Anderson Cancer Center; The University of North Carolina at Chapel Hill; University of Michigan Comprehensive Cancer Center; The Sidney Kimmel Cancer Center at Thomas Jefferson University; The University of Chicago; University of California, San Francisco, University of Michigan

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Presented by: M. Hussain, MD, FACP, FASCO

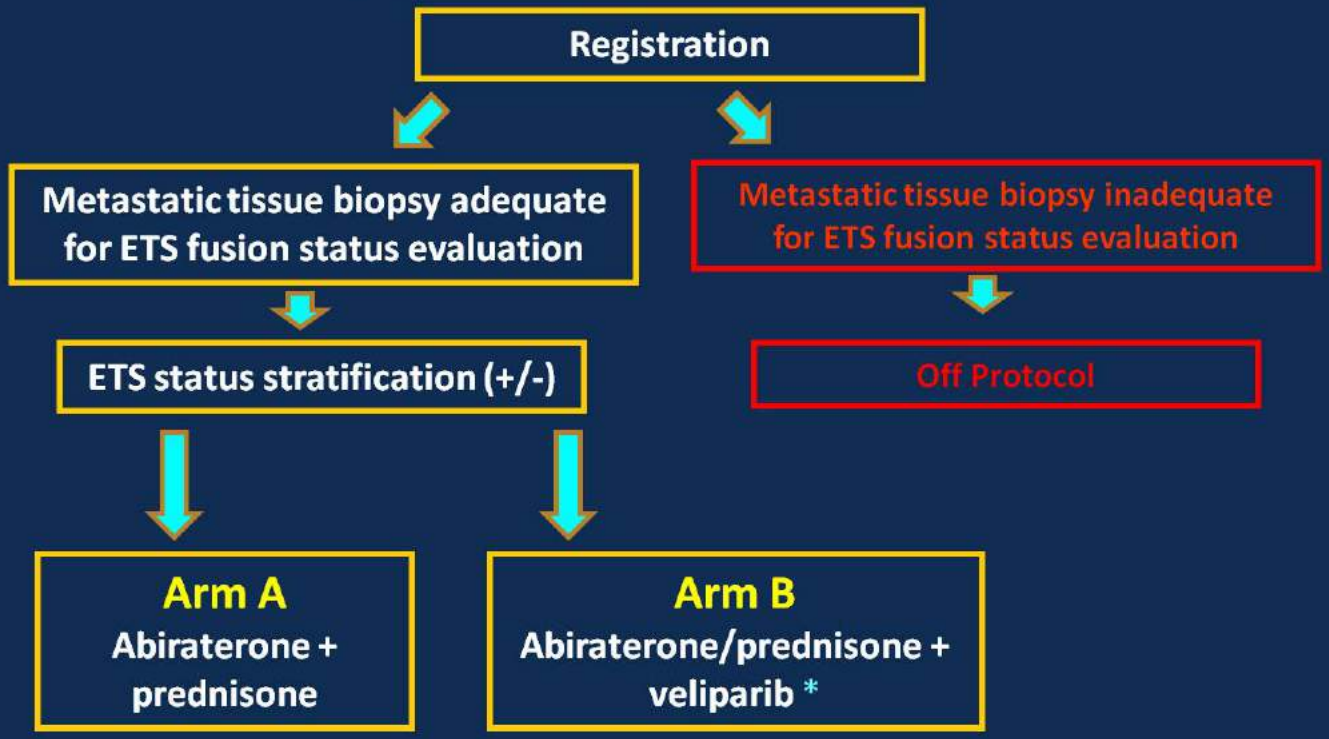
DRD : what is the proper treatment?

Presented By Charles Ryan at 2017 ASCO Annual Meeting

Study Design

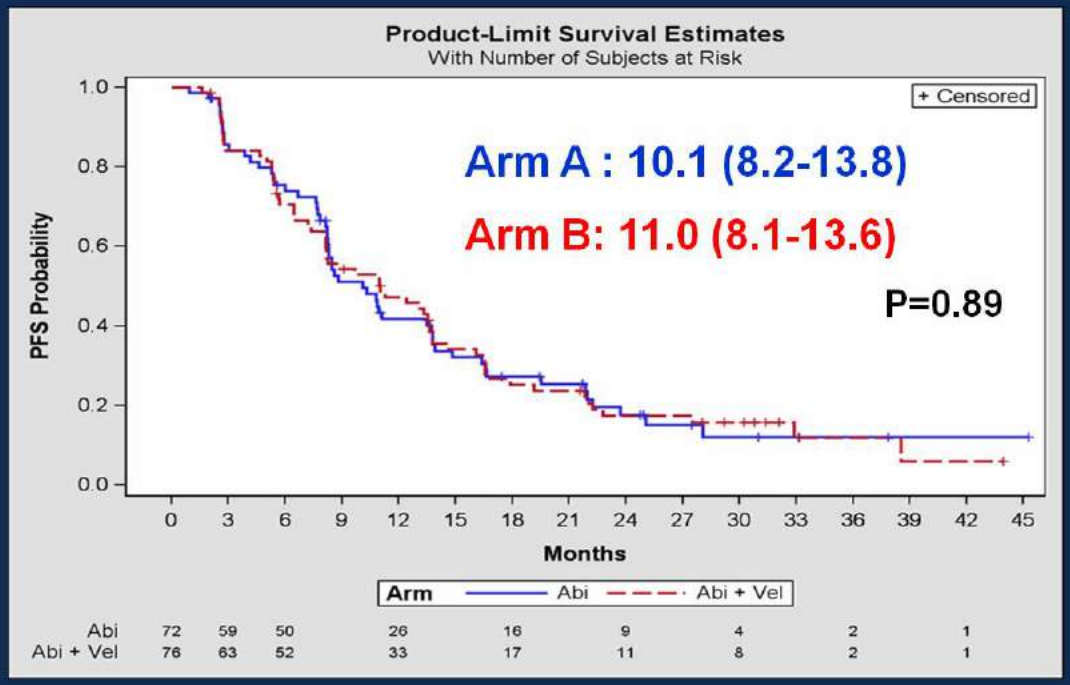
Key inclusion criteria

- Progressive mCRPC by at least 1 criteria:
  a. PSA progression;
  b. Measurable disease;
  c. .Bone disease
- No prior abiraterone.
- Prior ketoconazol & chemo is allowed
- Agree to undergo a biopsy of metastatic site with adequate fresh tissue unless adequate metastatic archival tissue is available



*Veliparib dose: 200 (300) mg PO bid daily

Progression Free Survival & Overall Survival



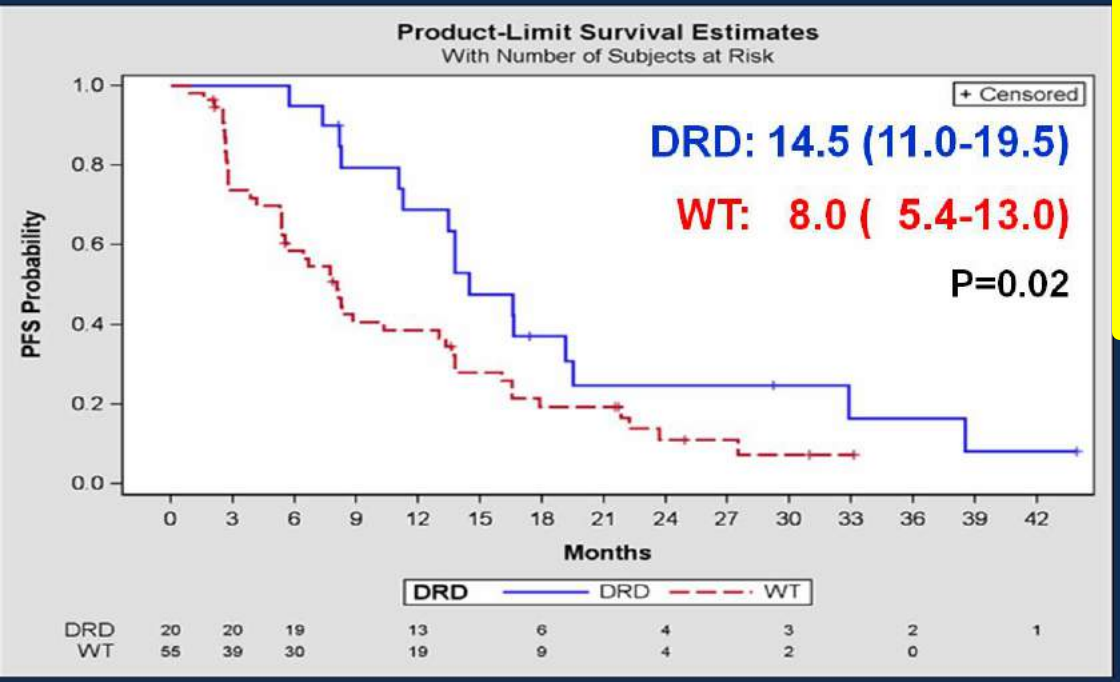
- **No difference in PFS by ETS status**

Arm A: Abi/Pred, Arm B: Abi+Veliparib

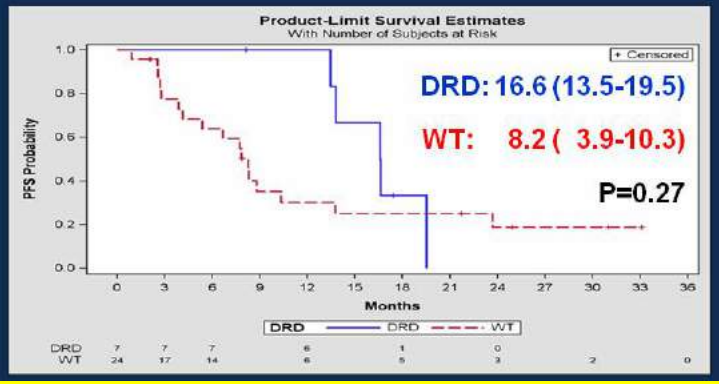
Median OS (95% CI): Arm A: 30.6 m (28.4 – NR), Arm B 32.3 m (28.4 – NR)

PFS by DRD status: Overall & By Arm

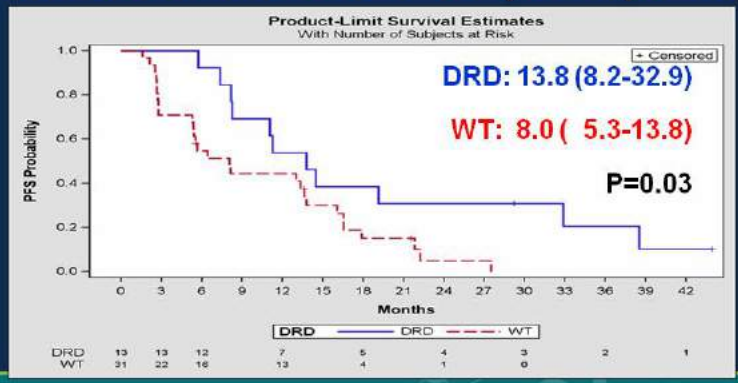
PFS by DRD status (N= 75)



Arm A: Abiraterone (N=31)



Arm B: Abiraterone + Veliparib (N=44)



Presented by: M. Hussain, MD, FACP, FASCO

Practice Changing?

- Not entirely, but suggests that treating a patient with BRCA2 /ATM with Abi is reasonable.
- You may not need to go right to the parp inhibitor or to carboplatin.
- Goes against other data consistently showing a worse prognosis in patients with BRCA2

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

UNIVERSITY OF BIRMINGHAM

CANCER RESEARCH UK

UCL

Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

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

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

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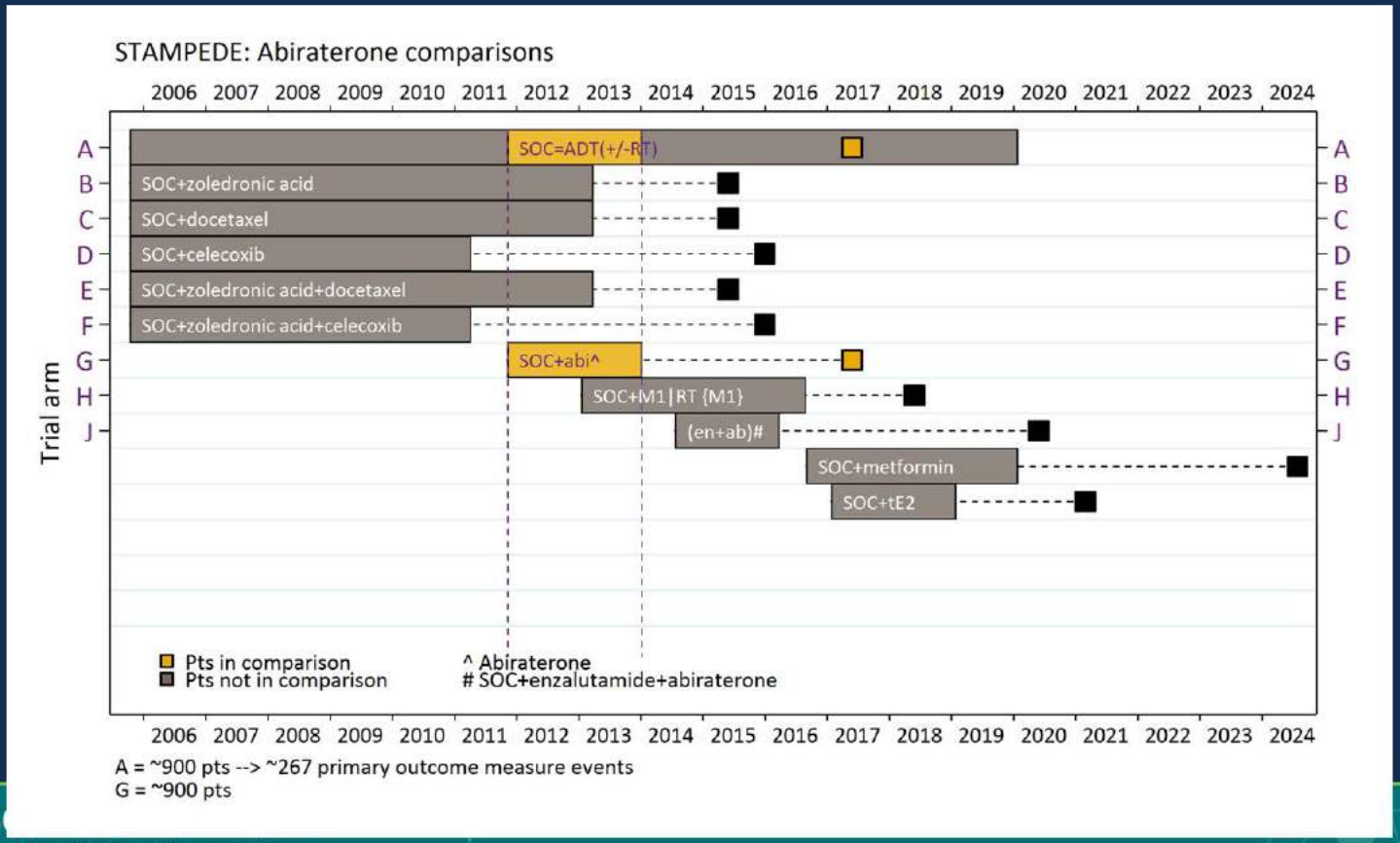
Abiraterone in HSPC

Presented By Charles Ryan at 2017 ASCO Annual Meeting

Abiraterone comparison: patients



Conclusions

- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  - Overall survival by 37%
  - Failure free survival by 71%
  - Symptomatic skeletal events by 55%
- Treatment was well tolerated
- Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy

LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

Karim Fizazi,[1] NamPhuong Tran,[2] Luis Fein,[3] Nobuaki Matsubara,[4] Alfredo Rodriguez-Antolin,[5] Boris Y. Alekseev,[6] Mustafa Özgüroğlu,[7] Dingwei Ye,[8] Susan Feyerabend,[9] Andrew Protheroe,[10] Peter De Porre,[11] Thian Kheoh,[12] Youn C. Park,[13] Mary B. Todd,[14] Kim N. Chi,[15] on behalf of the LATITUDE Investigators

[1]Gustave Roussy, University of Paris Sud, Villejuif, France; [2]Janssen Research & Development, Los Angeles, CA; [3]Instituto de Oncologia de Rosário, Rosário, Argentina; [4]National Cancer Center Hospital East, Chiba, Japan; [5]12 de Octubre University Hospital, Madrid, Spain; [6]P.A. Hertsen Moscow Cancer Research Institute, Moscow, Russian Federation; [7]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [8]Fudan University Shanghai Cancer Center, China; [9]Studienpraxis Urologie, Nürtingen, Germany; [10]Oxford University Hospitals Foundation NHS Trust, Oxford, UK; [11]Janssen Research & Development, Beerse, Belgium; [12]Janssen Research & Development, San Diego, CA; [13]Janssen Research & Development, Raritan, NJ; [14]Janssen Global Services, Raritan, NJ; [15]BC Cancer Agency, Vancouver, BC, Canada

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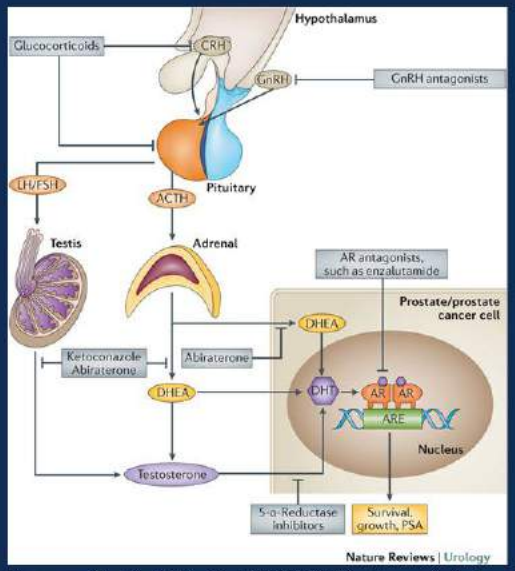
Presented By Karim Fizazi at 2017 ASCO Annual Meeting

De novo metastatic prostate cancer

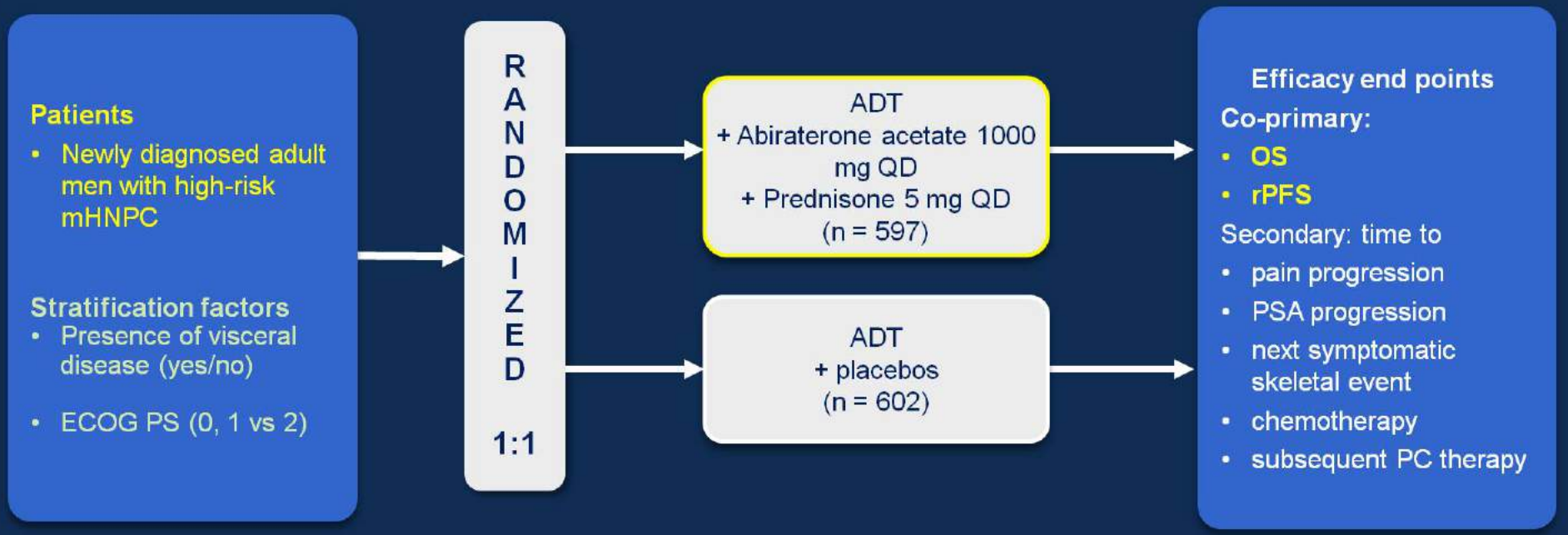
- Metastatic castration-naïve prostate cancer (mCNPC) incidence is[1-5]:
  - ~3% in US and rising;
  - ~6% across Europe
  - ~4-10% in Latin America
  - ~60% in Asia-Pacific
- Historically, androgen deprivation therapy (ADT) has been the standard of care[6]
- Most men with metastases progress to mCRPC largely driven by reactivation of AR signaling[6]



Narayanan S, et al. *Nat Rev Urol*. 2016;13:47-60, with permission from Nature Publishing Group.

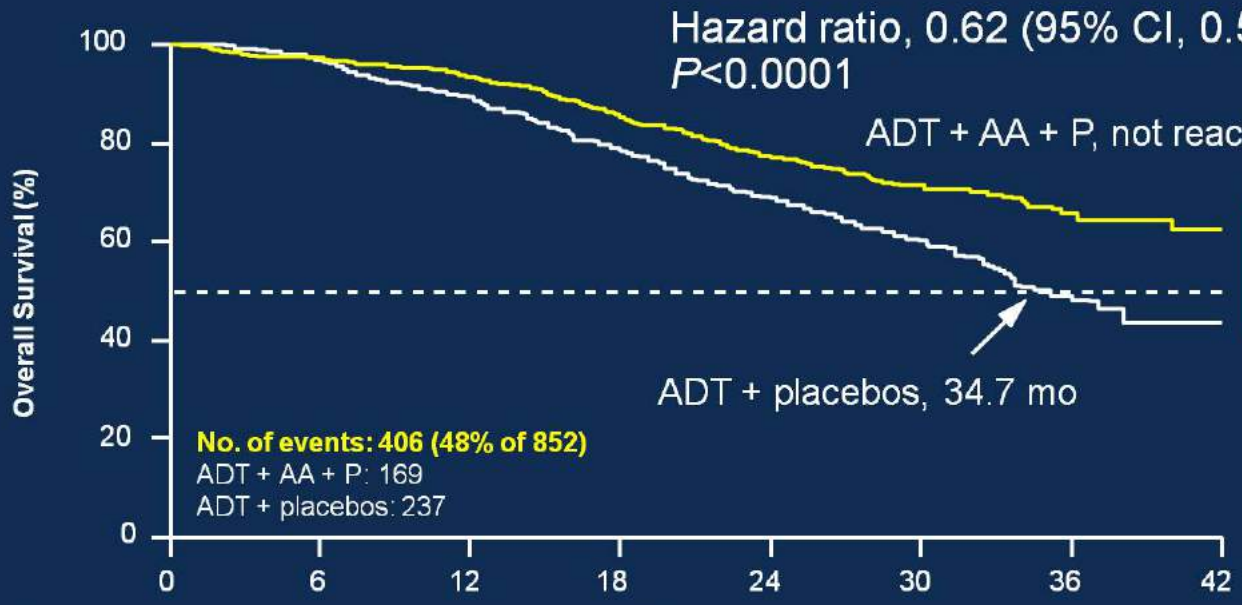
1. Weiner AB, et al. *Prostate Cancer Prostatic Dis*. 2016;19:395-397. 2. Buzzoni C, et al. *Eur Urol*. 2015;68:885-890. 3. Chen R, et al. *Asian J Urol*. 2014;1:15-29. 4. Ito K. *Nat Rev Urol*. 2014;11:15-29. 5. Nardi AC. *Int Braz J Urol*. 2012;38:155-166. 6. Yamaoka M, et al. *Clin Cancer Res*. 2010;16:4319-4324.

Overall study design of LATITUDE



- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

Statistically significant 38% risk reduction of death



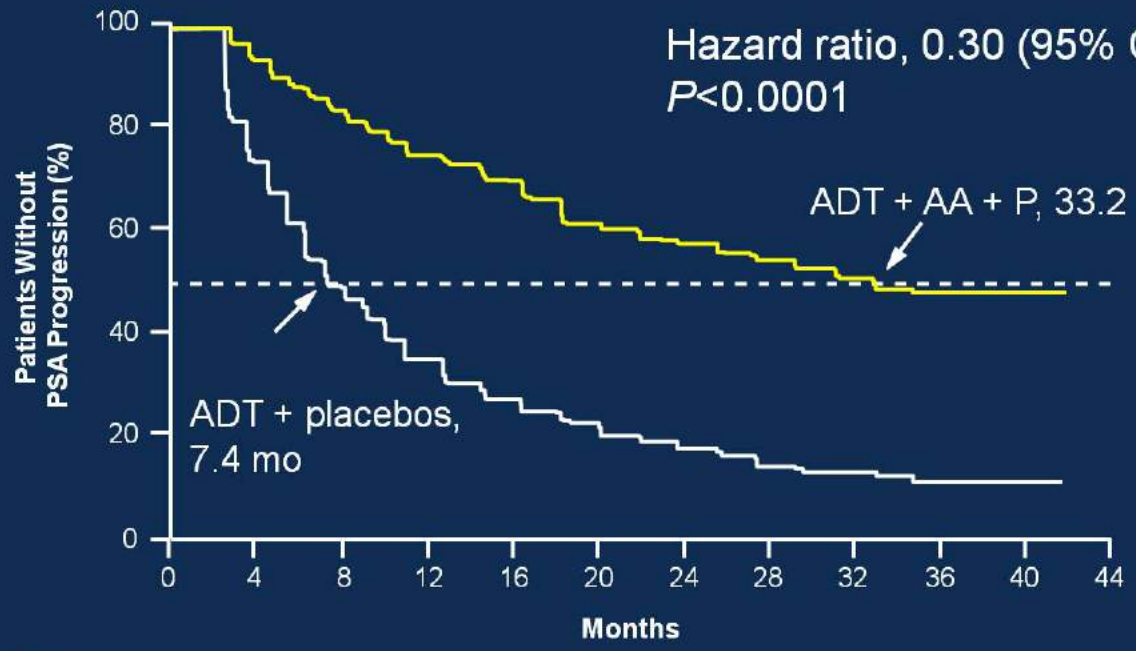
OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

Median follow-up: 30.4 months

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

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

Statistically significant 70% risk reduction of time to PSA progression



No. at risk												
ADT + AA + P	597	520	447	379	340	285	227	162	95	48	18	0
ADT + placebos	602	393	250	172	129	102	65	33	19	8	5	0

Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a 38% reduction in the risk of death
  - Significantly prolonged rPFS (53% reduction) and all secondary end points

- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with mCRPC

Comparing CHAARTED High Volume Patients and LATITUDE Patients

	N	Eligibility Criteria
LATITUDE All Patients	**1199**	**Meets at least 2 of 3 high-risk criteria:** • Presence of ≥ 3 lesions on bone scan • Presence of measurable visceral lesion • Gleason score of ≥ 8
CHAARTED High Volume	**513**	**Meets one or both criteria:** • Presence of ≥ 4 lesions on bone scan (with at least one lesion outside pelvis and spine) • Presence of measurable visceral lesion

Comparing LATITUDE Patients and CHAARTED High Volume Patients

	N	Overall Survival (Control Arm: ADT)
LATITUDE	1199 (406 deaths)	34.7 mos
CHAARTED (High Volume)	513 (299 deaths)	34.4 mos

Similar Overall Survival in ADT-only (control) groups suggests similar populations

Comparing Overall Survival Across Studies

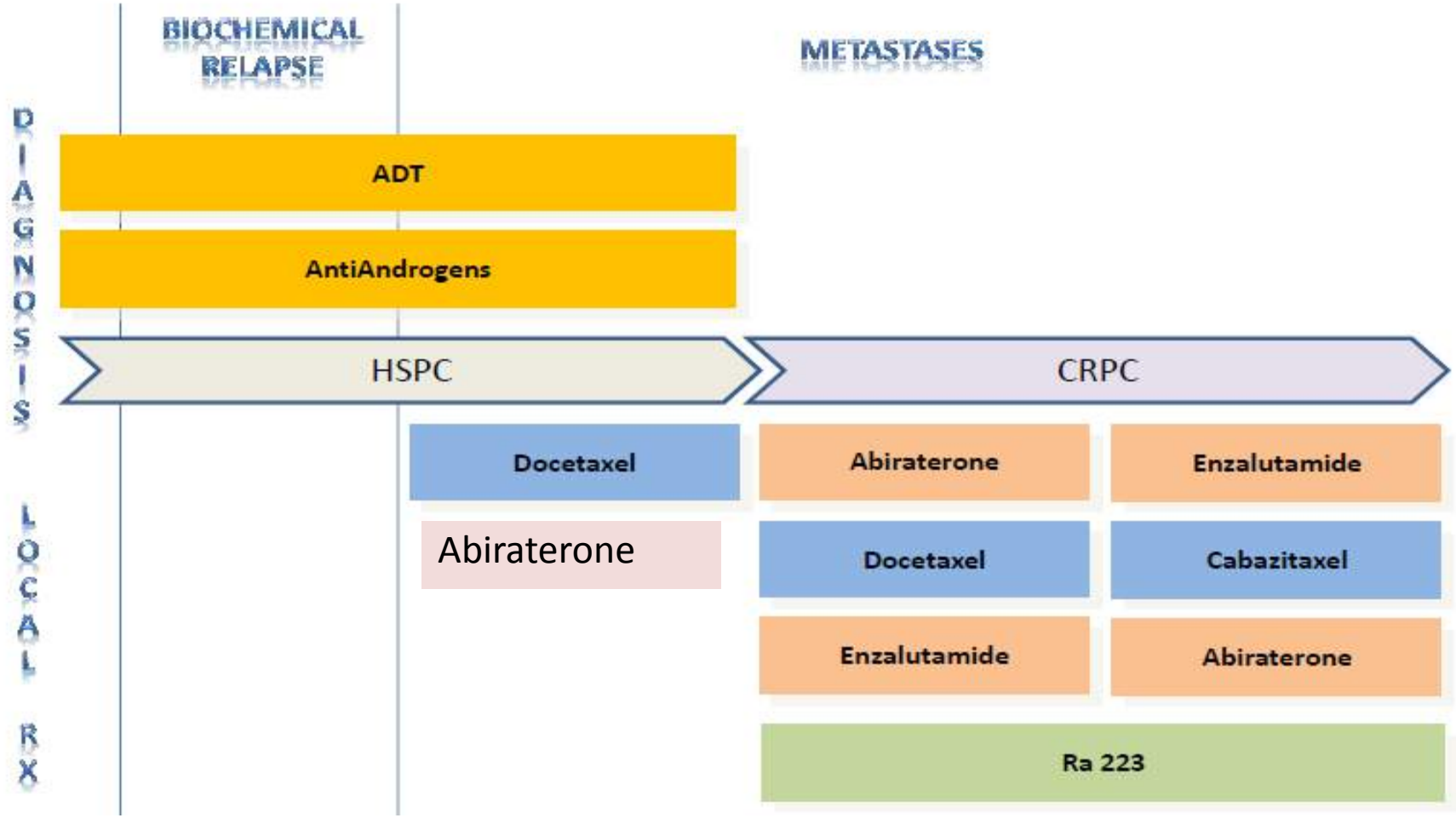
	Median OS			3 yr OS rate*	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%	~65%

* Estimated from KM plots

Take Homes from Latitude

- The benefit obtained from adding abiraterone to ADT appears to be the same as that seen with docetaxel.
- The use of abiraterone
  - Avoids Chemotherapy
  - Avoids (rare) neutropenic complication/ treatment-associated deaths
  - Replaces short term IV treatment with long term oral treatment
  - May be more appropriate in elderly or debilitated
- Future evaluation
  - QOL and financial toxicity
  - Testing earlier (eg climbing PSA patients)
  - Combination with docetaxel

Progress in Metastatic CRPC



Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Overall conclusions

- Management of CRPC is rapidly evolving
- New drugs in development: need to move to a tailored therapy
- The most appropriate sequencing of these new agents remains to be determined and chemotherapy remains a valid treatment option in mCRPC

'The right drug, at the right time, for the right patient, at the right place and by the right team'

Ramathibodi Comprehensive Cancer Center