State of the Art: Hormone-sensitive Prostate Cancer

15th California Cancer Consortium Conference

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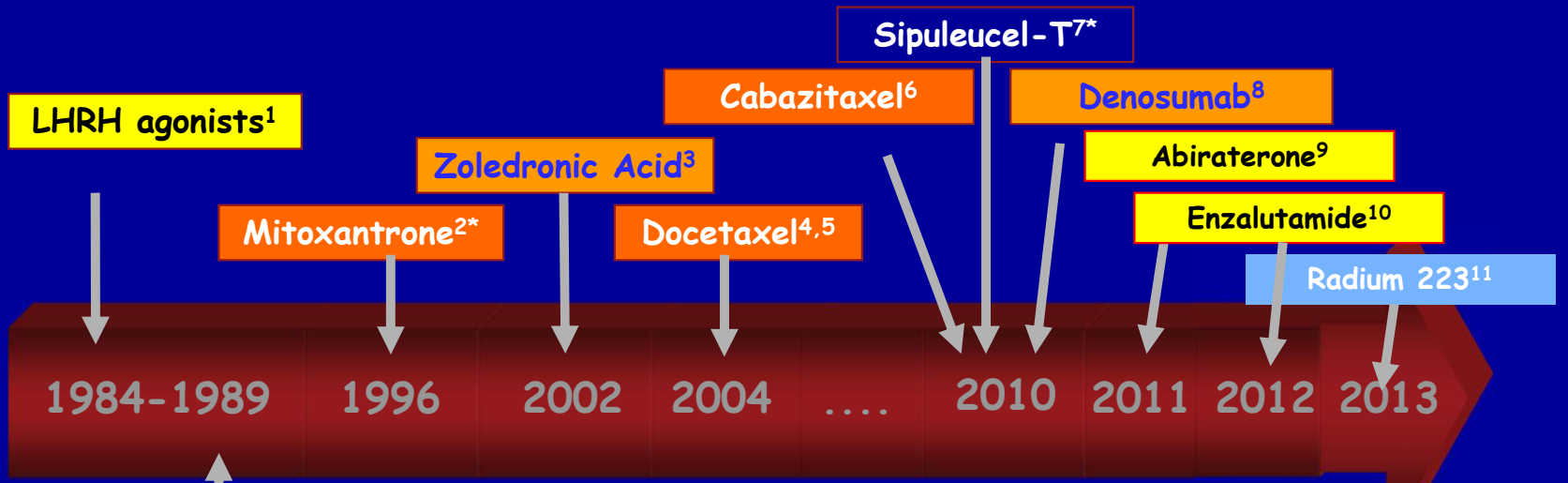
Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
• Astellas	• Honoraria	• Advisory Board
• Bayer	• Honoraria	• Advisory Board
• AstraZeneca	• Honoraria	• Advisory Board
• Novartis	• Honoraria	• Advisory Board
• Dendreon	• Honoraria/Res funds	• Advisory Board / Research
• Janssen	• Honoraria	• Advisory Board
• Genentech	• Honoraria/Res funds	• Advisory Board / Research
• Merck	• Honoraria/Res funds	• Advisory Board / Research
• Exelixis	• Honoraria	• Advisory Board
• Pfizer	• Honoraria	• Advisory Board
• BMS	• Honoraria	• Advisory Board
• Genzyme Sanofi	• Honoraria/Res funds	• Advisory Board / Research
• Peleton	• Honoraria	• Advisory Board

Regarding metastatic hormone sensitive prostate cancer, which of the following is correct?

A. The combination of of docetaxel and enzalutamide have an additive affect on overall survival when combined with ADT
B. Docetaxel improves overall survival when added to ADT in low volume patients
C. The combination of of docetaxel and abiraterone acetate + prednisone have an additive affect on overall survival when combined with ADT
D. Enzalutamide improves overall survival when added to ADT in low volume patients
E. Radiation therapy to the primary tumor may improve overall survival when added to ADT in high volume patients

Treatment options for prostate cancer snowballed after a 6 year hiatus… then another quiet period



…but this rapid change has left many unanswered questions, including the optimal selection and sequence of therapy

Aptalutamide[12]

Darolutamide [13]

Reversible AR blockers[1]

Journal of Clinical Oncology | Original Report

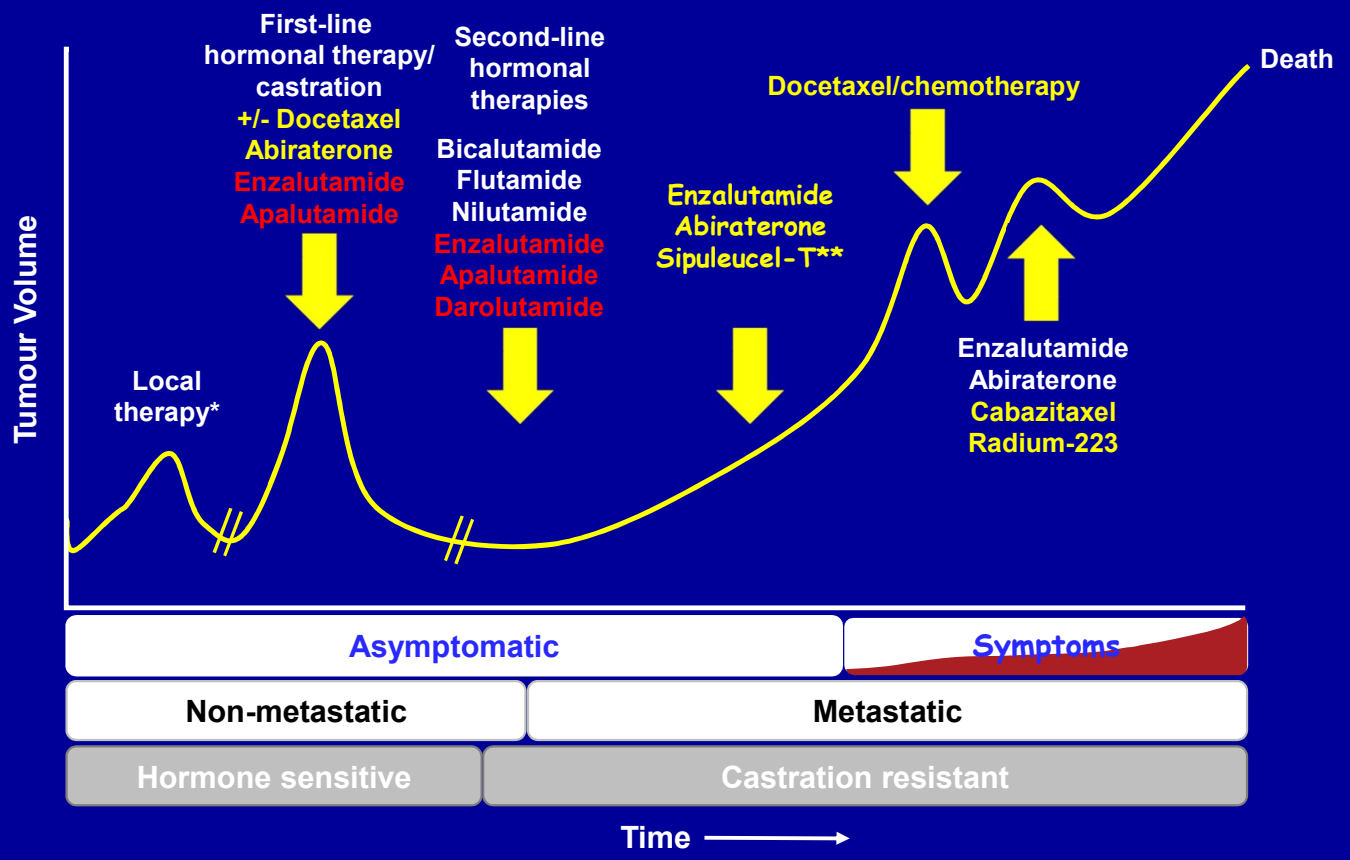
Official Journal of the American

THE LANCET

The NEW ENGLAND JOURNAL of MEDICINE

1. The Leuprolide Study Group New Engl J Med 311: 1281-61984; Crawford ED et al. *N Engl J Med* 321:419-24, 1989
2. Tannock I et al. *J Clin Oncol 14: 1756-64, 1996*
3. Saad F et al. J Natl Cancer Inst 94: 1458-68, 2002
4. Petrylak DP et al. *N Engl J Med* 2004
5. Tannock I et al. *N Engl J Med 2004.*
6. Sartor O et al. Lancet 2010
7. Kantoff P et al. N Engl J Med 2010
8. Fizazi K et al. J Clin Oncol 2010
9. deBono JS et al. N Engl J Med 364:1995-2005, 2011
10. Scher HI et al. N Engl J Med Aug 15, 2012
11. Parker C et al. NEJM 2013
12. GU ASCO 2018 13. GU ASCO 2019

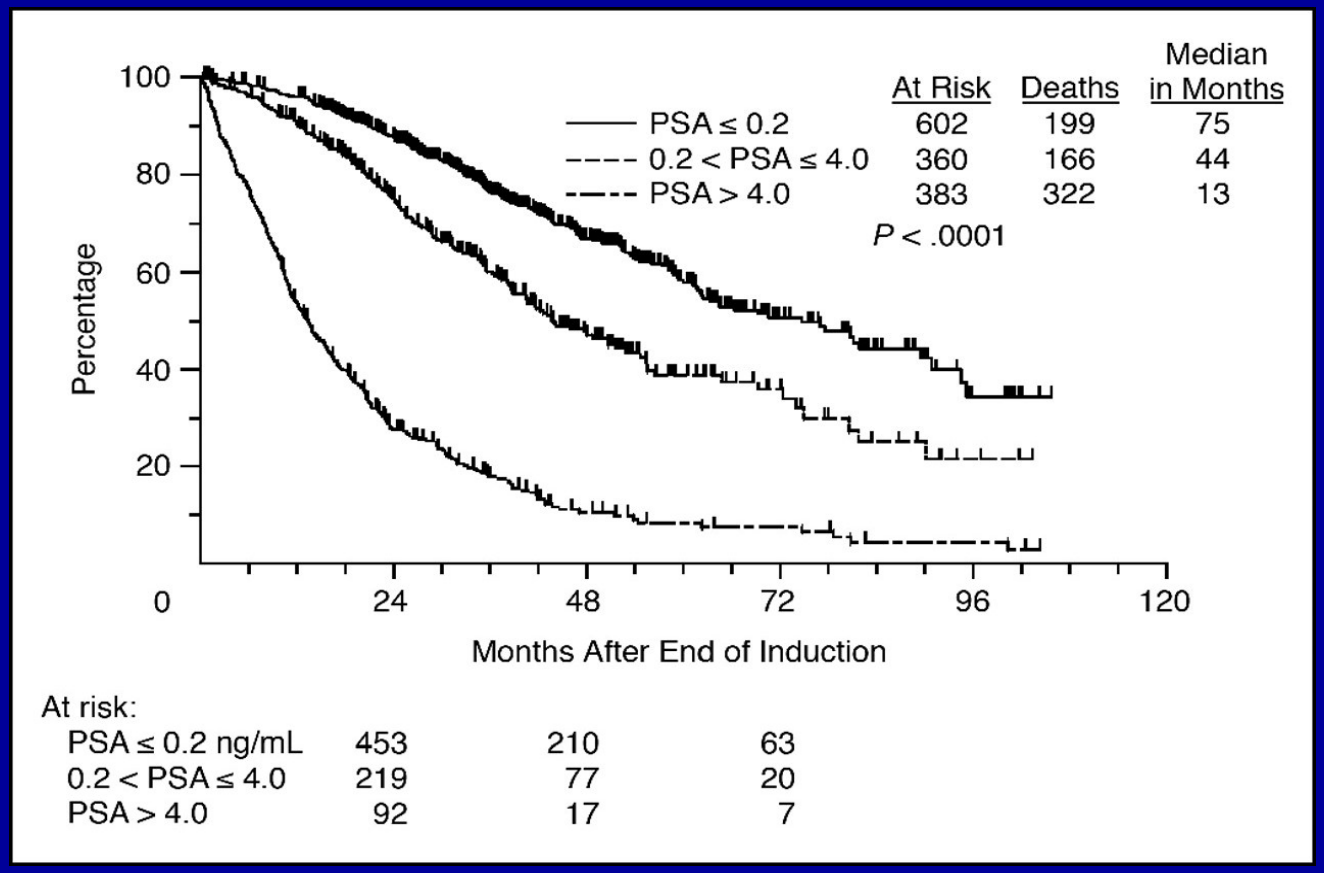
The Disease Continuum in Prostate Cancer



*For example, surgery and radiotherapy.
** Not approved outside US for the treatment of prostate cancer
Kohli M, Tindall DJ. *Mayo Clin Proc.* 2010;85:77-86. Diagram modified from Celestina Higano MD

Adapted from Higano CS. In: Figg WD et al. *Drug Management of Prostate Cancer.* 2010:321.

SWOG 9346 - PSA response data



Hussain MH et al. JCO 24:3984-90, **2006**

Overall Survival Benefit in Recent mCRPC Studies: 2004-2014

Agent	Trial	Disease State	Comparator	Median OS (mo)	HR (*P* value)
Sipuleucel-T	IMPACT	Chemo-naïve CRPC	Placebo	**25.8**	0.759 (0.017)
Docetaxel	TAX327	Chemo-naïve CRPC	Mitoxantrone Prednisone	**18.9**	0.76 (0.009)
Cabazitaxel	TROPIC	Post-docetaxel CRPC	Mitoxantrone Prednisone	**15.1**	0.70 (< 0.0001)
Abiraterone acetate + prednisone	COU-AA-301	Post-docetaxel CRPC	Placebo Prednisone	**14.8**	0.646 (< 0.0001)
Abiraterone acetate + prednisone	COU-AA-302	Progressive chemo-naïve CRPC	Placebo + Prednisone	**Not Reached (34.7*)**	0.75 (0.01)
Enzalutamide	AFFIRM	Post-docetaxel CRPC	Placebo	**18.4**	0.631 (< 0.0001)
Enzalutamide	PREVAIL	Progressive chemo-naïve CRPC	Placebo	**32.4**	0.70 (< 0.0001)
Radium-223	ALSYMPCA	Post-docetaxel CRPC	Placebo	**14.9**	0.695 (0.002)

Metastatic Hormone Sensitive Prostate Cancer Summary 2019

ADT: continuous vs intermittent: continuous as SOC

Docetaxel in mPSPC: CHAARTED, STAMPEDE arm C
Abiraterone: LATITUDE, STAMPEDE arm G

Possible role for radiation to the primary:
STAMPEDE arm H: low volume / low risk mHSPC

Enzalutamide in mHSPC: ENZAMET, ARCHES
Apalutamide in mHSPC: TITAN

To come: Darolutamide: ARESENS; PEACE studies
Combinations and sequencing

USC NORRIS

ORIGINAL ARTICLE

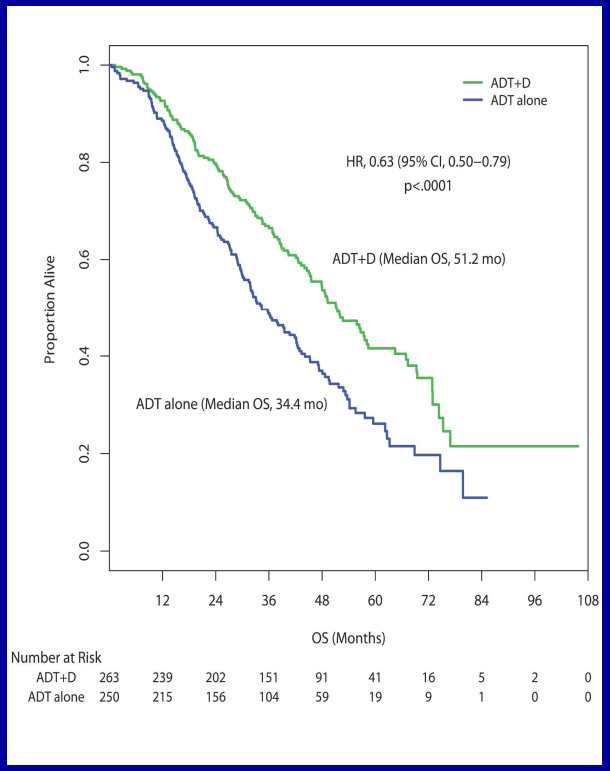
Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

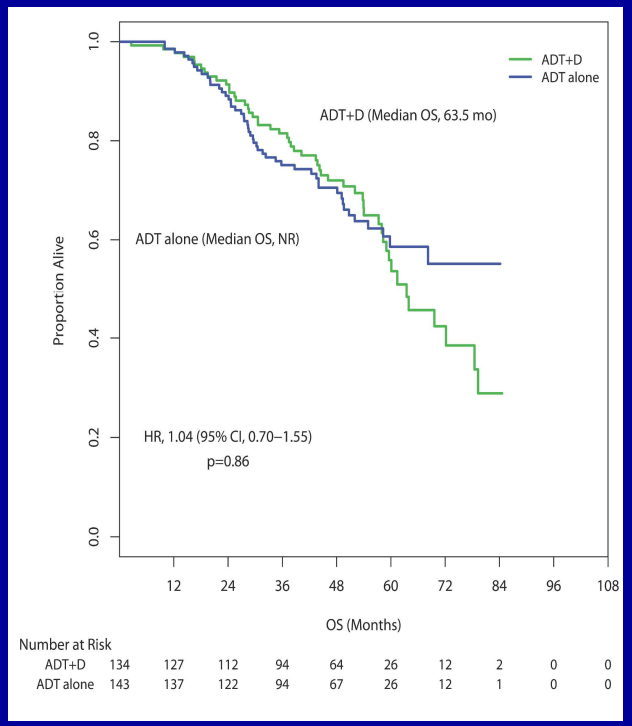
Sweeney CJ et al. N Engl J Med 2015

OS by extent of metastatic disease at start of ADT:updated analysis

High volume



Low volume



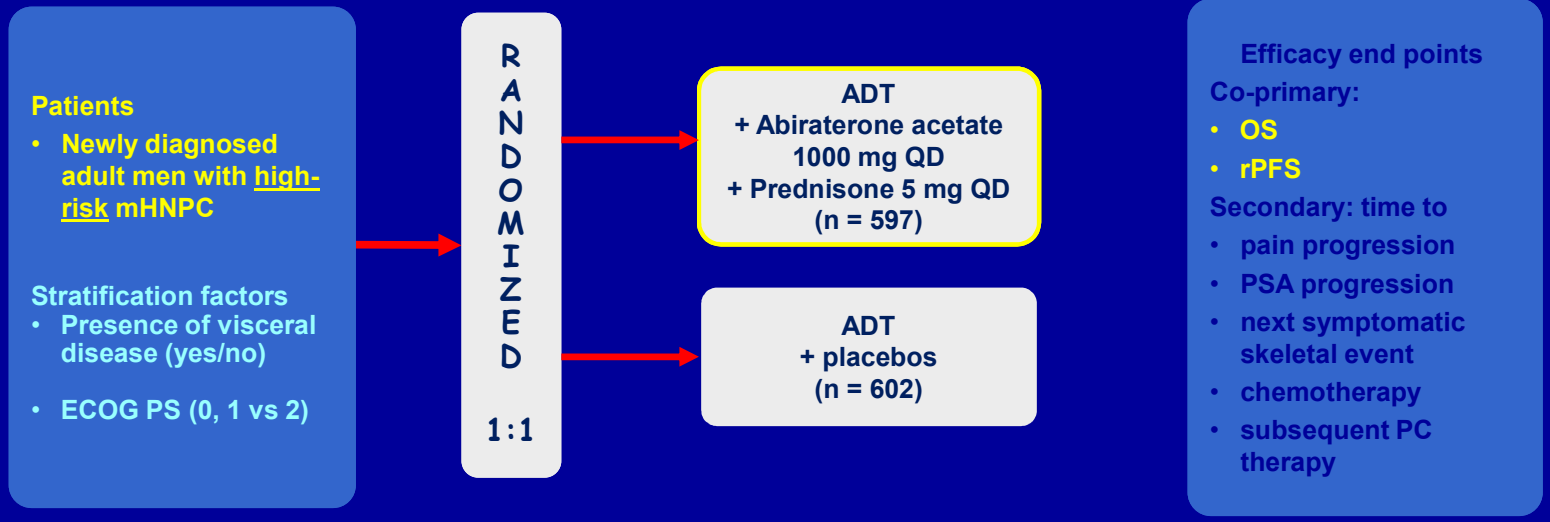
Sweeney CJ et al. ESMO 2016

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

Overall study design of LATITUDE



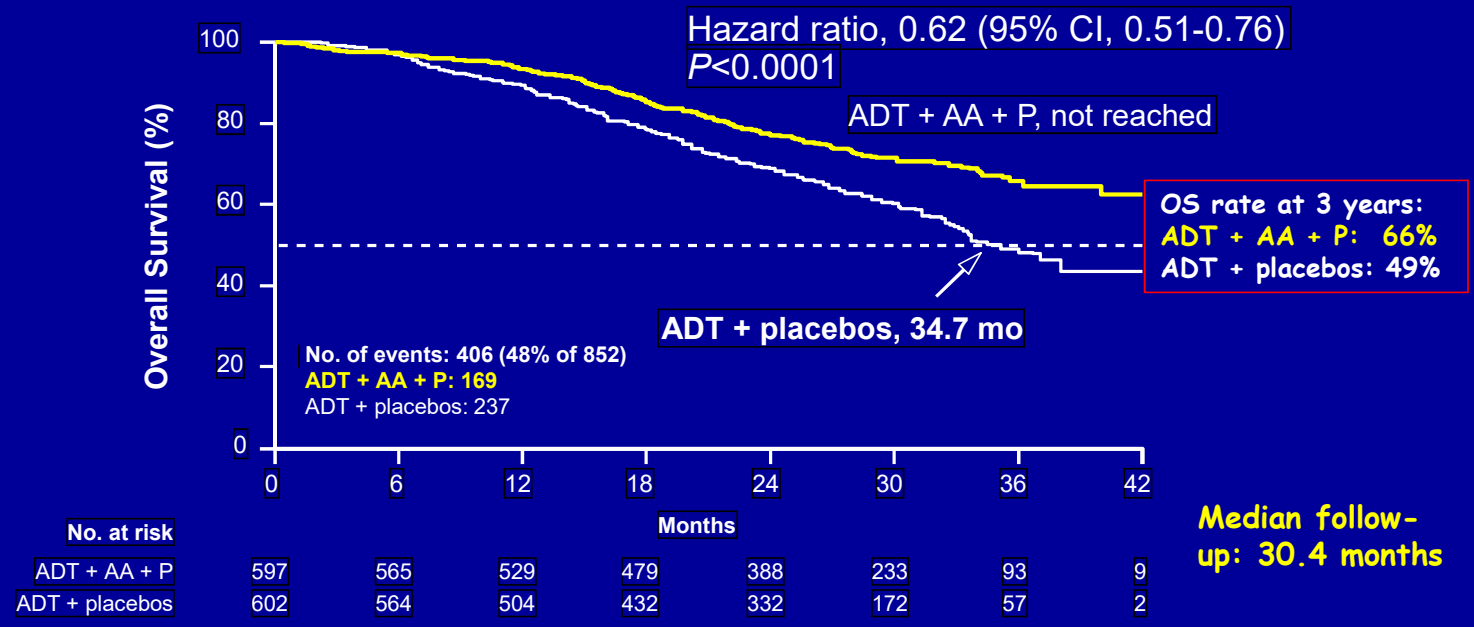
- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Presented by: Karim Fizazi

Slide 13

BJ1 presented where? ansd when
Binko, Justin, 3/24/2019

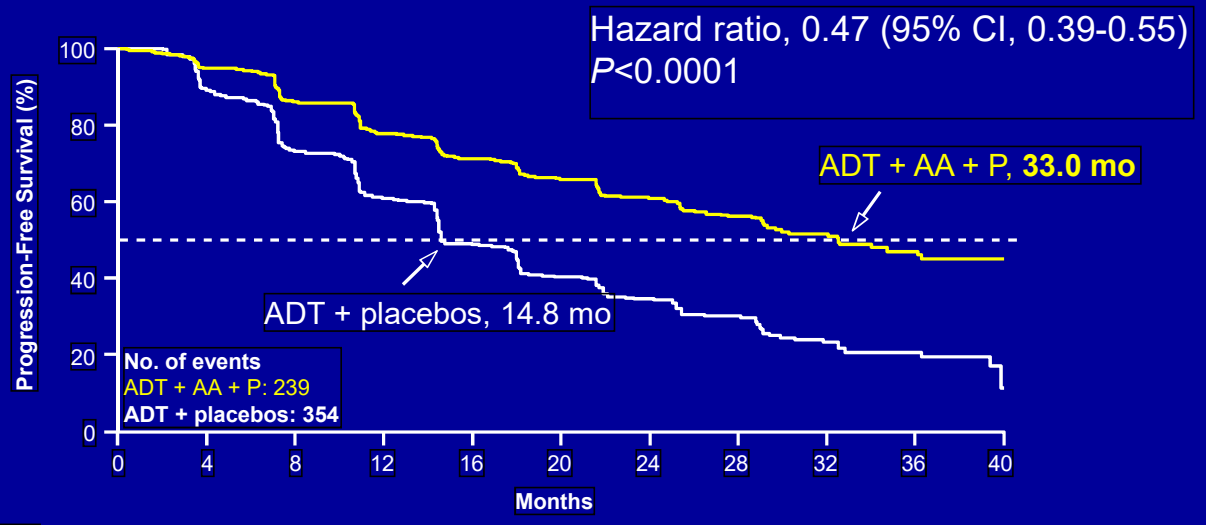
Statistically significant 38% risk reduction of death



Median follow-up: 30.4 months

Presented by: Karim Fizazi

Statistically significant 53% risk reduction of radiographic progression or death



No. at risk											
ADT + AA + P	597	533	464	400	353	316	251	177	102	51	21
ADT + placebos	602	488	367	289	214	168	127	81	41	17	7

Presented by: Karim Fizazi

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

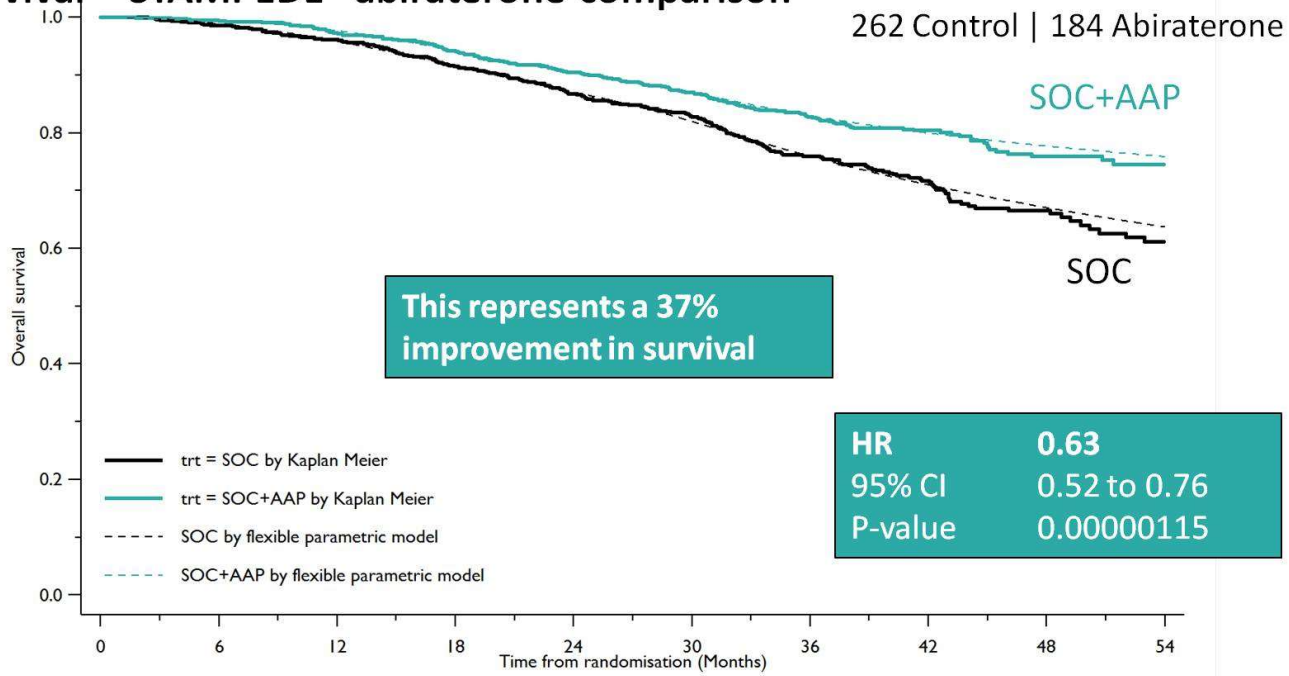
Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew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

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented By Nicholas James at 2017 ASCO Annual Meeting

Overall Survival – STAMPEDE "abiraterone comparison"

Events
262 Control | 184 Abiraterone



This represents a 37% improvement in survival

HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.00000115

Number of patients (events)

SOC	957	(37)	909	(88)	806	(92)	491	(36)	123
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161

	SOC-only	SOC+AAP
Safety population		
Patients included in adverse event analysis	960	948
Grade 1-5 AE	950 (99%)	943 (99%)
Grade 3-5 AE	315 (33%)	443 (47%)
Grade 5 AE	3	9
Grade 3-5 AEs by category (*incl. expected AEs*)		
Endocrine disorder (*incl. hot flashes, impotence*)	133 (14%)	129 (14%)
Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*):	41 (4%)	92 (10%)
Musculoskeletal disorder:	46 (5%)	68 (7%)
Gastrointestinal disorder:	40 (4%)	49 (5%)
Hepatic disorder (*incl. increased AST, increased ALT*):	12 (1%)	70 (7%)
General disorder (*incl. fatigue, oedema*):	29 (3%)	45 (5%)
Respiratory disorder (*incl. breathlessness*):	23 (2%)	44 (5%)
Lab abnormalities (*incl. hypokalaemia*):	21 (2%)	34 (4%)

Role of Abiraterone Acetate + Prednisolone + ADT in High and Low Risk Metastatic Hormone Naïve Prostate Cancer

Mr Alex Hoyle MBChB MRCS

(Christie GenitoUrinary Research Group Fellow, UK)

Adnan Ali, Nick James, Chris Parker, Adrian Cook, Gert Attard, Simon Chowdhury, Bill Cross, David Dearnaley, Johann de Bono, Clare Gilson, Silke Gillessen, Rob Jones, David Matheson, Malcolm Mason, Alastair Ritchie, Martin Russell, Max Parmar, Matt Sydes, Noel Clarke;

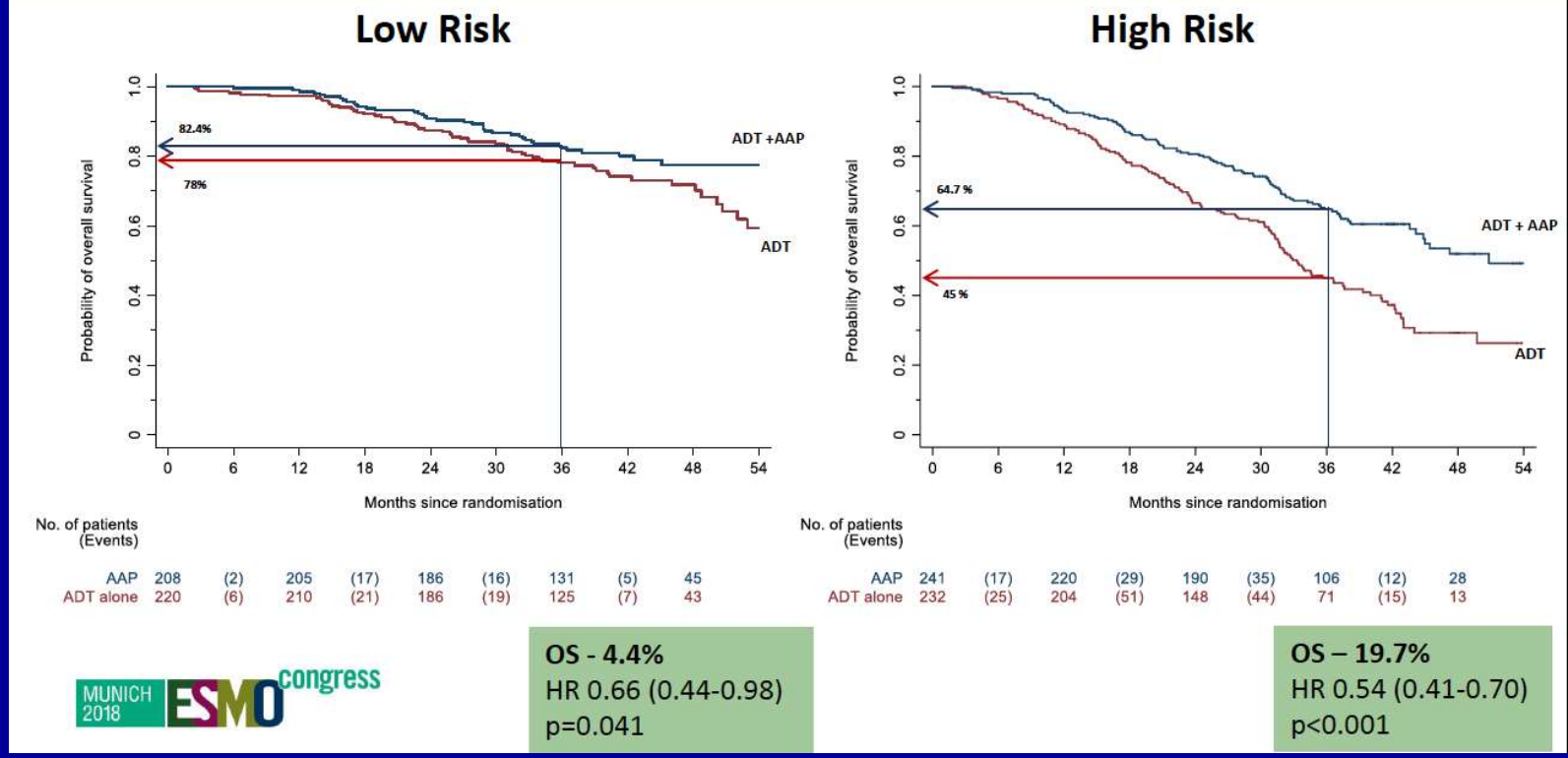
for the STAMPEDE trial

esmo.org

Should we consider AA in low risk HSPC?

Subgroup analysis from STAMPEDE Arm G: Abiraterone

RESULTS: OVERALL SURVIVAL



MUNICH 2018 ESMO congress

OS - 4.4%
HR 0.66 (0.44-0.98)
p=0.041

OS – 19.7%
HR 0.54 (0.41-0.70)
p<0.001

4.4% OS benefit at 3 years; Grade 3+ toxicity increment 33 to 47%; Grade 5 increment 3 to 9%
Treatment duration > 48 months Hoyle A et al. ESMO 2018

Prostate Cancer Patients With Cardiovascular Disease Had Higher Mortality After Starting Abiraterone Acetate

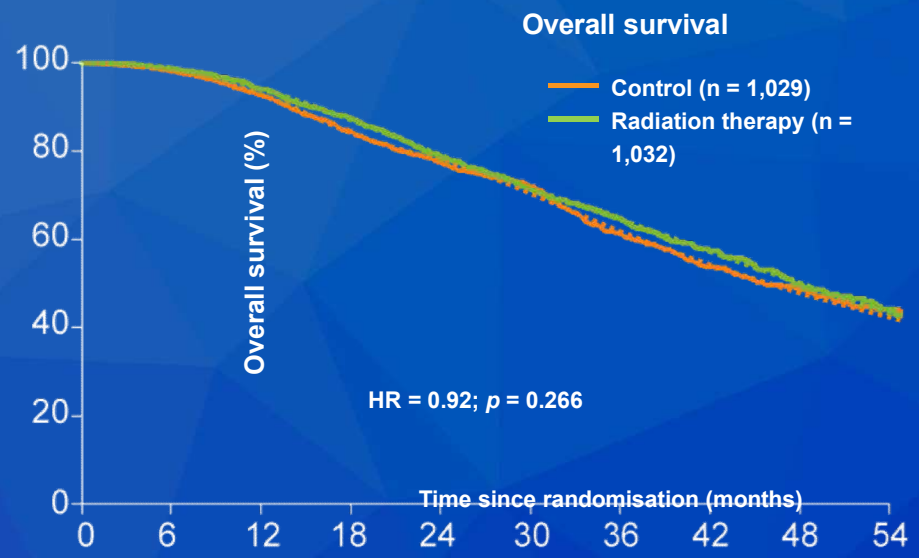
- Patients with cardiovascular disease or uncontrolled hypertension are almost always excluded from clinical trials of abiraterone acetate
- Surveillance, Epidemiology and End Results (SEER)–Medicare linked identified 2,845 patients
- 1924 (67.6 percent) patients had at least one serious cardiovascular condition
  - acute myocardial infarction, atrial fibrillation, congestive heart failure, stroke, and ischemic heart disease
- before starting treatment with abiraterone acetate
- crude risk of overall mortality by six months of abiraterone ranged from 21.4 to 25.6% depending on the type of pre-existing cardiovascular condition, versus 15.8 percent for those with no pre-existing cardiovascular disease

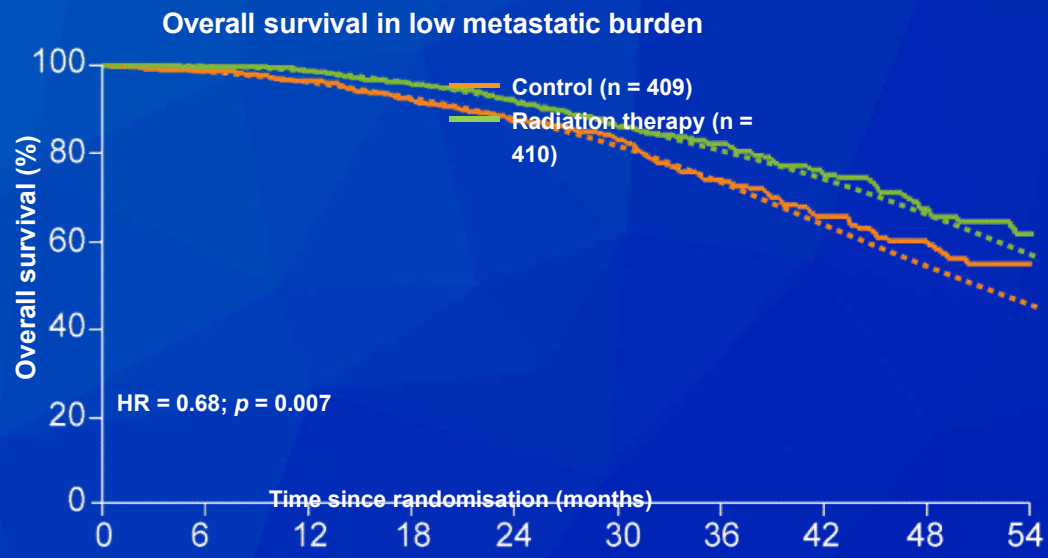
Grace Lu-You,
Nikita Nikita, Scott Keith, Krupa Gandhi, TimothyR. Rebbeck, Jennifer Cullen, Ginah Nightingale, Mark Mann and Andrew Chapman
AACR 2019 Abstract 4469
. **https://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=1272**

Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial

Christopher C Parker, Nicholas D James, Christopher D Brawley, Noel W Clarke, Alex P Hoyle, Adnan Ali, Alastair W S Ritchie, Gerhardt Attard, Simon Chowdhury, William Cross, David P Dearnaley, Silke Gillessen, Clare Gilson, Robert J Jones, Ruth E Langley, Zafar I Malik, Malcolm D Mason, David Matheson, Robin Millman, J Martin Russell, George N Thalmann, Claire L Amos, Roberto Alonzi, Amit Bahl, Alison Birtle, Omar Din, Hassan Douis, Chinnamani Eswar, Joanna Gale, Melissa R Gannon, Sai Jonnada, Sara Khaksar, Jason F Lester, Joe M O'Sullivan, Omi A Parikh, Ian D Pedley, Delia M Pudney, Denise J Sheehan, Narayanan Nair Srihari, Anna T H Tran, Mahesh K B Parmar, Matthew R Sydes*, on behalf of the Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators†*

STAMPEDE Arm H: Standard Therapy with or without Radiation Therapy to the Primary Tumor in Newly Diagnosed Metastatic Prostate Cancer





Parker CC et al. *Lancet* 2018;392(10162):2353-66.

Phase 3 study of androgen deprivation therapy with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer: the ARCHES trial

Andrew J. Armstrong,[1] Russell Szmulewitz,[2] Daniel Petrylak,[3] Arnauld Villers,[4] Arun Azad,[5,*] Antonio Alcaraz,[6] Boris Alekseev,[7] Taro Iguchi,[8] Neal D. Shore,[9] Brad Rosbrook,[10] Jennifer Sugg,[11] Benoit Baron,[12,†] Lucy Chen,[11] Arnulf Stenzl[13]

[1]Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC; [2]The University of Chicago, Chicago, IL; [3]Yale Cancer Center, New Haven, CT; [4]University Hospital Centre, Lille University, Lille, France; [5]Monash Health, Melbourne, Victoria, Australia; [6]Hospital Clinic de Barcelona, Barcelona, Spain; [7]Hertzen Moscow Cancer Research Institute, Moscow, Russia; [8]Osaka City University Graduate School of Medicine, Osaka, Japan; [9]Carolina Urologic Research Center, Myrtle Beach, SC; [10]Pfizer Inc., San Diego, CA; [11]Astellas Pharma Inc., Northbrook, IL; [12]Astellas Pharma Inc., Leiden, the Netherlands; [13]Department of Urology, University Hospital, Eberhard Karls University, Tübingen, Germany

*Current affiliation: Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
†Current affiliation: B-value, Leiden, the Netherlands

PRESENTED AT: **2019 Genitourinary Cancers Symposium | #GU19**

Presented by: Andrew J. Armstrong, MD

Presented By Andrew Armstrong at 2019 Genitourinary Cancers Symposium

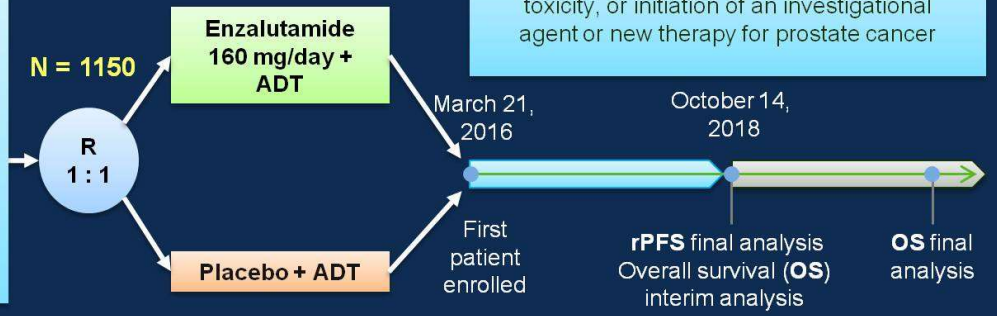
ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

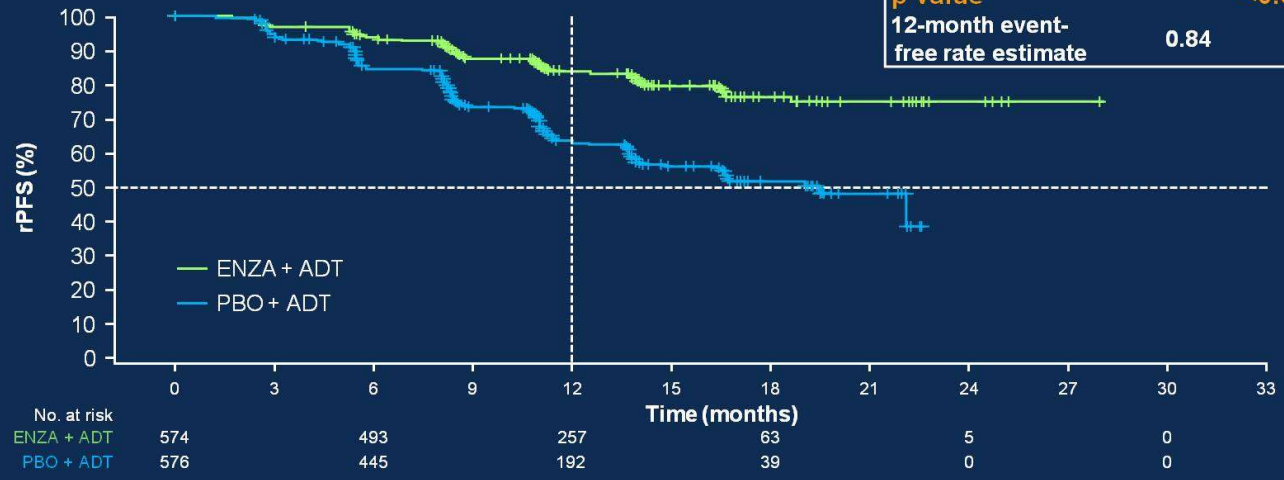
Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first
  - Radiographic disease progression was defined by RECIST 1.1 criteria for soft tissue disease or by appearance of ≥2 new lesions on bone scan compared to baseline (at week 13) or vs. best response on treatment (week 25 or later). New bone scan lesions observed at week 13 required confirmation of ≥2 additional new bone lesions on subsequent scans

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

Primary endpoint: rPFS

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64



No. at risk						
ENZA + ADT	574	493	257	63	5	0
PBO + ADT	576	445	192	39	0	0

- At data cut-off, there were 262 events of radiographic progression (enzalutamide + ADT, 77; placebo + ADT, 185) and 25 deaths without radiographic progression (enzalutamide + ADT, 12; placebo + ADT, 13)
- Median follow-up time is 14.4 months; median duration of therapy was 12.8 (range 0.2–26.6) months for enzalutamide + ADT and 11.6 (range 0.2–24.6) months for placebo + ADT
- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

Adverse events (AEs)

Event, n (%)	Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
Any AE leading to treatment withdrawal	41 (7.2)		30 (5.2)	
Any AE leading to death*	14 (2.4)		10 (1.7)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	487 (85.1)	139 (24.3)	493 (85.9)	147 (25.6)
Most common AEs (any grade) occurring in ≥5% of patients in either group†				
Hot flush	155 (27.1)	2 (0.3)	128 (22.3)	0
Fatigue	112 (19.6)	5 (0.9)	88 (15.3)	6 (1.0)
Arthralgia	70 (12.2)	2 (0.3)	61 (10.6)	4 (0.7)
Back pain	43 (7.5)	5 (0.9)	62 (10.8)	3 (0.5)
Increased weight	35 (6.1)	2 (0.3)	44 (7.7)	1 (0.2)
Hypertension	46 (8.0)	19 (3.3)	32 (5.6)	10 (1.7)
Diarrhea	34 (5.9)	0	33 (5.7)	1 (0.2)
Peripheral edema	29 (5.1)	1 (0.2)	38 (6.6)	1 (0.2)
Nausea	37 (6.5)	1 (0.2)	29 (5.1)	0
Asthenia	31 (5.4)	6 (1.0)	28 (4.9)	3 (0.5)
Constipation	28 (4.9)	0	31 (5.4)	0
Musculoskeletal pain	36 (6.3)	1 (0.2)	23 (4.0)	1 (0.2)
Dizziness	29 (5.1)	0	20 (3.5)	0

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT

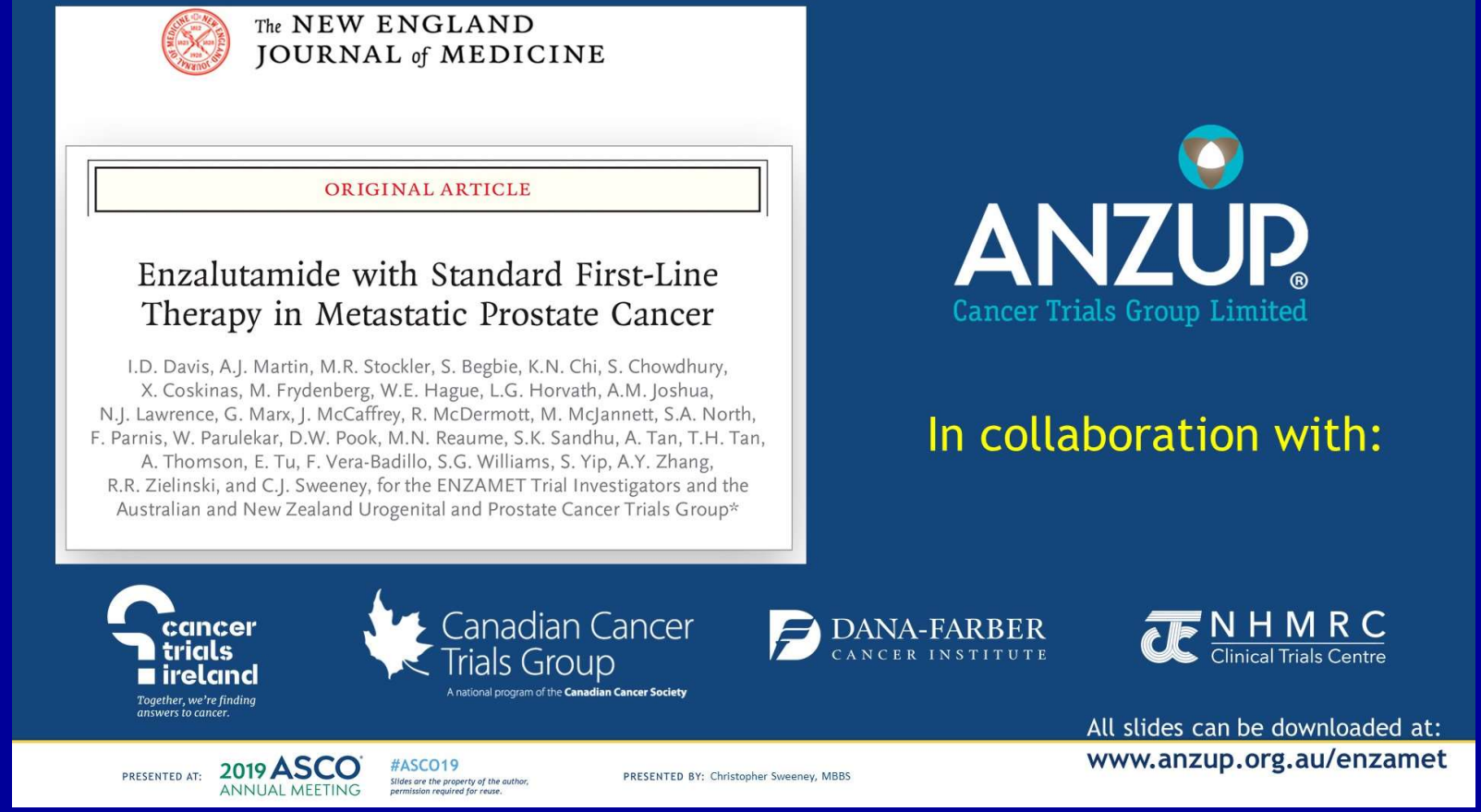
*Of the AEs leading to death, none were considered related to treatment in the enzalutamide + ADT group and one in the placebo + ADT group (general physical health deterioration); †None of the most common AEs were grade 5

AEs of special interest

Event, n (%)	Enzalutamide + ADT (n = 572)		Placebo + ADT (n = 574)	
Any AE of special interest*	324 (56.6)		291 (50.7)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Convulsion	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Hypertension	49 (8.6)	19 (3.3)	36 (6.3)	12 (2.1)
Neutrophil count decreased	5 (0.9)	2 (0.3)	4 (0.7)	2 (0.3)
Cognitive / memory impairment	26 (4.5)	4 (0.7)	12 (2.1)	0
Ischemic heart disease	10 (1.7)	3 (0.5)	8 (1.4)	6 (1.0)
Other selected cardiovascular events	13 (2.3)	6 (1.0)	9 (1.6)	5 (0.9)
Posterior reversible encephalopathy syndrome	0	0	0	0
Fatigue	138 (24.1)	10 (1.7)	112 (19.5)	9 (1.6)
Fall	21 (3.7)	2 (0.3)	15 (2.6)	1 (0.2)
Fractures	37 (6.5)	6 (1.0)	24 (4.2)	6 (1.0)
Loss of consciousness	9 (1.6)	6 (1.0)	1 (0.2)	1 (0.2)
Thrombocytopenia	3 (0.5)	0	3 (0.5)	0
Musculoskeletal events	151 (26.4)	9 (1.6)	159 (27.7)	12 (2.1)
Severe cutaneous adverse reactions	0	0	1 (0.2)	0
Angioedema	7(1.2)	1 (0.2)	1 (0.2)	0
Rash	15 (2.6)	0	9 (1.6)	0
Second primary malignancies	11 (1.9)	9 (1.6)	11 (1.9)	7 (1.2)

Bold: AEs (all grades) that occur >2% in enzalutamide + ADT compared with placebo + ADT

*Based on pre-specified combinations of preferred terms (MedDRA 21.0) related to the AE of special interest; the only AEs of special interest that were grade 5 were in the enzalutamide + ADT group (ischemic heart disease, n=1; other selected cardiovascular events, n=1)



Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

OVERALL SURVIVAL (OS) RESULTS OF A PHASE III RANDOMIZED TRIAL OF STANDARD OF CARE THERAPY WITH OR WITHOUT ENZALUTAMIDE FOR METASTATIC HORMONE SENSITIVE PROSTATE CANCER (mHSPC)

ENZAMET (ANZUP 1304): AN ANZUP-LED INTERNATIONAL CO-OPERATIVE GROUP TRIAL (NHMRC CTC, CCTG, CTI, DFCI)

Christopher Sweeney, Andrew Martin, Robert Zielinski, Alastair Thomson, Thean Hsiang Tan, Shahneen Sandhu, M. Neil Reaume, David Pook, Francis Parnis, Scott North, Gavin Marx, John McCaffrey, Ray McDermott, Nicola Lawrence, Lisa Horvath, Mark Frydenberg, Simon Chowdhury, Kim Chi, Martin Stockler, Ian Davis

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Christopher Sweeney, MBBS

ANZUP Cancer Trials Group Limited

Presented By Christopher Sweeney at 2019 ASCO Annual Meeting

ENZAMET Treatment

STRATIFICATION

Volume of metastases*
-High vs Low
Planned Early Docetaxel
Yes vs No
ECOG PS
- 0-1 vs 2
Anti-resorptive therapy
-Yes vs No
Comorbidities
ACE-27**: 0-1 vs 2-3
Study Site

→ RANDOMIZE

ARM A:
Testosterone Suppression
+ standard NSAA
→ Evaluate every 12 weeks

ARM B:
Testosterone Suppression
+ Enzalutamide (160 mg/d)
→ Evaluate every 12 weeks

→ CRPC therapy at investigator's discretion at progression

Follow for time to progression and overall survival

- Prior to randomization testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed.
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide; nilutamide; flutamide
- *High volume: visceral metastases and/or 4 or more bone metastases (at least 1 beyond pelvis and vertebral column)
- **Adult Co-morbidity Evaluation-27

Study Endpoints

- **Primary Endpoint**
  - Overall survival
- **Secondary Endpoints**
  - Prostate specific antigen progression free survival (includes clinical progression if occurs first, PCWG2)
  - Clinical progression free survival (imaging, symptoms, signs)
  - Adverse events (CTCAE v4.03)
  - Health related quality of life (EORTC QLQ C-30, PR-25 and EQ-5D-5L)
  - Health outcomes relative to costs
  - Translational biological studies

PCWG2: Prostate Cancer Working Group Criteria version 2
CTCAE: NCI Common Terminology Criteria for Adverse Events

Key Eligibility Criteria

- Metastatic adenocarcinoma of the prostate
  - Histology confirmed or
  - Clinical scenario c/w PrCa (PSA > 20 and rising and distribution of metastases)
- Prior ADT limited to
  - 12 weeks prior to randomization
  - Adjuvant Rx allowed if ≤24 months and completed >12 months prior
- Organ function
  - ECOG PS: 0-2 (2 only if due to PrCa)
  - CrCl > 30 mL/min; Bilirubin < 1.5 ULN
  - No major cardiovascular disease within prior 3 months
  - No prior seizures or conditions predisposing to seizures

Statistical Design and History of Amendments

Intent to treat analysis, 1,100 patients and 470 deaths; > 80% power to detect a 25% reduction in the hazard of death (HR 0.75), with a 2-sided type 1 error rate of 0.05 (with all versions)

	Version 1	Version 2	Version 3
Date	March 2014	November 2014	March 2018
Sample size	1,100	1,100	1,100
Purpose	IA with 67% of events	To allow early docetaxel*	Added IA with 50% and 80% of planned 470 events**
Enrollment	0	88	1,125 patients by March 2017 prior to any IA

IA: Interim Analyses

*Based on results of CHAARTED presented ASCO 2014 (Sweeney et al NEJM 2015)

**Based on results of abiraterone in mHSPC in 2017 (Fizazi et al NEJM 2017, James et al NEJM 2017)

Patient characteristics

	TS + NSAA (N=562)		TS + ENZA (N=563)	
	N	%	N	%
Age				
Median	69.0		69.2	
Interquartile Range	(63.6 to 74.5)		(63.2 to 74.5)	
Region				
Australia	321	57%	324	58%
Canada	107	19%	97	17%
United Kingdom	50	9%	63	11%
Ireland	43	8%	39	7%
United States*	22	4%	20	4%
New Zealand	19	3%	20	4%
ECOG PS				
0	405	72%	405	72%
1	151	27%	150	27%
2**	6	1%	8	1%

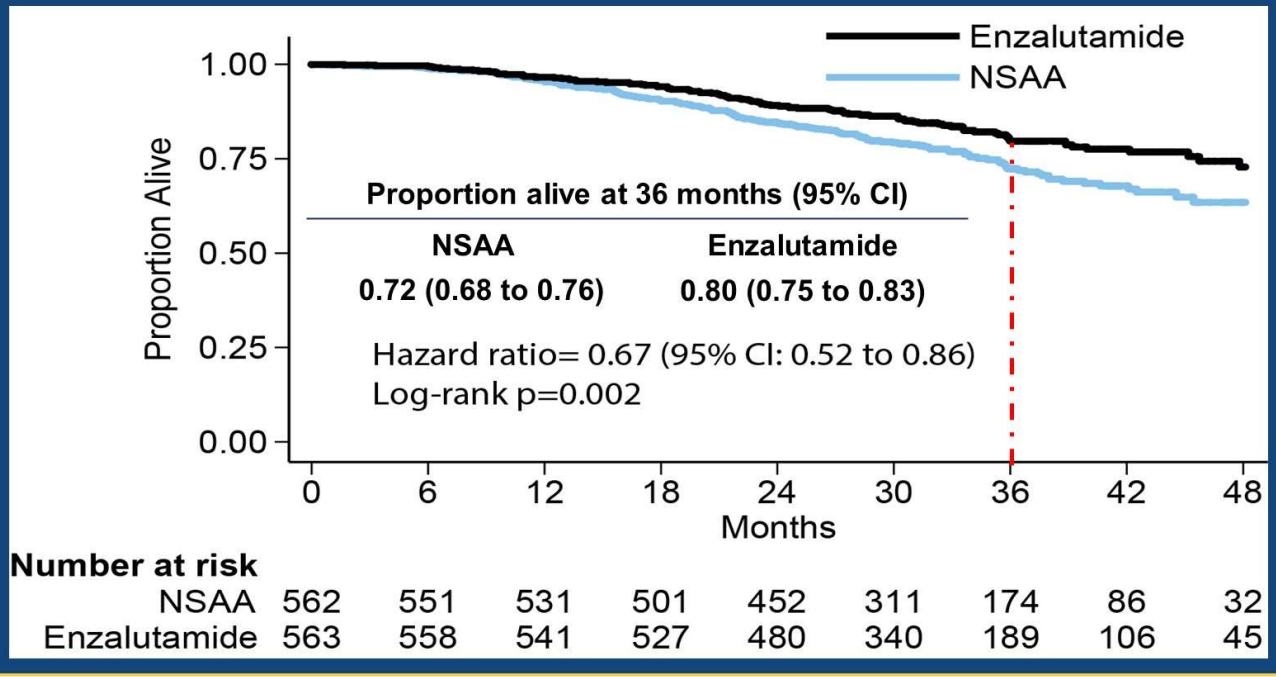
* Dana Farber Cancer Institute Only
** Limited to PrCa related PS 2

Patient characteristics

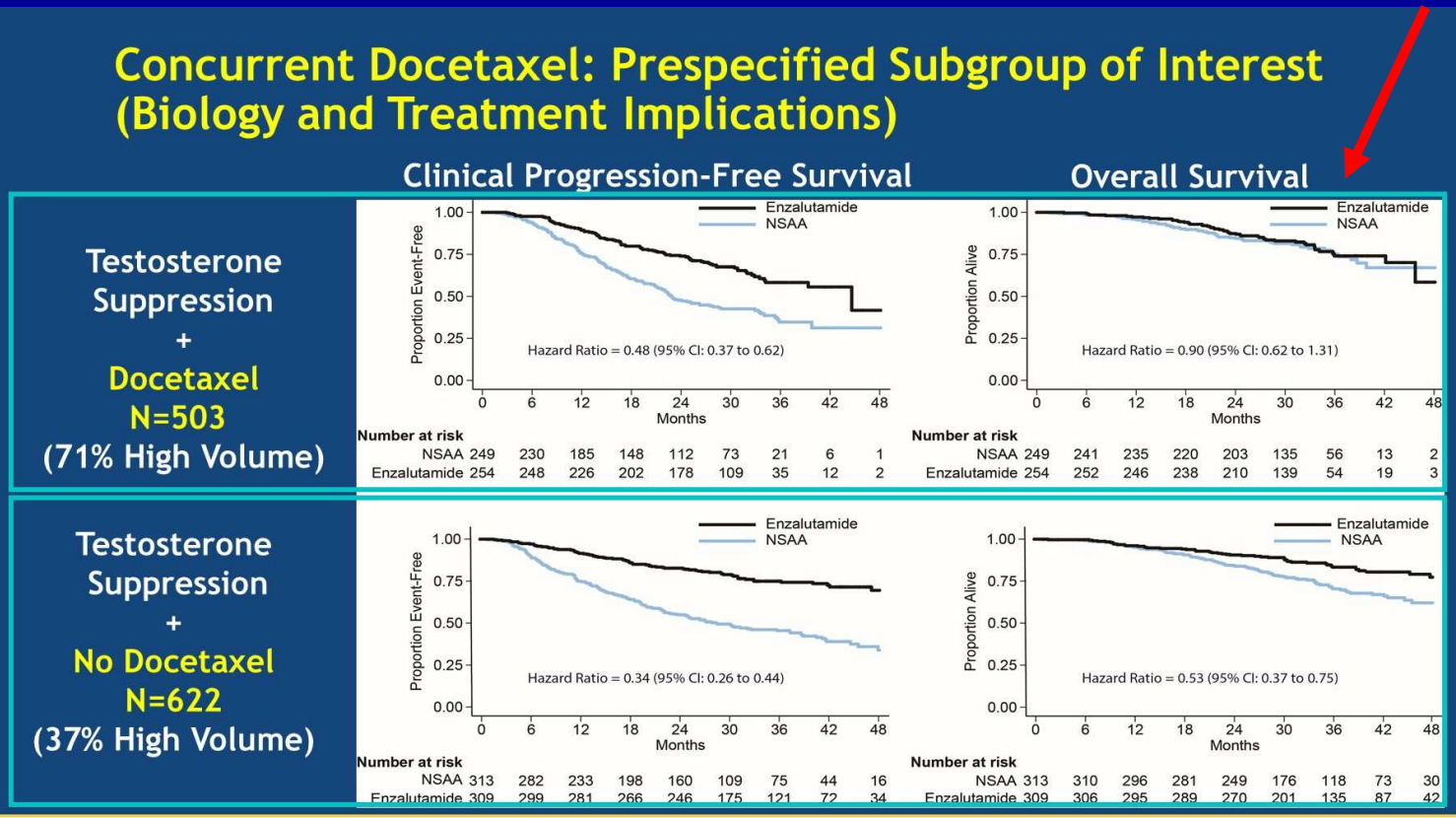
- Early docetaxel
  - 61% high volume; 27% of low volume
- ADT: androgen deprivation therapy
- ACE: Adult Co-morbidity Evaluation-27
- SRE Rx: Skeletal related event antiresorptive bone therapy
- **Prostatectomy or radiation

	TS + NSAA (N=562)		TS + Enzalutamide (N=563)	
	N	%	N	%
Planned Early Docetaxel				
Yes	249	44%	254	45%
No	313	56%	309	55%
Volume of Metastases				
High	297	53%	291	52%
Low	265	47%	272	48%
ACE-27 Stratum				
0-1	419	75%	422	75%
2-3	143	25%	141	25%
Prostate Cancer Related Therapies				
Planned SRE Rx	58	10%	55	10%
Prior Local Rx**	235	42%	238	42%
Prior Adjuvant ADT	40	7%	58	10%

Primary endpoint: Overall survival



Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)



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3 year OS point-estimates in biologically and clinically relevant predefined subgroups

	TS + NSAA (N=562)		TS + Enzalutamide (N=563)	
	3 year OS (%)	95% CI	3 year OS (%)	95% CI
Early Docetaxel				
Yes	75	68 to 81	74	66 to 80
No	70	64 to 76	83	78 to 87
Volume of Metastases				
*High	64	58 to 70	71	64 to 76
Low	82	75 to 87	90	84 to 93

**356 (61%) of 588 high volume patients received early docetaxel - OS is better than testosterone suppression alone in CHAARTED and LATITUDE: ~50% 3 year OS*

Sweeney et al NEJM 2015, Fizazi et al NEJM 2017

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Selected adverse events (AE)*:

All patients at anytime

	TS + NSAA N=558		TS + ENZA N=563	
Serious AE rate per yr of Rx exposure	0.33	95% CI: 0.28-0.39	0.34	95% CI: 0.29-0.40
AEs of Interest	N	%	N	%
Hypertension: Gde 3	24	4%	43	8%
Gde 2	30	5%	60	11%
Fatigue: Gde 3	4	1%	31	6%
Gde 2	80	14%	142	25%
Falls: Gde 3	2	<1%	6	1%
Gde 2	8	1%	28	5%
Syncope	7	1%	20	4%
Concentration Impairment: Gde 1/2	6	1%	24	4%
Any Seizure	0	0%	7	1%

*worst grade AE shown

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Clinical interpretation

- Enzalutamide added to testosterone suppression represents an appropriate option for men with metastatic prostate cancer commencing testosterone suppression
- Clear benefit in patients with low and high volume metastatic disease
  - Delays progression and improvement in overall survival
  - More expected toxicity was seen with enzalutamide alone
  - More docetaxel-related toxicity was reported with addition of enzalutamide
- For patients who are candidates for docetaxel when starting testosterone suppression, quality of life analyses and longer follow-up are needed to determine whether the delay in progression with concurrent enzalutamide
  - Results in a meaningful clinical benefit and / or
  - Is compounded by CRPC therapy and augments survival beyond 3 years

Abstract 5006

First Results From TITAN: a Phase 3 Double-Blind, Randomized Study of Apalutamide Versus Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Kim N. Chi,[1] Neeraj Agarwal,[2] Anders Bjartell,[3] Byung Ha Chung,[4] Andrea Juliana Pereira de Santana Gomes,[5] Robert W. Given,[6] Álvaro Juárez Soto,[7] Axel S. Merseburger,[8] Mustafa Özgüroğlu,[9] Hirotsugu Uemura,[10] Dingwei Ye,[11] Kris Deprince,[12] Vahid Naini,[13] Jinhui Li,[13] Shinta Cheng,[14] Margaret K. Yu,[15] Ke Zhang,[13] Julie S. Larsen,[15] Sharon A. McCarthy,[14] Simon Chowdhury[16] on behalf of the TITAN investigators

[1]BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]Skåne University Hospital, Lund University, Malmö, Sweden; [4]Yonsei University College of Medicine and Gangnam Severance Hospital, Seoul, South Korea; [5]Liga Norte Riograndense Contra O Cancer, Natal, Brazil; [6]Urology of Virginia, Eastern Virginia Medical School, Norfolk, VA; [7]Hospital Universitario de Jerez de la Frontera, Cadiz, Spain; [8]University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [9]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [10]Kindai University Faculty of Medicine, Osaka, Japan; [11]Fudan University Shanghai Cancer Center, Shanghai, China; [12]Janssen Research & Development, Beerse, Belgium; [13]Janssen Research & Development, San Diego, CA; [14]Janssen Research & Development, Raritan, NJ; [15]Janssen Research & Development, Los Angeles, CA; [16]Guy's, King's, and St. Thomas' Hospitals, and Sarah Cannon Research Institute, London, UK

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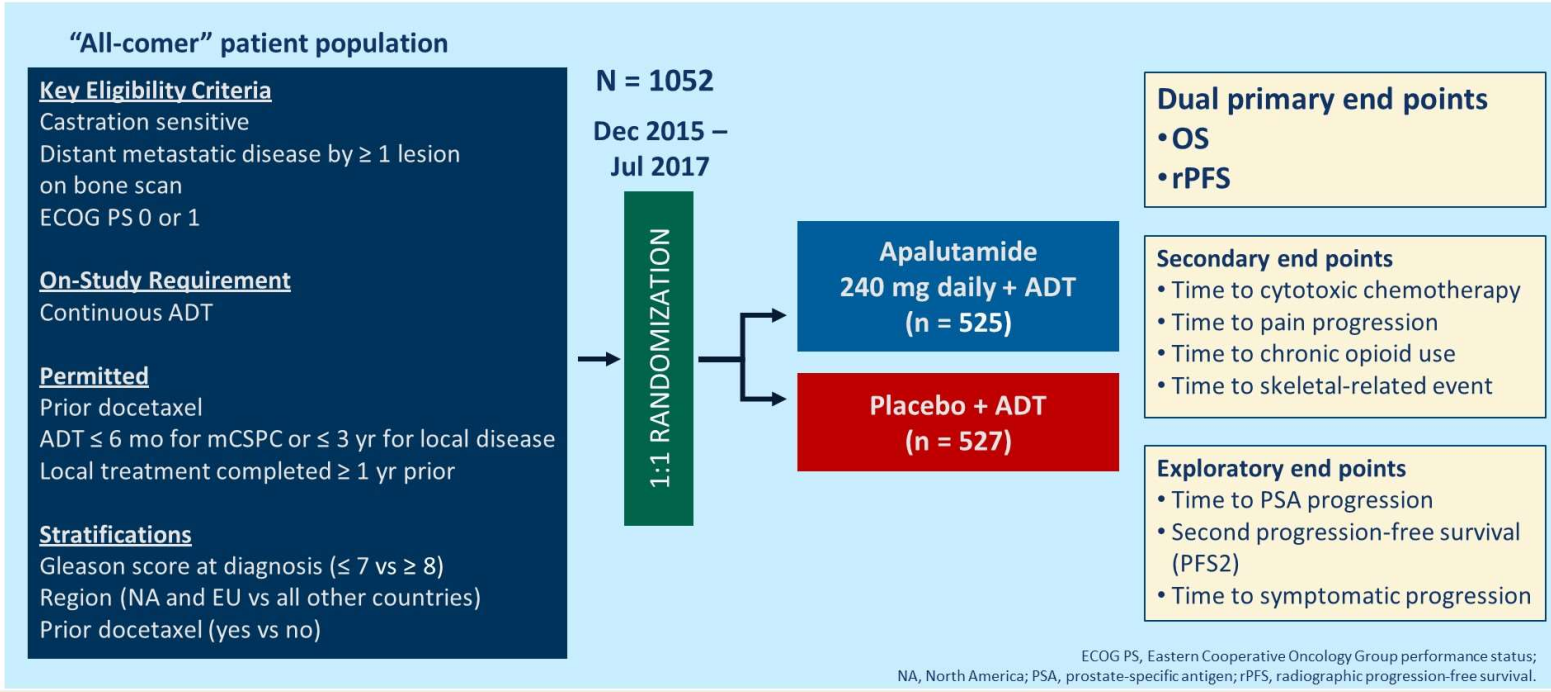
TITAN Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

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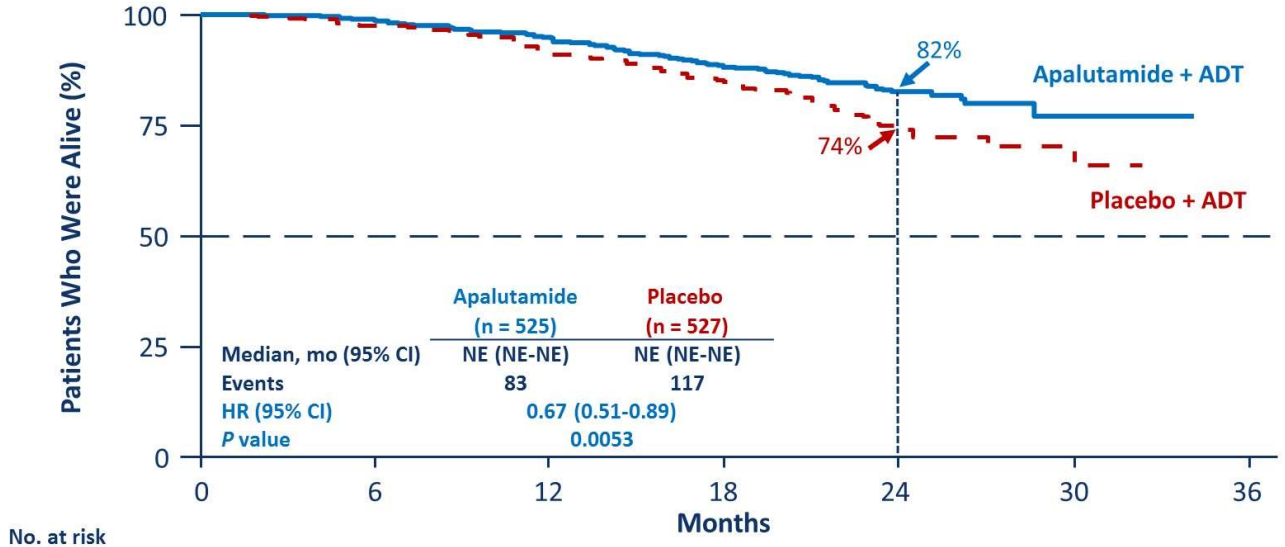
TITAN OS: Apalutamide Significantly Reduced the Risk of Death by 33%

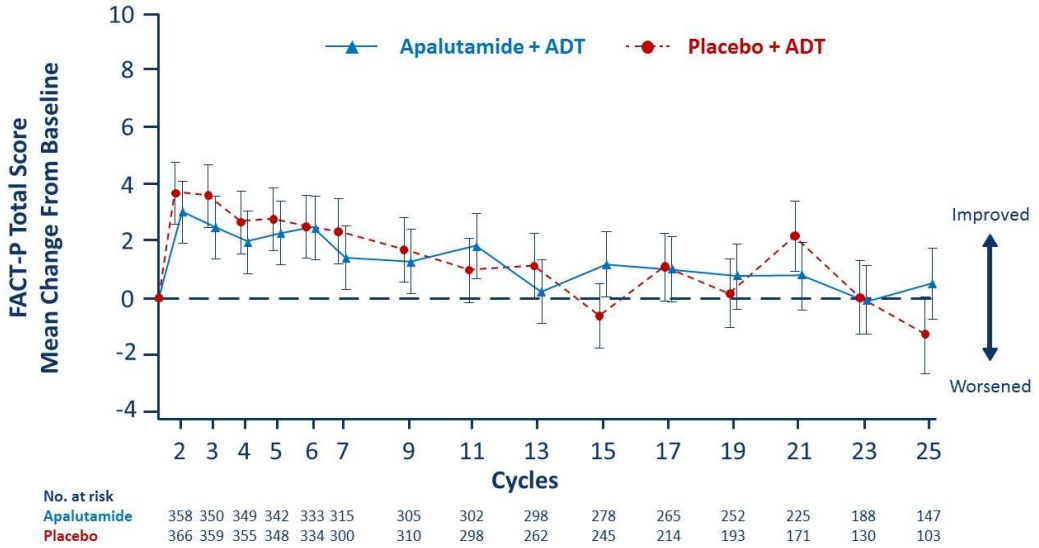


No. at risk							
Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

TITAN OS Benefit Consistent Across Subgroups

Variable		Hazard Ratio (95% CI)	Events (n/n) Apalutamide + ADT	Events (n/n) Placebo + ADT
All patients		0.68 (0.51-0.90)	83/525	117/527
Baseline ECOG PS	0	0.71 (0.47-1.05)	41/328	60/348
	1	0.59 (0.40-0.89)	42/197	57/178
Geographic region	EU/NA	0.71 (0.40-1.25)	21/173	29/173
	Other	0.66 (0.48-0.91)	62/352	88/354
Bone metastasis only at baseline	YES	0.47 (0.30-0.75)	28/289	53/269
	NO	0.88 (0.61-1.26)	55/236	64/258
Visceral disease and bone metastasis at baseline	YES	0.99 (0.55-1.77)	20/56	25/72
	NO	0.63 (0.46-0.87)	63/469	92/455
Prior docetaxel use	YES	1.27 (0.52-3.09)	11/58	9/55
	NO	0.63 (0.47-0.85)	72/467	108/472
Age, yr	< 65	0.56 (0.33-0.94)	21/149	43/182
	65-74	0.73 (0.48-1.10)	42/243	51/232
	≥ 75	0.74 (0.41-1.35)	20/133	23/113
Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192
Metastasis stage at initial diagnosis	M0	0.40 (0.15-1.03)	7/85	11/59
	M1	0.72 (0.53-0.98)	71/411	101/441

TITAN Health-Related Quality of Life Was Preserved With Apalutamide + ADT and Not Different From Placebo + ADT



Error bars are standard errors of the mean. Raw FACT-P scores range from 0 to 156, with higher scores indicating more favorable health-related quality of life; a 6- to 10-point change in FACT-P total score would be the minimally important difference. However, this figure presents mean changes in total scores compared with baseline rather than raw total scores.
FACT-P, Functional Assessment of Cancer Therapy-Prostate.

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Outcomes in mHSPC ADT +/- Single agents (docetaxel, abiraterone, enzalutamide, apalutamide)

STUDY	Progression (rPFS or PFS or FFS or time to CRPC)	OS (months)	High Volume Survival	Low Volume Survival
CHAARTED	ADT+docetaxel	ADT+docetaxel	ADT + docetaxel	NSD
GETUG-AFU15	ADT + Docetaxel	NSD	NSD	NSD
STAMPEDE/Chemo	ADT + Docetaxel	ADT + Docetaxel	NR	NR
STAMPEDE/ABI	NSD	ADT + Abi	NR	NR
LATITUDE/ABI	ADT + Abi	ADT + Abi	Most patients	NA
ARCHES	ADT + Enza	Too early	Too early	Too early
TITAN	ADT + Apa **but NOT if :** > 65 , visceral disease , prior docetaxel)	ADT + Apa **but NOT if :** > 65 , visceral disease , prior docetaxel)	ADT + Apa **but NOT if:** > 65, visceral disease	NSD
ENZAMET	**ADT + Enza**	**ADT + Enza but not if prior docetaxel**	**ADT + Enza**	**ADT + Enza**

NR -not reported
NSD- no significant difference

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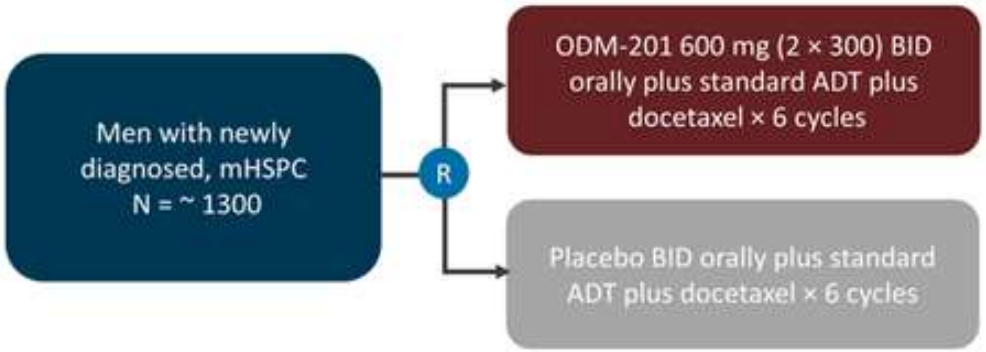
USC NORRIS

ARASENS: Randomized, Double-Blind, Phase 3 Trial of ODM-201* in mHSPC

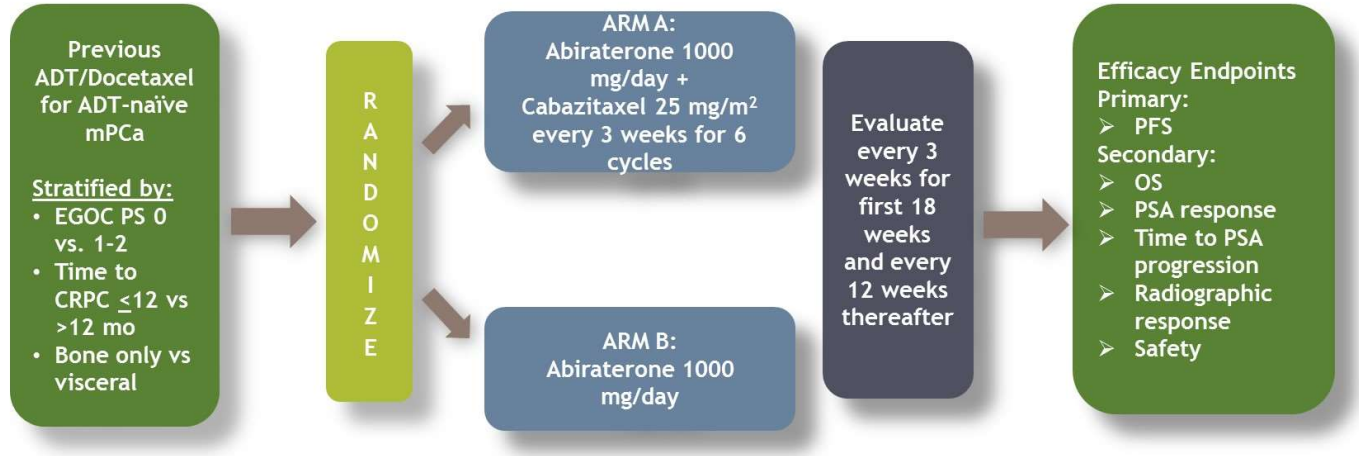
- Study initiated: November 2016
- Primary endpoint: OS
- Approach: combining chemotherapy and AR-targeted therapy



*Darolutamide.
ClinicalTrials.gov. NCT02799602.

EA8153: CabazitaxelwitH AbiraterONE versus Abiraterone alone Randomized Trial for Extensive Disease following Docetaxel (CHAARTED2)

Study Chair: Christos Kyriakopoulos, MD



210 PATIENTS RANDOMIZED (1:1)
All patients will continue ADT as per SOC
All patients will receive Prednisone 5 mg twice daily

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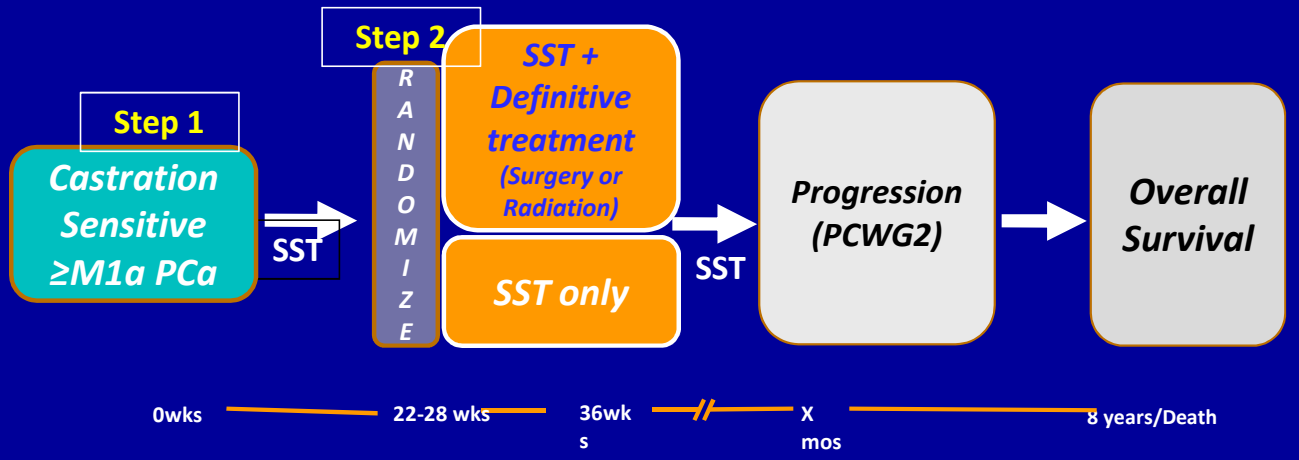
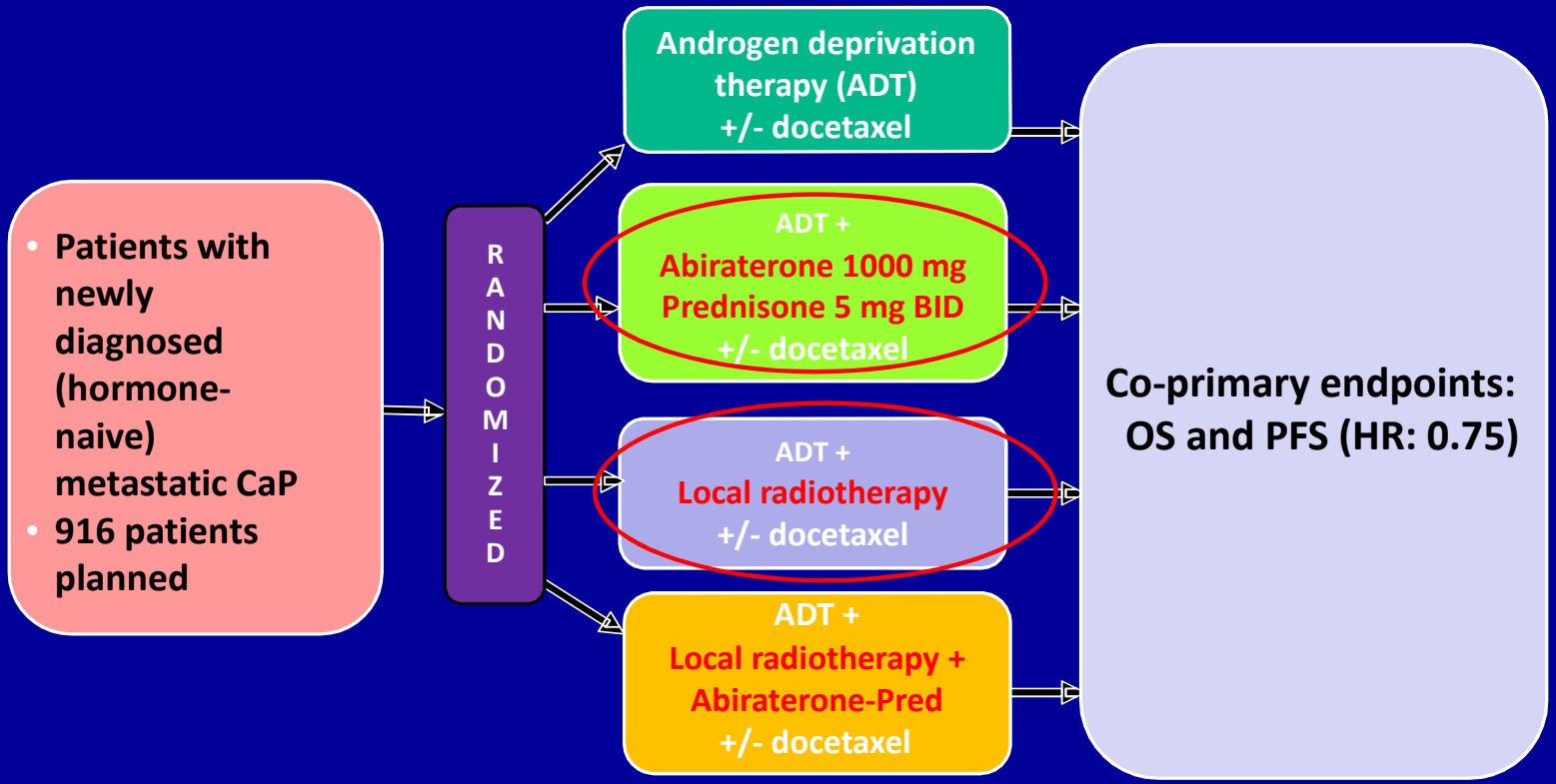
Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (SWOG S1802-Actively Enrolling)



Southwest Oncology Group
A National Clinical Research Group

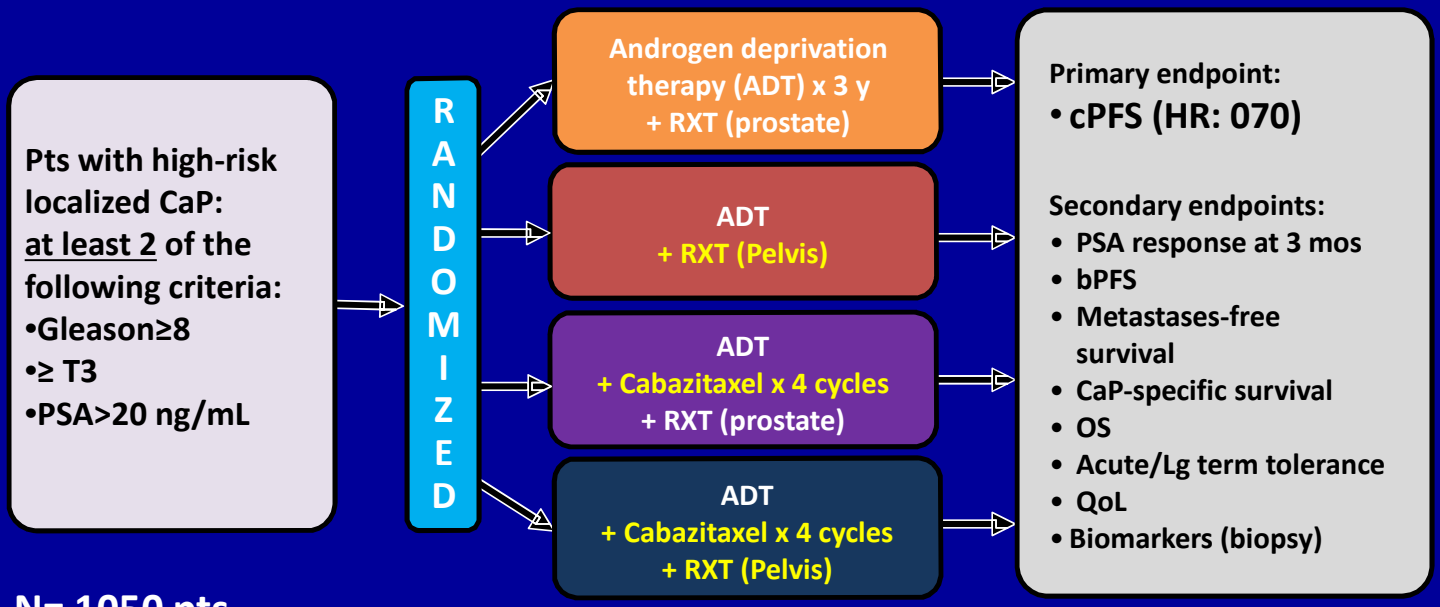
PEACE-1: European Phase III Trial in *de novo* Metastatic Prostate Cancer (revised design)



Study sponsor: Unicancer

ClinicalTrials.gov. Identifier: NCT01957436.

PEACE-2: European Phase III Trial of Cabazitaxel and Pelvic Irradiation in Patients With High-risk Localized Prostate Cancer

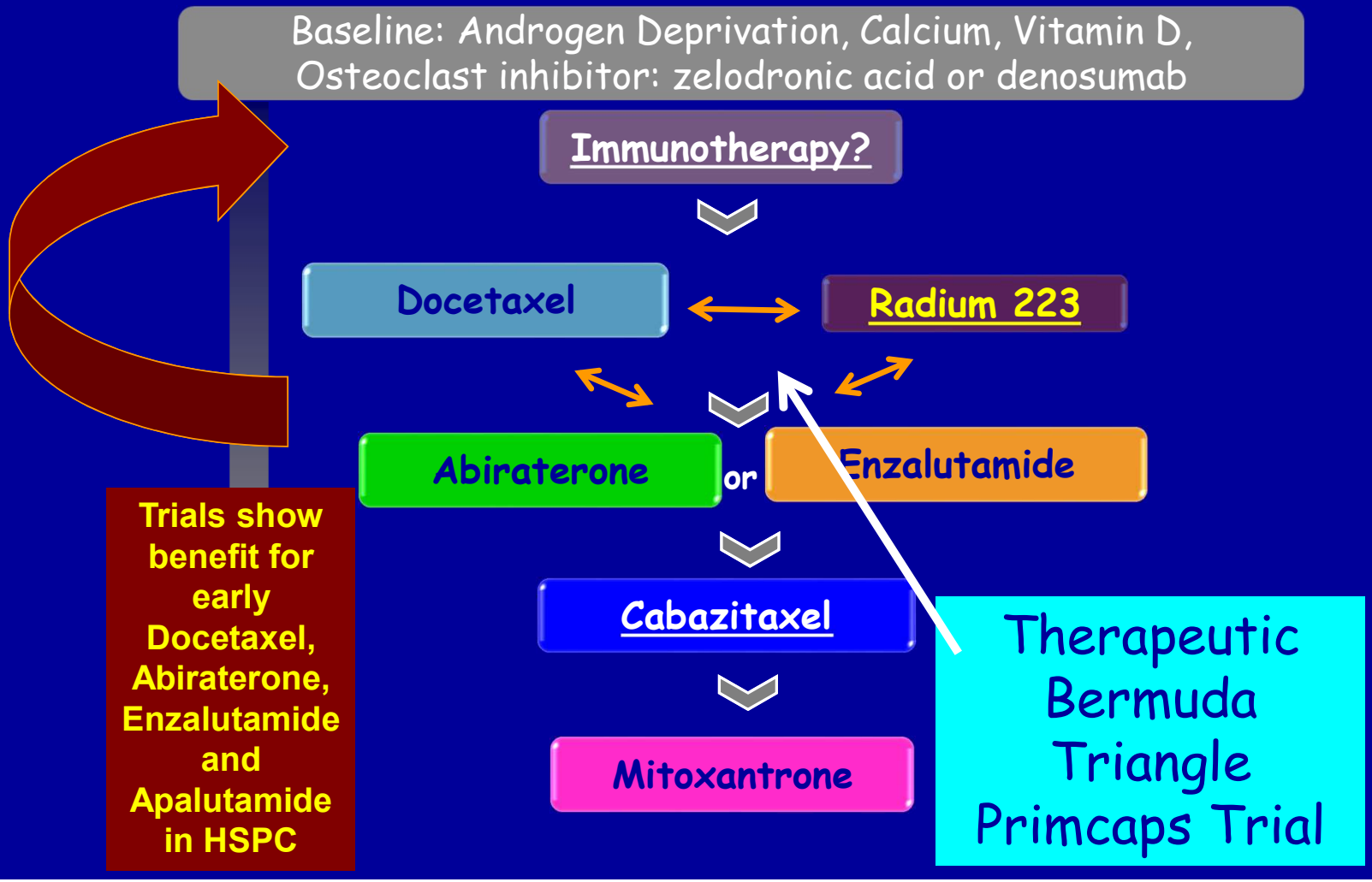


N= 1050 pts planned

Study sponsor: Unicancer
Planned accrual duration: 4 years

NCT01952223

Preferred Therapeutic Sequencing For Metastatic Prostate Cancer possible changes for 2019



Regarding metastatic hormone sensitive prostate cancer, which of the following is correct?

A. The combination of of docetaxel and enzalutamide have an additive affect on overall survival when combined with ADT
B. Docetaxel improves overall survival when added to ADT in low volume patients
C. The combination of of docetaxel and abiraterone acetate + prednisone have an additive affect on overall survival when combined with ADT
D. Enzalutamide improves overall survival when added to ADT in low volume patients
E. Radiation therapy to the primary tumor may improve overall survival when added to ADT in high volume patients

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