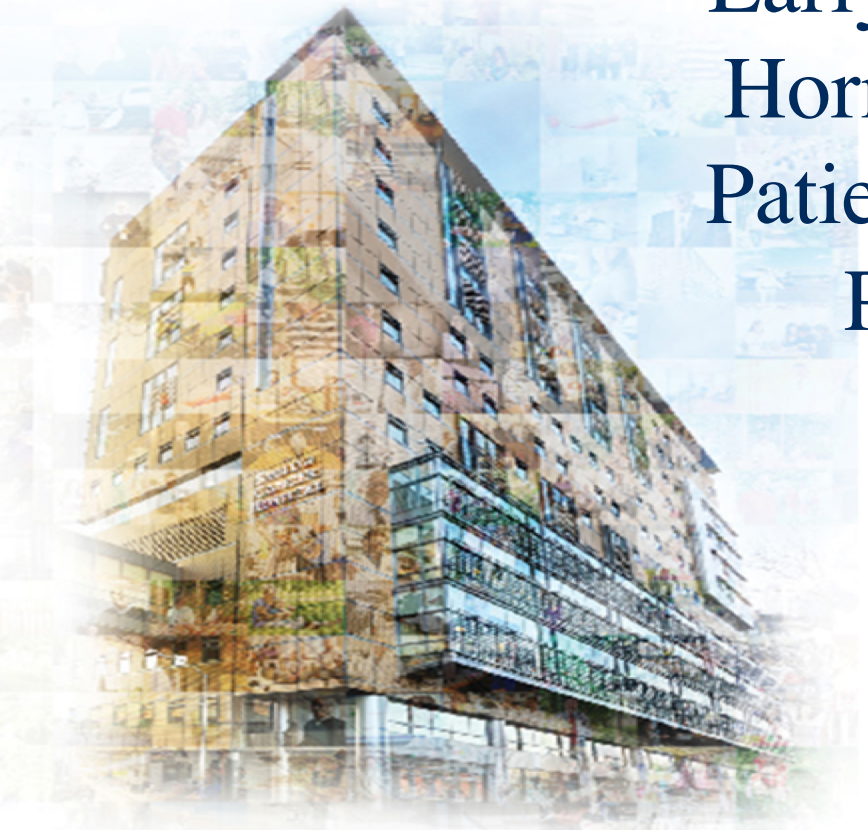

Early Chemotherapy and Hormonal Therapy for Patients with Advanced Prostate Cancer

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Director, Genitourinary DART
Co-Director, Signal Transduction Program
Smilow Cancer Center
Yale University School of medicine

November 17, 2016

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

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DART

Case Review

55 yo M without significant PMHx who had a PSA of 4.0 in November 2016 (Previously 2.0 in 2015)

Biopsy revealed Adenocarcinoma of the Prostate with Gleason 4+5=9/10 in 60% of the initial core biopsy (total 2/6 cores involved)

CT negative for metastasis

Referred to Yale Urologic Oncology

Case Review

Robotic Prostatectomy at YNHH on 1/25/17

T3aN0, Stage III (0/9 LN)

Gleason 4+5=9/10 High Grade Adenocarcinoma

Non-Focal Extraprostatic Extension

Surgical Margins Negative

Seminal Vesicles Not Involved

Perineural Invasion

LVI Indeterminate

Case Review

- One week post-op developed high fevers, and intense myalgias
- CT (1/31/17) neg for DM or significant source
- Fevers persisted and repeat CT (2/13/17) again was negative. LFTs increasing.
- Admitted to YNHH for FUO
- Cultures all negative

Case Review

- ID rec Liver Bx which was c/w Extramedullary Hematopoiesis and no Fibrosis
- Repeat CT and Bone Scan (3/8/17) now revealed widespread bony metastasis
- PSA noted to be 327.00
- Medical Oncology consulted and started Bicalutamide 50 mg po qd and NSAIDs

Case Review

- Fevers, bony aches and myalgias resolved within one week
- Patient received Leuprolide 22.5 mg on 3/23/17
- Continued Bicalutamide
- Started Docetaxel on 4/10/17

Case Review

Treatment		PSA
Bicalutamide	(3/09/17)	327.00
Leuprolide	(3/23/17)	140.52
Docetaxel	(4/10/17)	23.40
Docetaxel	(5/01/17)	1.917
Docetaxel	(5/28/17)	0.377
Docetaxel	(6/12/17)	0.184

Plan to complete 6 cycles

Case Review

- Patient remains asymptomatic and working full time
- Repeat CT and Bone Scan c/w stable bony disease with sclerosis and probable treatment effect. No evidence for visceral involvement

Does the Earlier Use of Chemotherapy or Next Generation AR Targeting Agents Improve Survival?

emohormonal therapy for CSPC

- CHAARTED Study
  - High volume disease: ≥4 bony metastases, at least one outside of axial skeleton and/or visceral metastases
  - 17 mo overall survival benefit **only in high volume disease** (pre-specified analysis)
  - **No overall survival benefit in low volume disease**

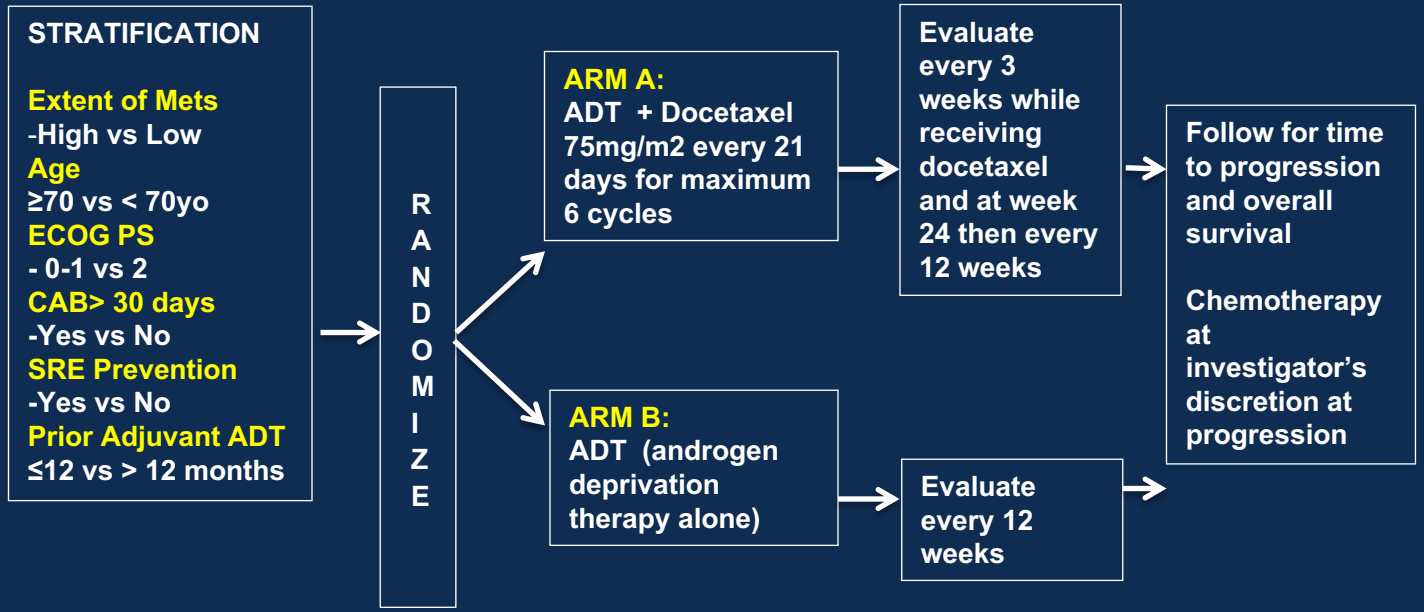
- STAMPEDE Study
  - Did not stratify by low vs high volume disease

- Conclusions
  - Standard of care for high volume disease: ADT + docetaxel
  - Standard of care for low volume disease:

    ADT alone (CHAARTED) or

    ADT + docetaxel (STAMPEDE)

E3805 – CHAARTED Treatment

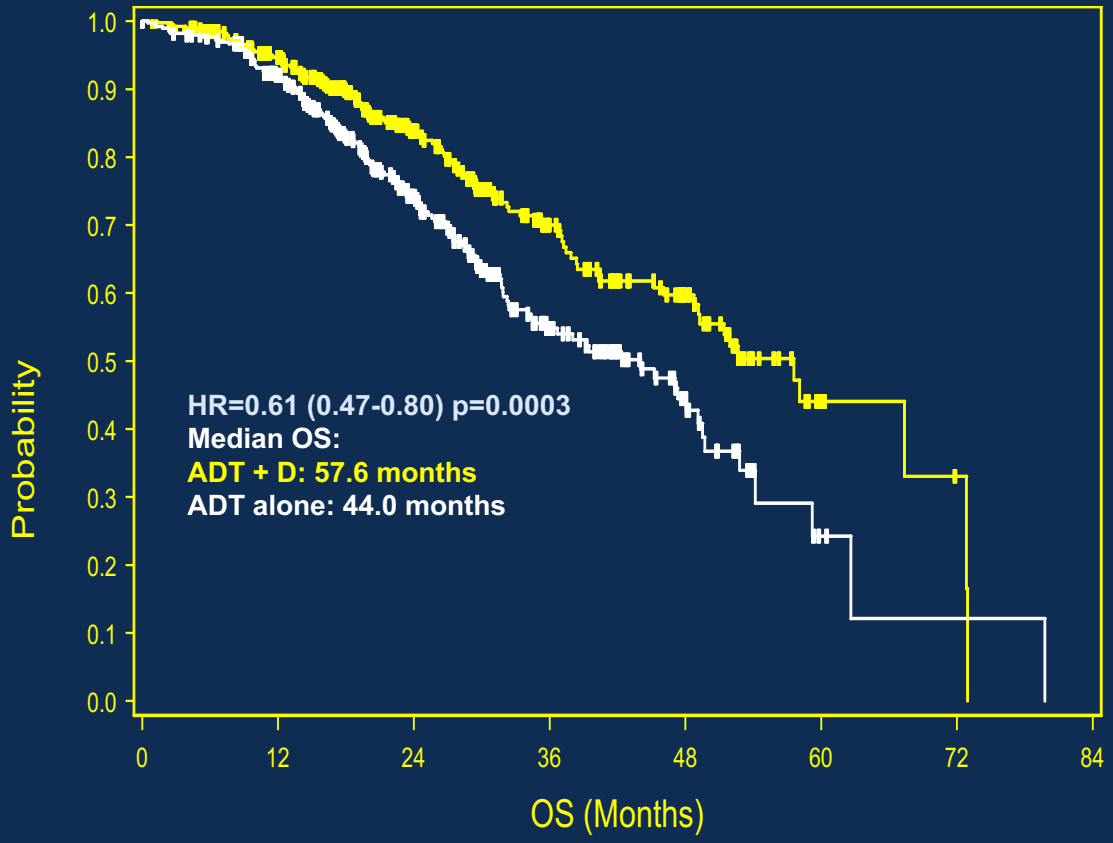


- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Results:

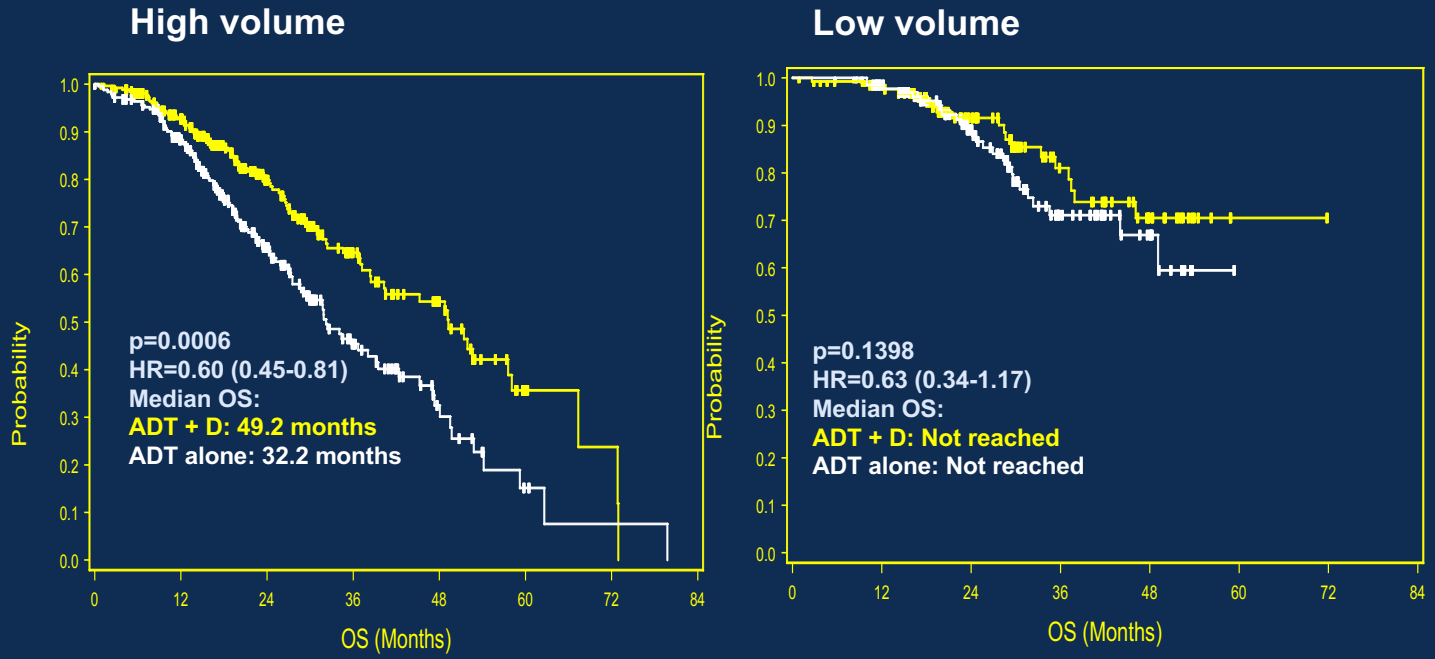
- 790 men accrued 7/28/2006 to 11/21/2012
  - Planned interim analysis at 53% information, Oct 2013 met pre-specified criteria for significance and release of data
  - Jan 16, 2014 median follow-up of 29 months
    - 136 deaths ADT alone vs. 101 deaths ADT+D

Primary endpoint: Overall survival



Presented by: Christopher J. Sweeney, MBBS

OS by extent of 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 SWOG9346 team

Presented by: Christopher J. Sweeney, MBBS

Secondary Endpoints

	ADT + Doc (N=397)	ADT alone (N=393)	P-value	Hazard Ratio (95%CI*)
PSA <0.2 ng/mL at 6 months	27.5%	14.0%	<0.0001	
PSA <0.2 ng/mL at 12 months	22.7%	11.7%	<0.0001	
Median time to CRPC - biochemical, symptoms, or radiographic (months)	20.7	14.7	<0.0001	0.56 (0.44, 0.70)
Median time to clinical progression - symptoms or radiographic (months)	32.7	19.8	<0.0001	0.49 (0.37, 0.65)
*CI: confidence intervals				

Clinical interpretation

- 6 cycles of docetaxel in addition to ADT represents an appropriate option 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
  - longer follow-up is required for patients with low volume metastatic disease

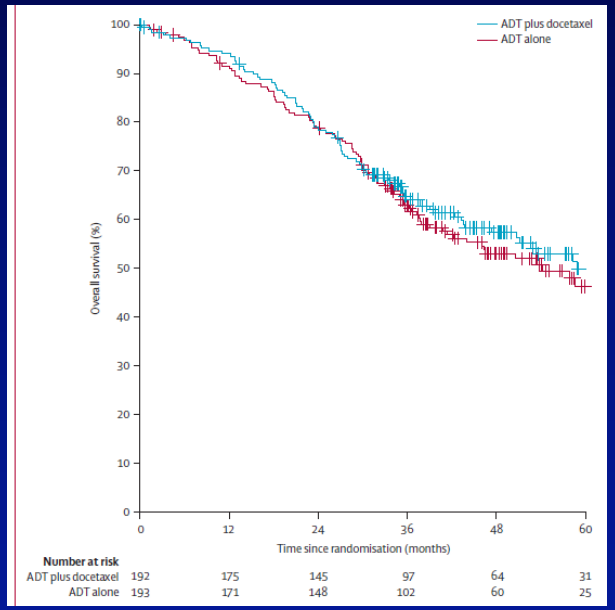
Gravis et al: Androgen Deprivation +/- Docetaxel(D): GETUG-AFU 15

Median survival (months)

ADT 54.2 (50.8-69.1)

ADT + D 58.9 (42.2-NR)

Biochemical PFS, and clinical PFS were improved in the docetaxel arm.



STAMPEDE: Metastatic Analysis

- Adding docetaxel to SOC showed significant improvement in OS in pts with M1 metastatic status (*P* = .002) but not M0 pts in preplanned analysis

Regimen (+ SOC)	Metastatic Status	Pts, n	OS Events	HR (95% CI)
ZA	M0	686	93	0.96 (0.62-1.48)
	M1	1091	509	0.92 (0.76-1.11)
	Overall	1777	602	0.93 (0.79-1.11)
DOC	M0	689	93	1.01 (0.65-1.56)
	M1	1087	477	0.73 (0.59-0.89)
	Overall	1776	570	0.76 (0.63-0.91)
ZA + DOC	M0	687	91	1.03 (0.66-1.61)
	M1	1090	495	0.78 (0.65-0.95)
	Overall	1777	586	0.81 (0.68-0.97)

James ND, et al. ASCO 2016. Abstract 5001.

MRC Clinical Trials Unit

Smarter studies
Global impact
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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

Setting and hypothesis

- Setting
  - Hormone therapy the mainstay of treatment since 1940s
  - Addition of radiotherapy to N0M0 disease improves outcomes
  - Recruitment prior to inclusion of docetaxel as part of standard care
- Hypothesis
  - Early use of therapies may give a larger absolute benefit in overall survival

Outcome measures

Primary outcome measure
Overall survival

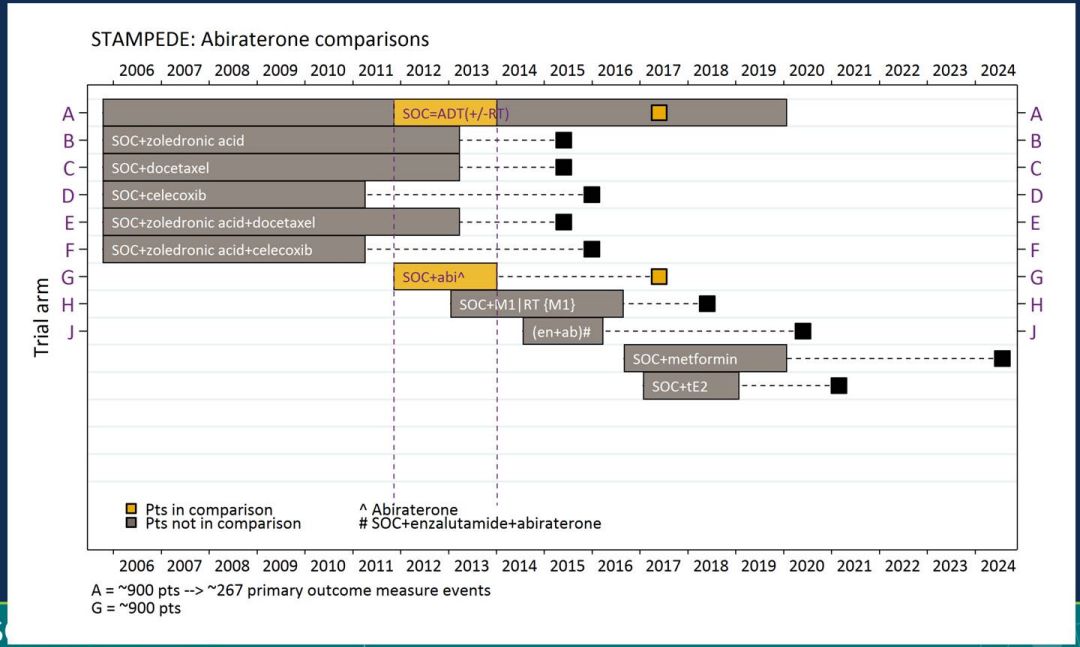
Secondary outcome measures
Failure-free survival (FFS)
Toxicity
Quality of life
Skeletal-related events
Cost effectiveness

FFS definition
First of:
- PSA failure
- Local failure
- Lymph node failure
- Distant metastases
- Prostate cancer death

PSA failure definition
PSA fall >= 50%
→ 24wk nadir + 50% **and**
→ >4ng/ml

PSA fall of <50%
→ failure at t=0

Abiraterone comparison: patients



Patient characteristics

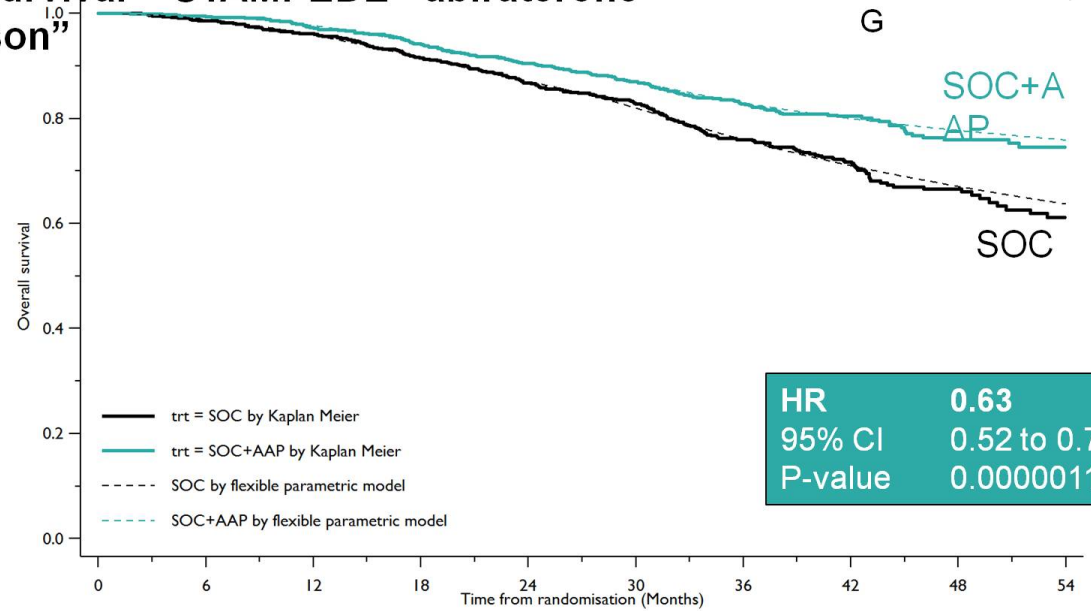
1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
67yr	Median age (min 39, max 85)	[s]
52%	Metastatic (88% Bony mets)	[s]
20%	N+M0	
28%	N0M0	
99%	LHRH analogues	[s]
41%	Planned for RT (96% of N0M0 pts; 62% of N+M0 pts)	[s]
5%	Previous local therapy	

Balanced by arm

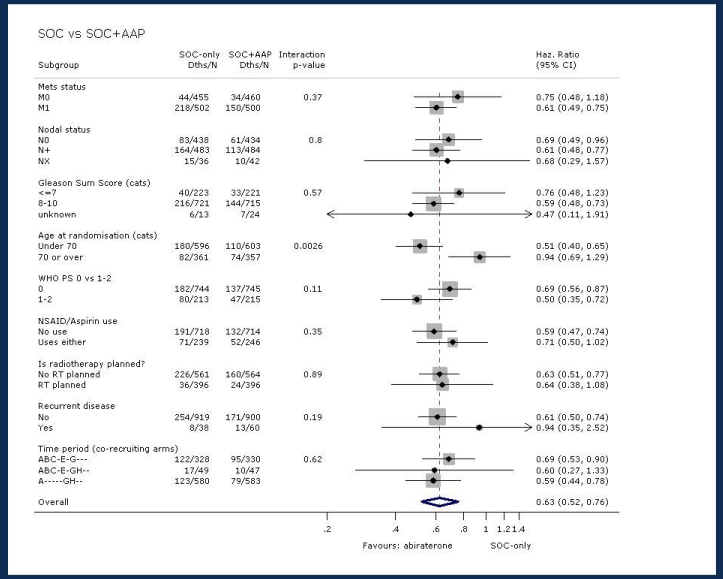
[s] = Stratification factors

Also stratified on
:: hospital
:: NSAID/aspirin

Overall Survival – STAMPEDE "abiraterone comparison"



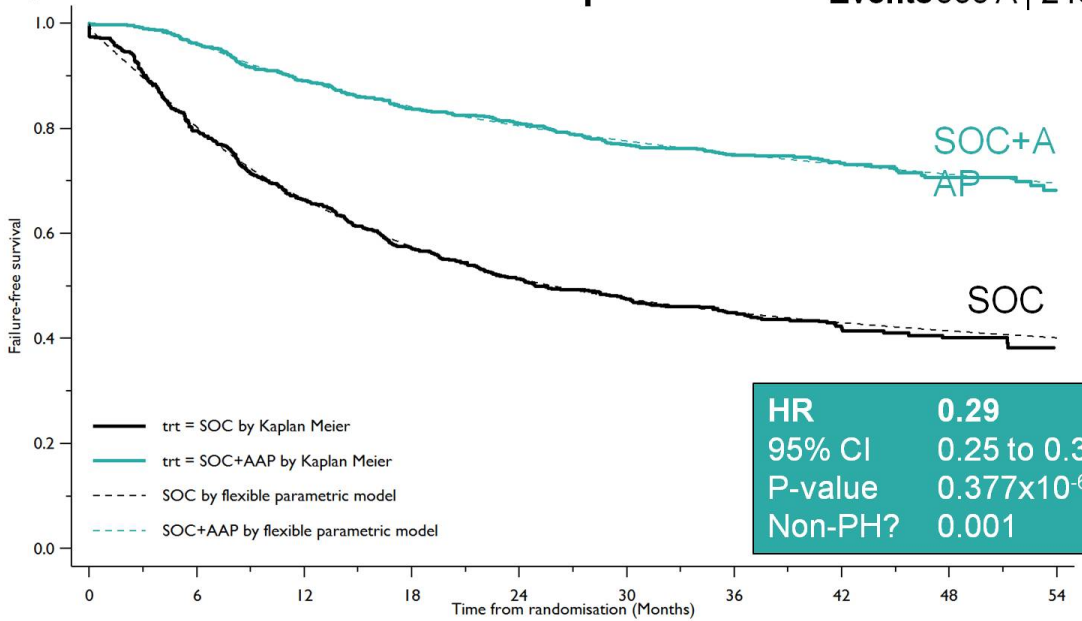
Overall Survival – STAMPEDE "abiraterone comparison"



No good evidence of heterogeneity by stratification factors

FFS – STAMPEDE "abiraterone comparison"

Events 535 A | 248 G



HR	**0.29**
95% CI	0.25 to 0.34
P-value	0.377×10^{-61}
Non-PH?	0.001

Number of patients (events)

SOC	957	(319)	625	(140)	476	(56)	284	(18)	62
SOC+AAP	960	(104)	837	(75)	737	(52)	477	(14)	141

	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, 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%)

Treatment compliance

Abiraterone

The administration of abiraterone is expected to be as follows:

- **1000mg *od*** abiraterone acetate
- prednisolone or prednisone 5mg od to prevent secondary ACTH excess.

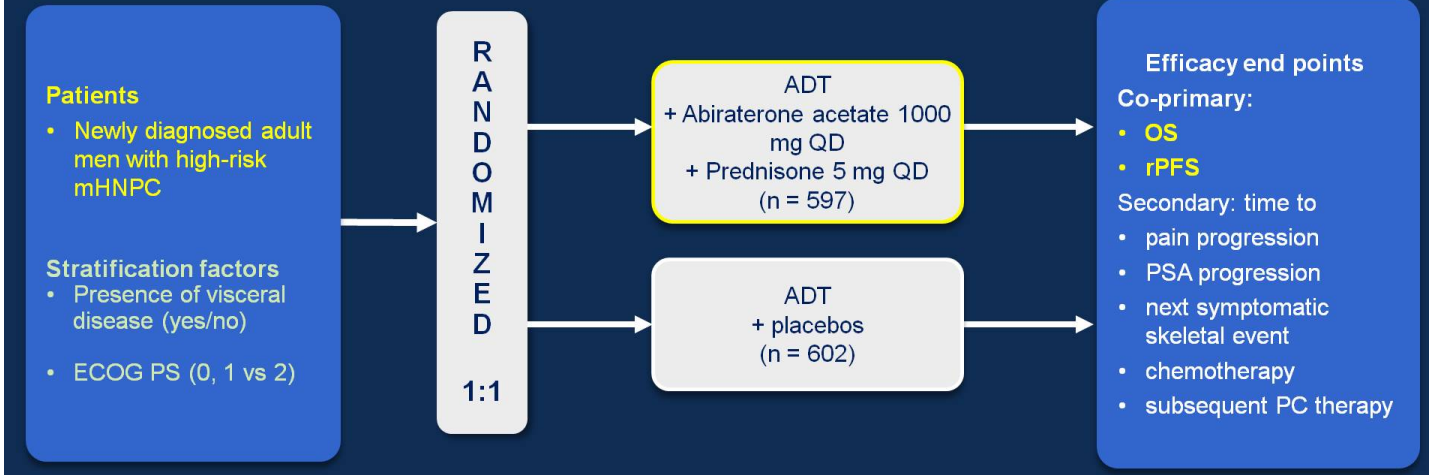
Duration of treatment:

- Capped at 2 years for N0M0 pts and N+M0 pts receiving RT
- Permitted through 3 types of progression for M1 pts and N+M0 pts not receiving RT

Conclusions

- Abiraterone acetate + prednisolone (AAP) improves survival for hormone-naive prostate cancer

Overall study design of LATITUDE

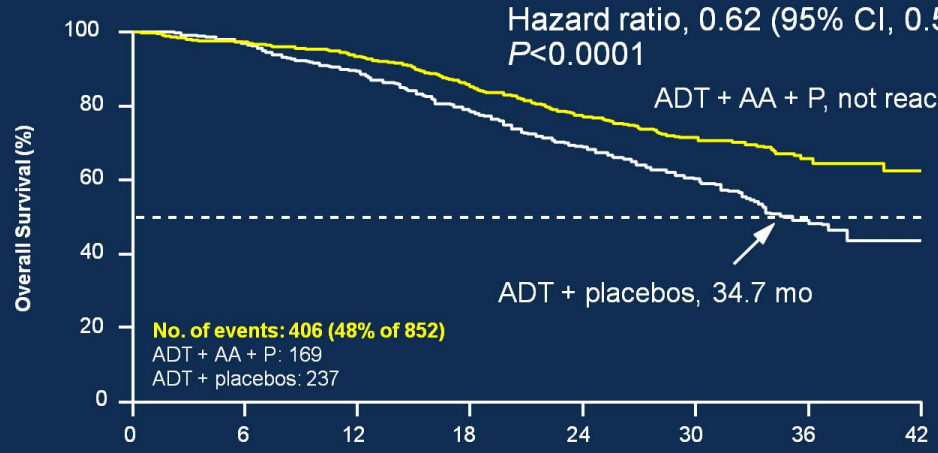


- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

Treatment arms were well balanced

	ADT + AA + P (n = 597)	ADT + Placebos (n = 602)
Median age, years (range)	68.0 (38-89)	67.0 (33-92)
Gleason score ≥ 8 at initial diagnosis	98%	97%
Patients with ≥ 3 bone metastases at screening	98%	97%
Extent of disease Bone Liver Lungs Node	 97% 5% 12% 47%	 98% 5% 12% 48%
Baseline pain score (BPI-SF Item 3) 0-1 2-3 ≥ 4	 50% 22% 29%	 50% 24% 27%

Statistically significant 38% risk reduction of death



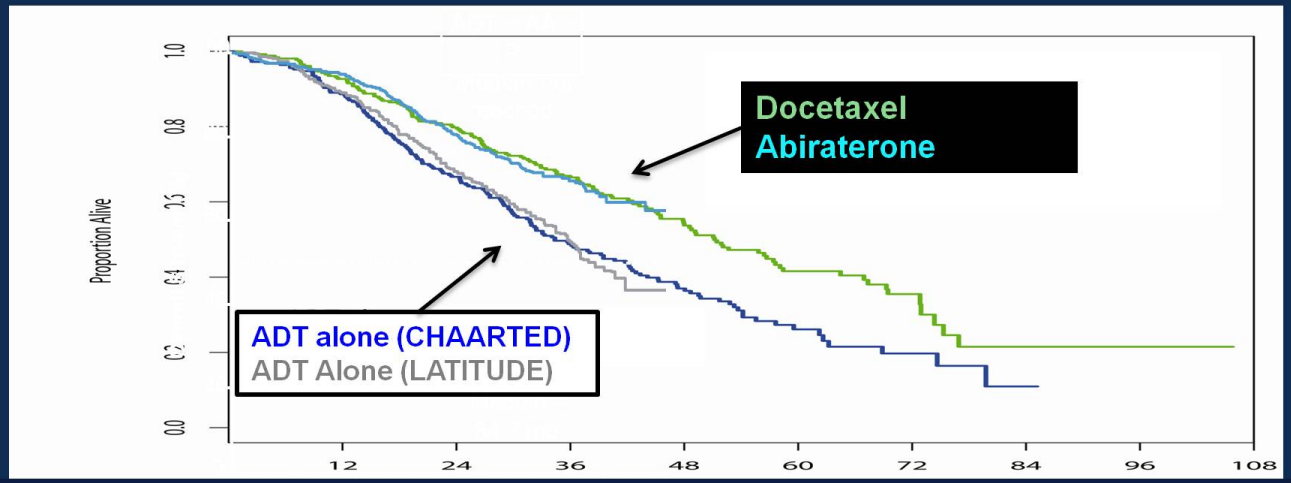
OS rate at 3 years:
ADT + AA + P: 66%
ADT + placebos: 49%

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

Median follow-up: 30.4 months

Comparing Overall Survival Across Studies

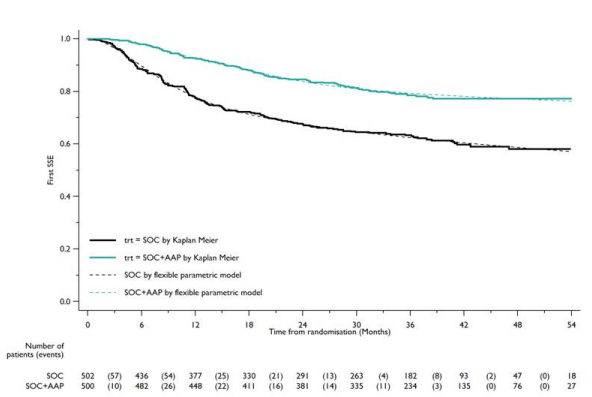
	Median OS			3 yr OS rate	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
STAMPEDE	0.63	not reached (0.52 – 0.76)			
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%*	~65%*



Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

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



Selection of Treatment

- Based on side effects
  - Preexisting neuropathy
  - CHF
  - Liver function abnormalities
  - Health care costs

Characterization of CRPC population Based on a Systematic Review

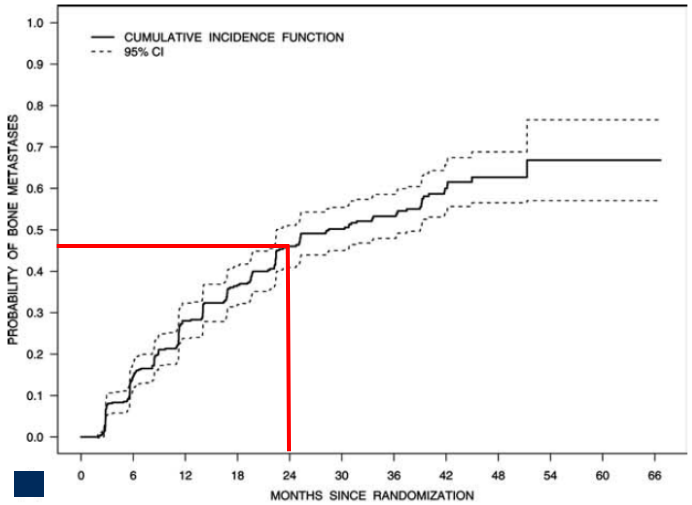
- CRPC is an advanced form of prostate cancer associated with frequent metastases, poor survival rates, poor quality of life, few therapeutic options

Data from retrospective and prospective observational studies involving a total of 71,179 patients observed for up to 12 years	
Prevalence	• 10–20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up
Metastases	• ≥84% of patients have metastases present at the time of CRPC diagnosis • In those without metastases at diagnosis, 33% of patients with CRPC develop metastases within 2 years of their diagnosis
Survival	• The median survival from CRPC diagnosis is 14 months

Kirby M et al. Int J Clin Pract. 2011;65(11):1180-1192.

Time to First Bone Metastasis and Death in Men With Progressive CRPC

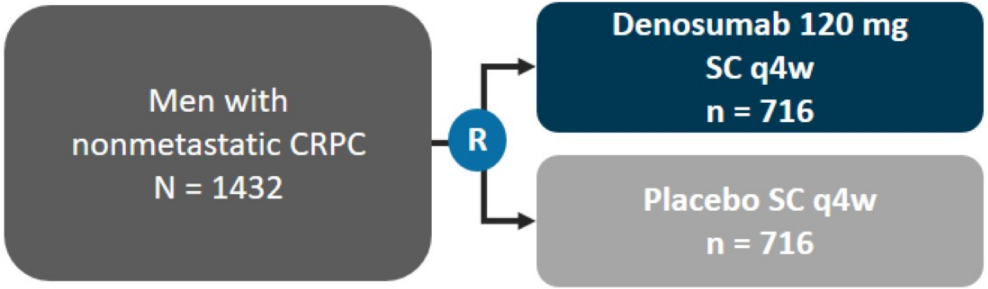
- In multivariate analyses, baseline PSA ≥13.1 ng/mL was associated with shorter overall survival (RR, 2.34; *P*<0.0001), time to first bone metastasis (RR, 1.98; *P*<0.0001), and bone metastasis-free survival (RR, 1.98; *P*< 0.0001)
- At 2 years, 46% of subjects (N=331) had developed bone metastases, and 20% had died



Smith MR et al. Cancer. 2011;117(10):2077-2085

RR= relative risk.

Phase 3 Trial of Denosumab in Nonmetastatic CRPC



Primary endpoint: BMFS (time to first bone metastasis or death)

	Denosumab n = 716	Placebo n = 716	HR (95% CI)	*P* Value
Median BMFS	29.5	25.2	0.85 (0.73, 0.98)	.028
Median time to first bone met, mo	33.2	29.5	0.84 (0.71, 0.98)	.032
Cumulative incidence of ONJ, %	4.6	0		

Smith MR, et al. Lancet. 2012;379:39-46.

IMAAGEN Trial Update: Effect of Abiraterone Acetate and Low Dose Prednisone on PSA in Patients With Non--mCRPC

Figure 1: IMAAGEN Study Design

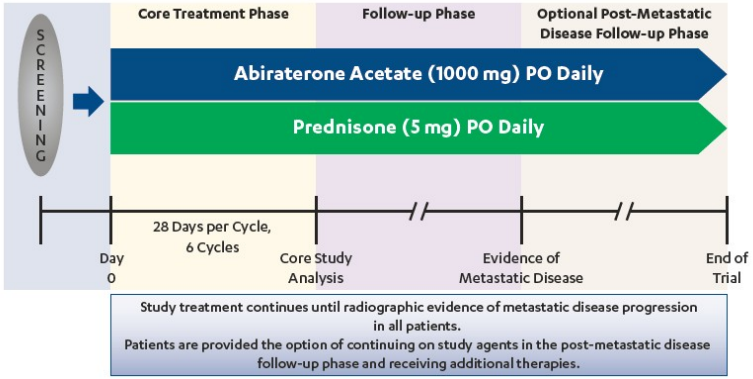


Table 2: PSA and PSADT at Screening

	Abiraterone Acetate Plus Prednisone
PSA, ng/ml	131
N	
Median, range	11.9 (1.3--167.8)
PSADT for subjects with	52
PSA <10 ng/mL, months	
N	
Median, range	3.4 (1.1--9.4)

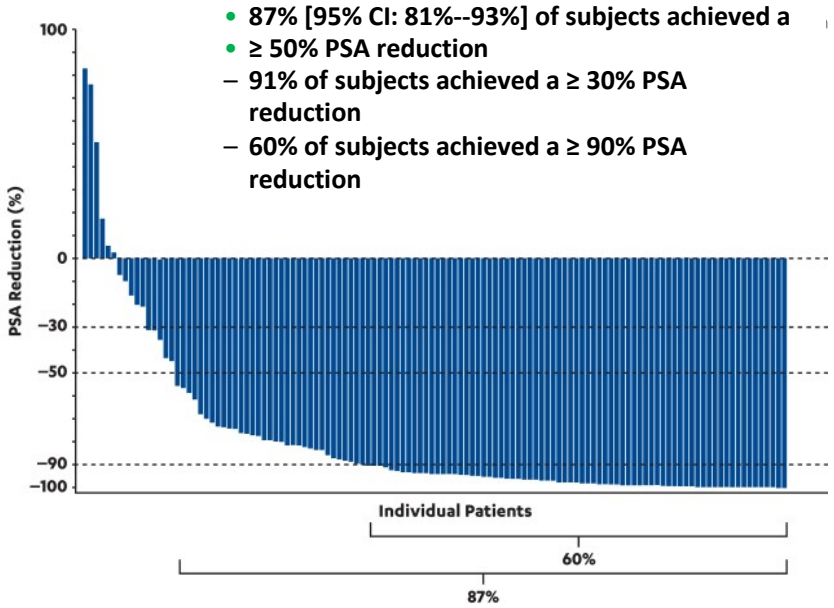
Table 1: Baseline Characteristics

	Abiraterone Acetate Plus Prednisone (n=131)
Age, years	71.2 (48.0--90.0)
Mean, range	
Race, n (%)	108 (82.4)
White	19 (14.5)
Black or African American	2 (1.5)
Asian Other	1 (0.8)
Not Reported	1 (0.8)
Calculated Gleason Score, n (%)	
n*	125
< 7	17 (13.6)
7	59 (47.2)
> 8	49 (39.2)
Mean, SD Median Range	7.5 (1.14)
	7.0
	4.0--10.0
Testosterone, ng/dL	116
n	
Mean	10.31
SD	11.49
Range	1.55--117.38

IMAAGEN Trial Update: Effect of Abiraterone Acetate and Low Dose Prednisone on PSA in Patients With Non--mCRPC

Primary Endpoint

Figure 3: Maximum PSA Reduction During Cycles 1-6



Secondary Endpoints

- The median Tme to PSA progression was 28.7 months (95% CI: 21.2, NE)
- Event--free rates for PSA progression at 12, 18 and 24 months were 79.7%, 68.4% and 56.6%, respectively
- As of this update:
  - 45 (34.4%) subjects showed evidence of PSA progression
  - In this update, 21 (16.0%) subjects had radiographic evidence of disease progression as reported by investigators
  - The median time to disease progression was not reached

IMAAGEN Trial Update: Effect of Abiraterone Acetate and Low Dose Prednisone on PSA in Patients With Non--mCRPC

Figure 5: PSA Progression

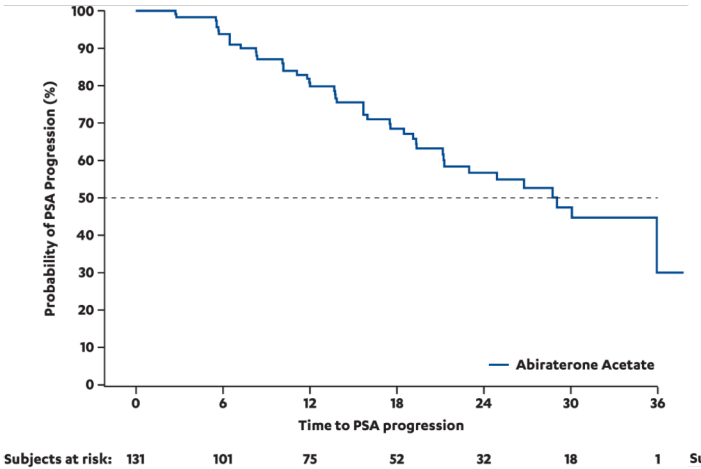
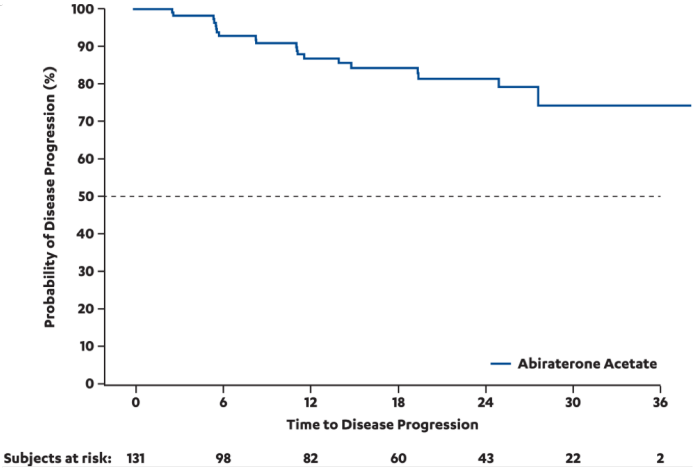
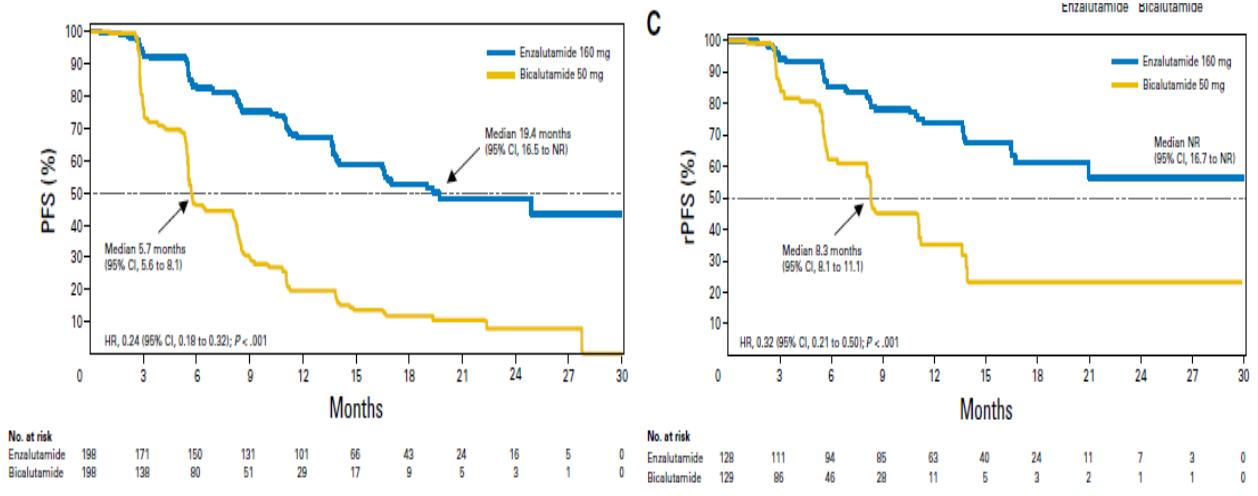


Figure 4: Radiographic Evidence of Disease Progression

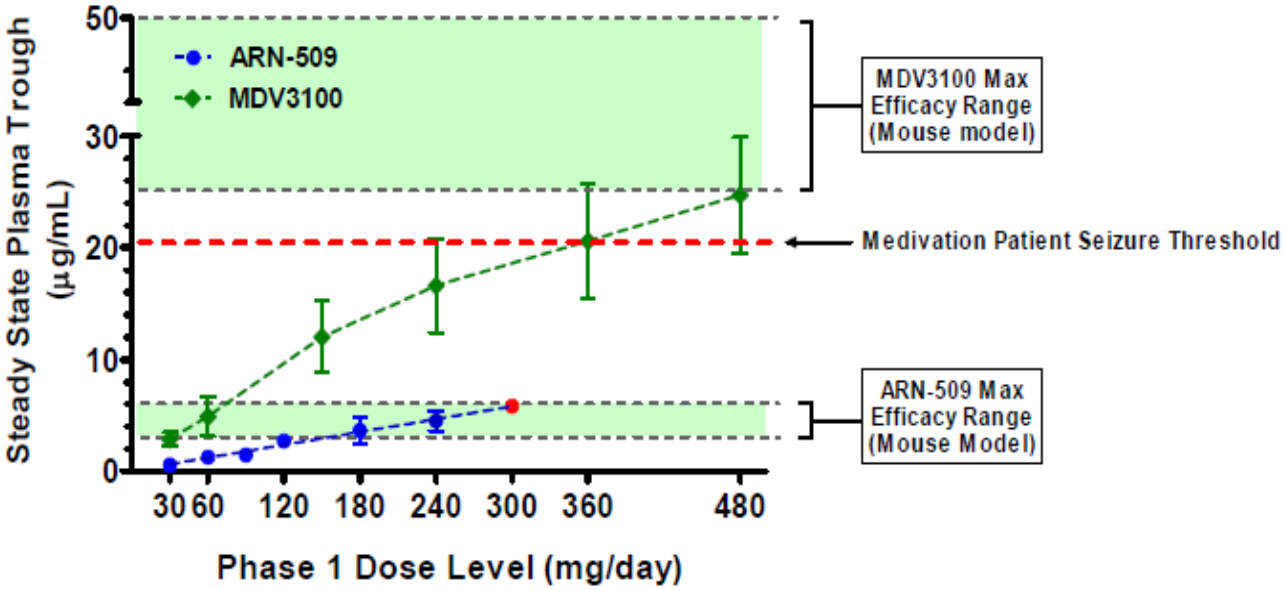


STRIVE: Enzalutamide vs Bicalutamide in Non-Metastatic Prostate Cancer

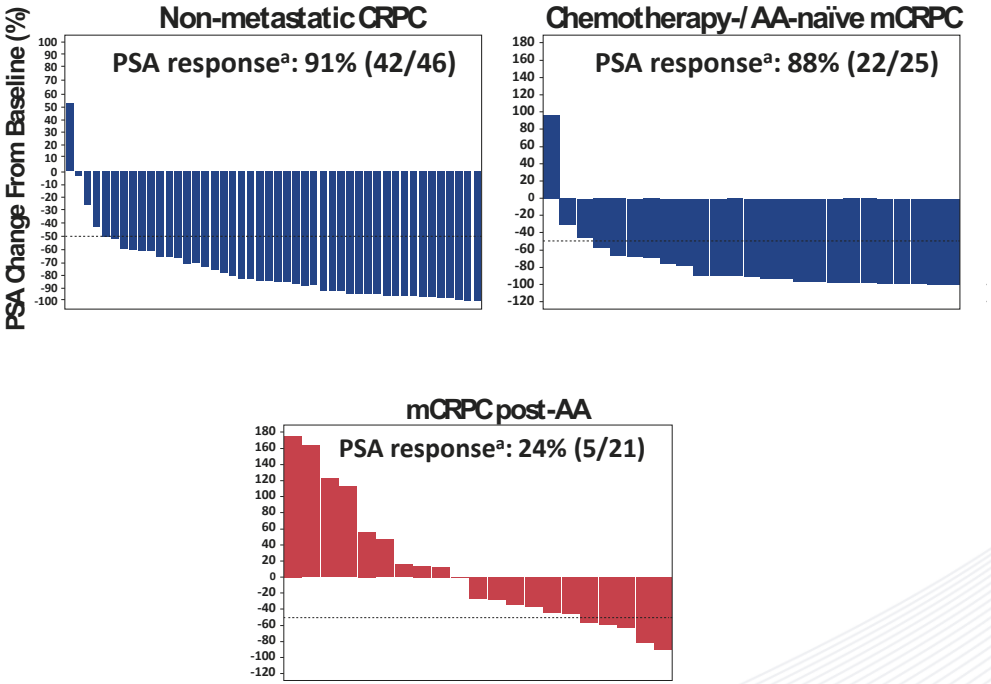


Penson et al., JCO 34:2098, 2016

ARN-509 (apalutamide)

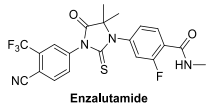


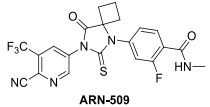
PSA Responses to ARN-509

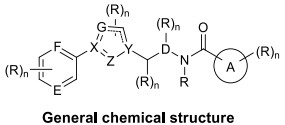


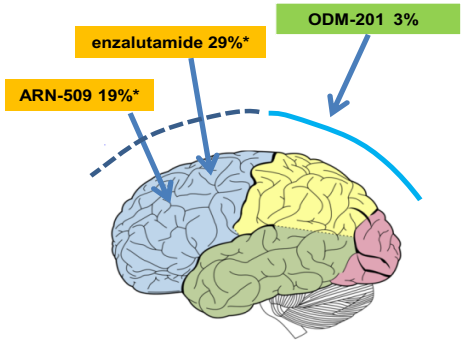
Rathkopf D et al. *ASCO Annual Meeting 2014*; Smith MR, et al. *Eur Urol. 2016*; epub ahead of print

ODM-201(Daralutamide) (Bayer)







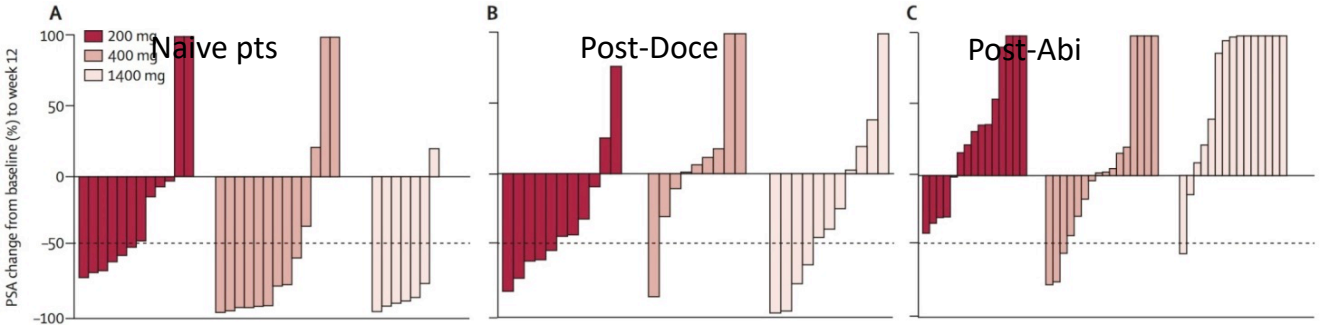


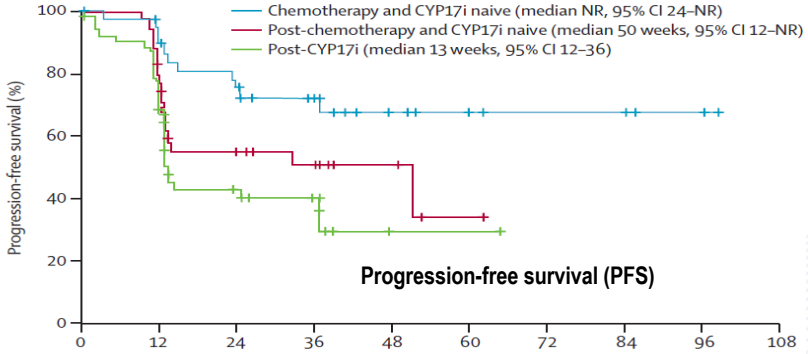
No CYP inhibition or induction with therapeutic doses

Compound	AR-WT affinity Ki (nM)	Antagonism AR-WT IC50 (nM)	Antagonism AR T878A IC50 (nM)	Antagonism AR F877L IC50 (nM)	Proliferation VCaP IC50 (nM)
Enzalutamide	78	155	296	agonist	400
ARN-509	53	168	1130	agonist	300
ODM-201	9	65	700	66	500

Meilanen A et al. Sci Rep 2015; 5:12007

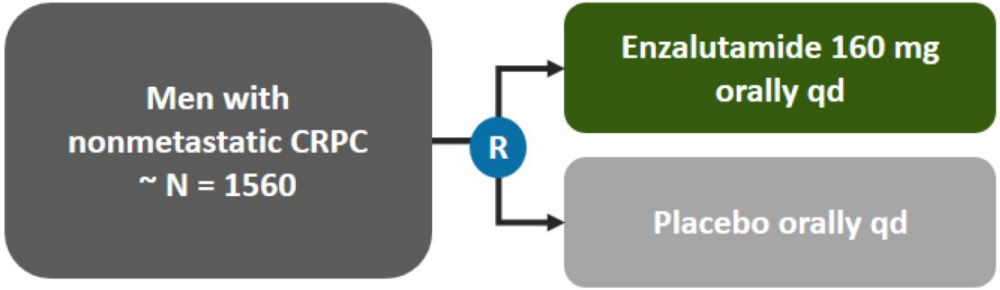
ODM-201: Phase 2 component





PROSPER

Randomized, Double-Blind, Phase 3 Trial of Enzalutamide in Nonmetastatic CRPC

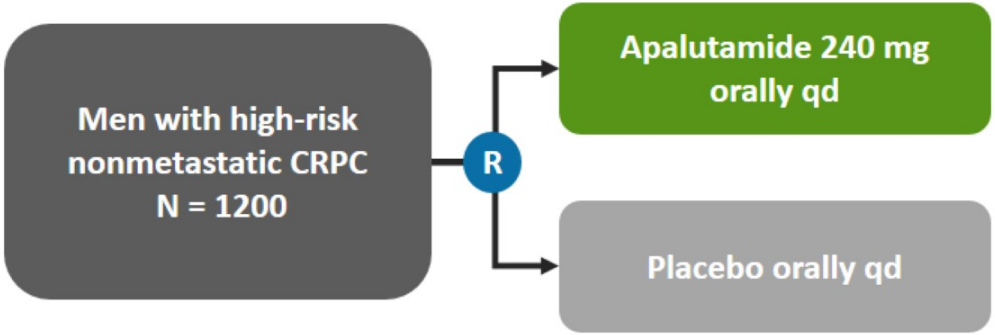


- **Primary endpoint:** metastasis-free survival
- **Secondary endpoints**: time to pain progression, time to first cytotoxic therapy, time to opiate use for cancer pain, time to first antineoplastic therapy, time to PSA progression, FACT-P Global Score, QoL assessment

ClinicalTrials.gov. NCT02003924.

SPARTAN

Randomized, Double-Blind, Phase 3 Trial of Apalutamide in Nonmetastatic CRPC



- **Primary endpoint**: metastasis-free survival
- **Secondary endpoints**: OS, time to symptomatic progression, time to first cytotoxic chemotherapy, PFS, time to metastasis, change in FACT-P and EQ-5D scores, AEs, pharmacokinetics

ClinicalTrials.gov. NCT01946204.

PROSPER VS SPARTAN

	PROSPER	SPARTAN
Met. Free Survival	21.9	24.3
TT PSA Progression	33.3	Not Reported
Duration of Treatment	7.3	Nor Reported
Survival	HR 0.8; P=0.15	HR 0.7 P=0.07

Conclusions and Clincal Implications

- Positive studies of enzalutamide and apalutamide in non metastatic CRPC
- Does treatment at a lower burden of disease improve survival?
- Is metastases free survival surrogate for overall survival?
- How do the results of PROSPER and SPARTAN affect subsequent treatment layering?