Prostate Cancer Management from Early Biochemical Recurrence to HRPC

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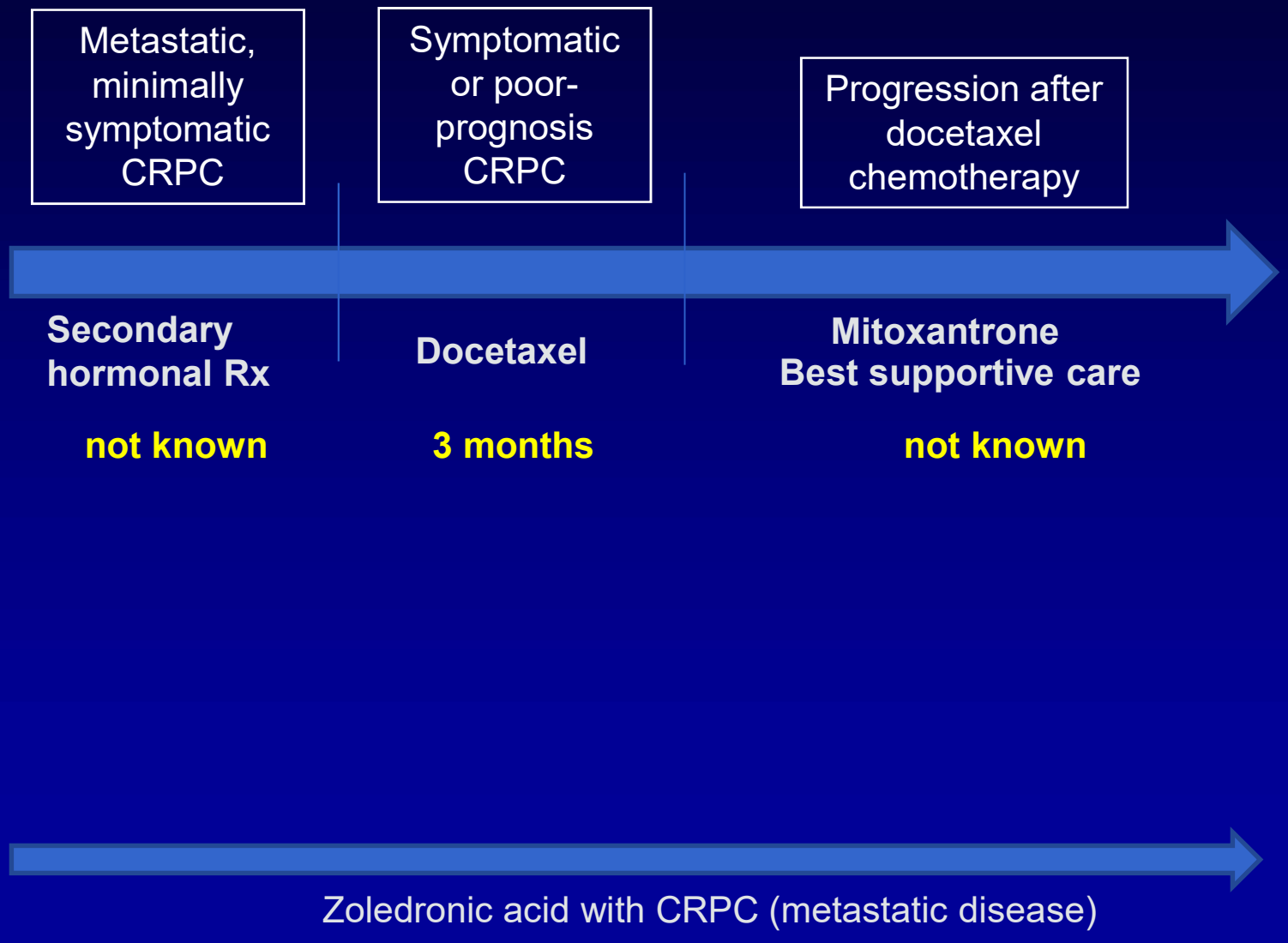
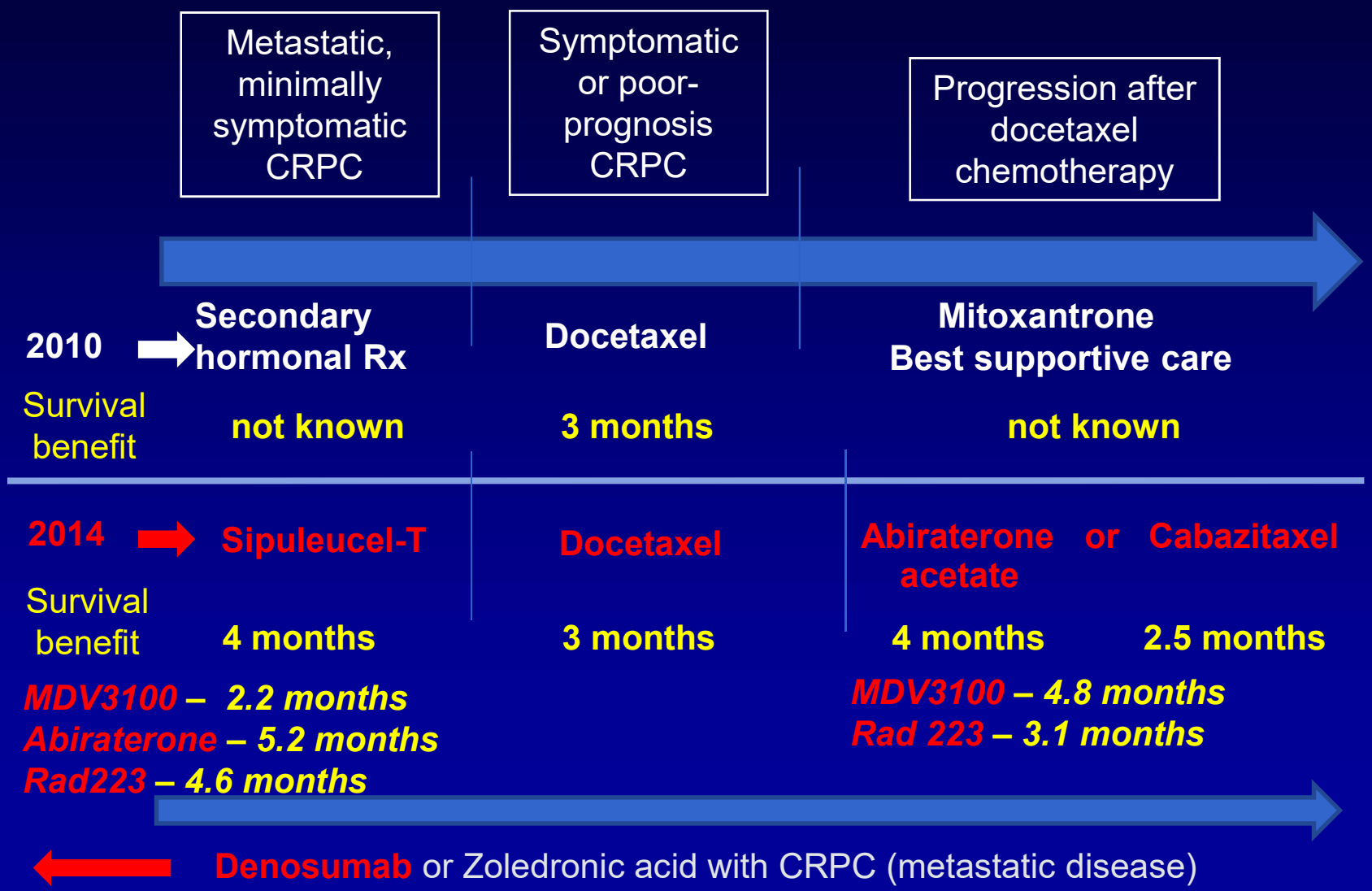
Sequencing CRPC therapy – 2010



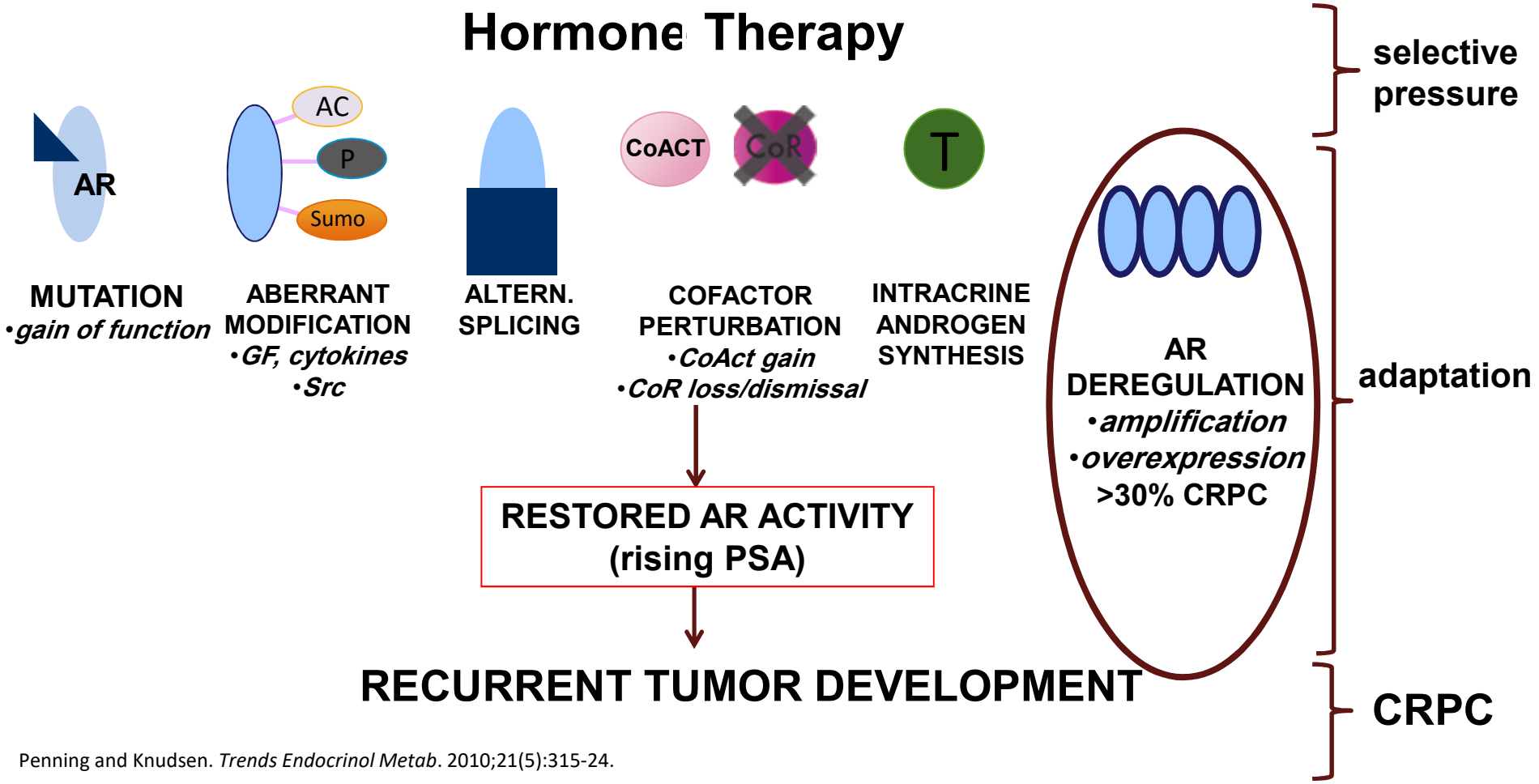
Sequencing CRPC therapy – 2019



Classes of Agents

- Immunotherapeutic
  - Sipuleucel T
- Hormonal
  - MDV3100, Abiraterone , ?Docetaxel
- Cytotoxic
  - Docetaxel, Cabazitaxel
- DNA Damage
  - Rad 223

Development of Castrate Resistant Prostate Cancer

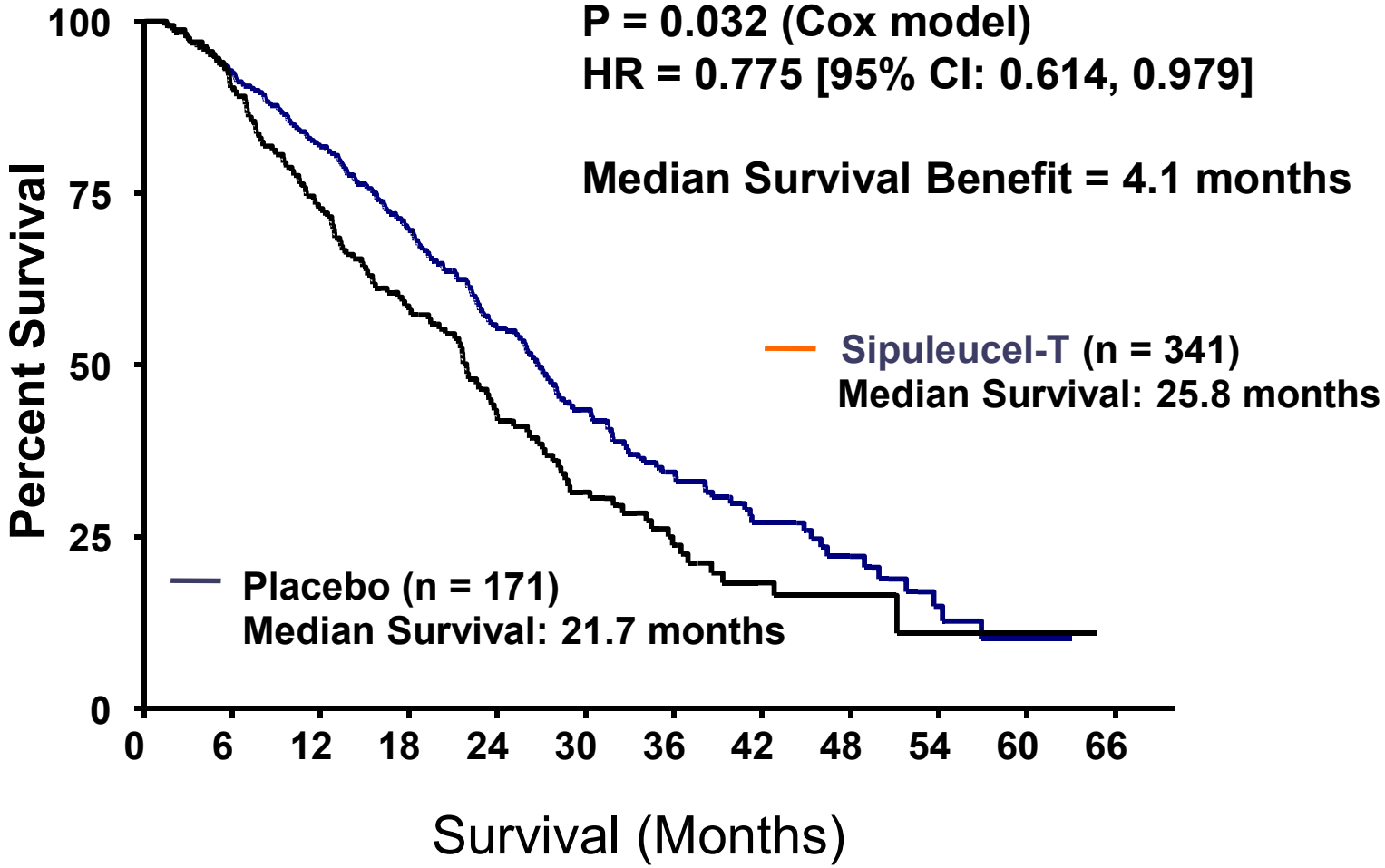


Penning and Knudsen. *Trends Endocrinol Metab*. 2010;21(5):315-24.

How do we sequence these agents?

- Clinical Characteristics
  - Symptomatic vs Asymptomatic
  - Visceral vs Non Visceral
  - Pre vs Post Docetaxel
- Biological Markers
  - Androgen Receptor
  - TRPMSS2-ERG

IMPACT Overall Survival
Intent-to-Treat Population



Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

E. David Crawford, M.D.[1], Adam S. Kibel, M.D.[2], Neal D. Shore, M.D., F.A.C.S.[3]

[1]University of Colorado Anschutz Medical Campus, Aurora, Colorado; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Atlantic Urology Clinics, Myrtle Beach, SC

Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

Baseline PSA ng/mL	≤22.1 (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, Difference, months	**13.0**	**7.1**	**5.4**	**2.8** 2.8
HR (95% CI)	0.51 (0.31 – 0.85)	0.74 (0.47 – 1.17)	0.81 (0.52 – 1.24)	0.84 (0.55 – 1.29)

- Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS
- The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively)

1. Crawford ED et al. AUA 2013. Abstract #960; 2. Schellhammer PF et al. *Urology*. 2013 Jun;81(6):1297-302

PDL-1 Expression in Prostate cancer

- Hormone sensitive radical prostatectomy specimens express high levels of PDL-1 52.2% of cases (Gevensleben et al Clin Cancer Res 2016)
- Patients progressing on enzalutamide have significantly increased PDL-1/2 dendritic cells in blood compared to those progressing on treatment. (Bishop et al. Oncotarget, 2016)
- Nivolumab treatment in men with CRPC demonstrated no objective responses in 17 patients; 2 patients who had tissue stained for PDL-1 demonstrated no immunoreactivity (Topalian NEJM2012)
- 3/20 samples (15%) had focal areas of PD-L1 positivity, although in only two of the three positive samples was plasma membrane staining clearly observed on malignant epithelial cell. (Martin et al. Prostate Cancer and Prostatic Disease 2015)

KEYNOTE-199: Study Design

- Multicohort phase II study (data cutoff: October 13, 2017)

Patients with metastatic CRPC and ECOG PS 0-2; 5 planned cohorts → **Pembrolizumab** 200 mg Q3W → ***For 35 cycles or until PD, unacceptable toxicity, or investigator/patient decision***

Assessments: imaging Q9W during Yr 1, then Q12W. Measurable disease per RECIST v1.1.
PD-L1 assessment with PD-L1 IHC 22C3 pharmDx assay; CPS ≥ 1 considered positive.

≥ 1 prior targeted endocrine therapy, 1-2 prior CT regimens including docetaxel (current analysis)
Cohort 1: measurable disease, PD-L1 positive (n = 131)
Cohort 2: measurable disease, PD-L1 negative (n = 67)
Cohort 3: bone metastases, no measurable disease, any PD-L1 status (n = 60)

Receiving enzalutamide, no prior CT, any PD-L1 status:
Cohort 4: measurable disease
Cohort 5: bone metastases, no measurable disease

- Primary endpoint: ORR per RECIST v1.1 by BICR in cohorts 1 and 2 (separately and combined)
- Secondary endpoints: DCR, DoR per RECIST v1.1, PCWG3-modified RECIST; OS, safety
- Exploratory endpoints: biomarker signature for benefit with PD-1 blockade

de Bono JS, et al. ASCO 2018. Abstract 5007.

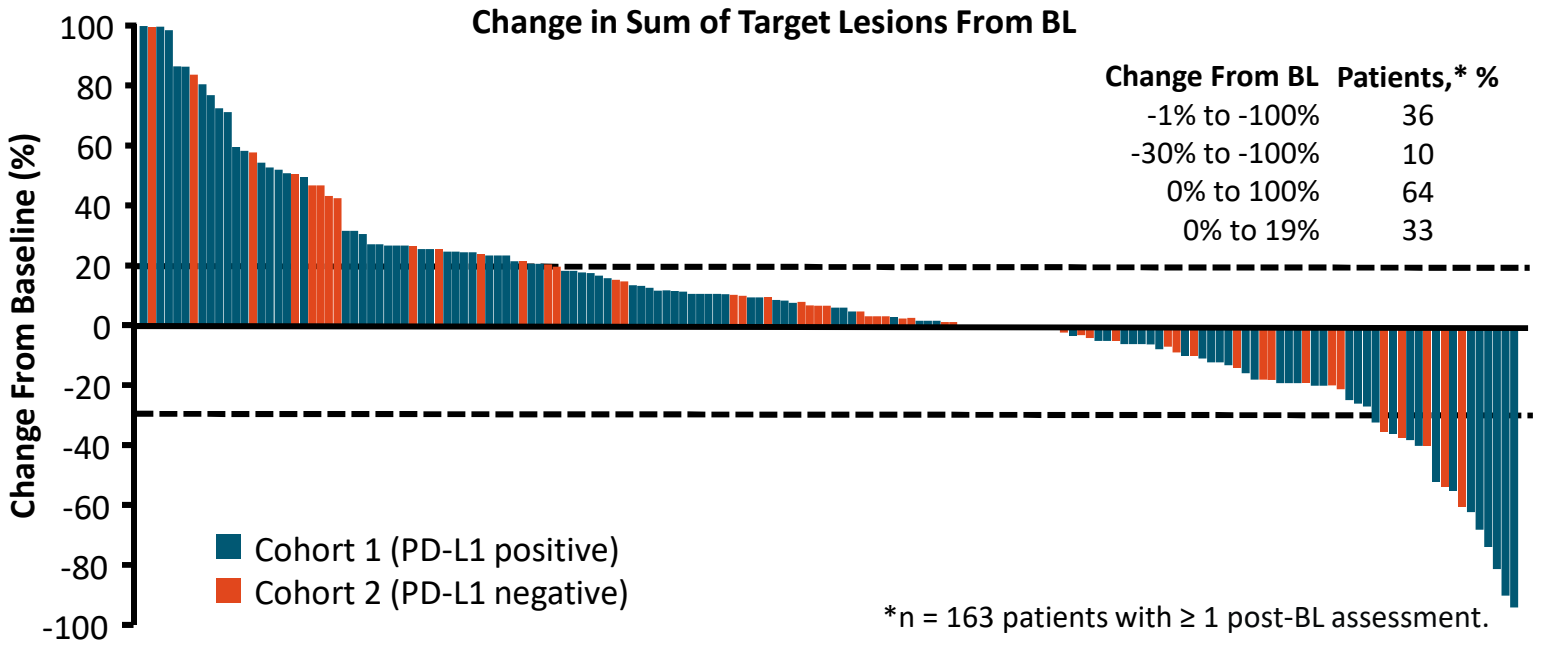
Slide credit: clinicaloptions.com

KEYNOTE-199: Baseline Patient Characteristics

Characteristic	Cohort 1: PD-L1 Positive (n = 131)	Cohort 2: PD-L1 Negative (n = 67)	Cohort 3: Bone Mets (n = 60)
Median age, yrs (range)	68 (48-85)	68 (53-84)	70 (53-90)
ECOG PS 0/1/2, %	31/56/12	39/54/6	43/47/10
Gleason score ≥ 8, %	63	64	57
Mean PSA, ng/mL (SD)	308.4 (655.9)	346.4 (646.2)	175.5 (375.1)
Visceral disease, %	66	45	12
Prior therapies, %			
▪ ≥ 2 CT	32	27	25
▪ ≥ 2 antiendocrine therapies	26	22	25
▪ Enzalutamide only	30	40	30
▪ Abiraterone only	44	37	45
▪ Enzalutamide + abiraterone	26	22	25

de Bono JS, et al. ASCO 2018. Abstract 5007.

KEYNOTE-199: Antitumor Activity (Cohorts 1 + 2)



- In 193 patients from all 3 cohorts, 11% experienced a ≥ 50% PSA reduction from BL

de Bono JS, et al. ASCO 2018. Abstract 5007. Reproduced with permission.

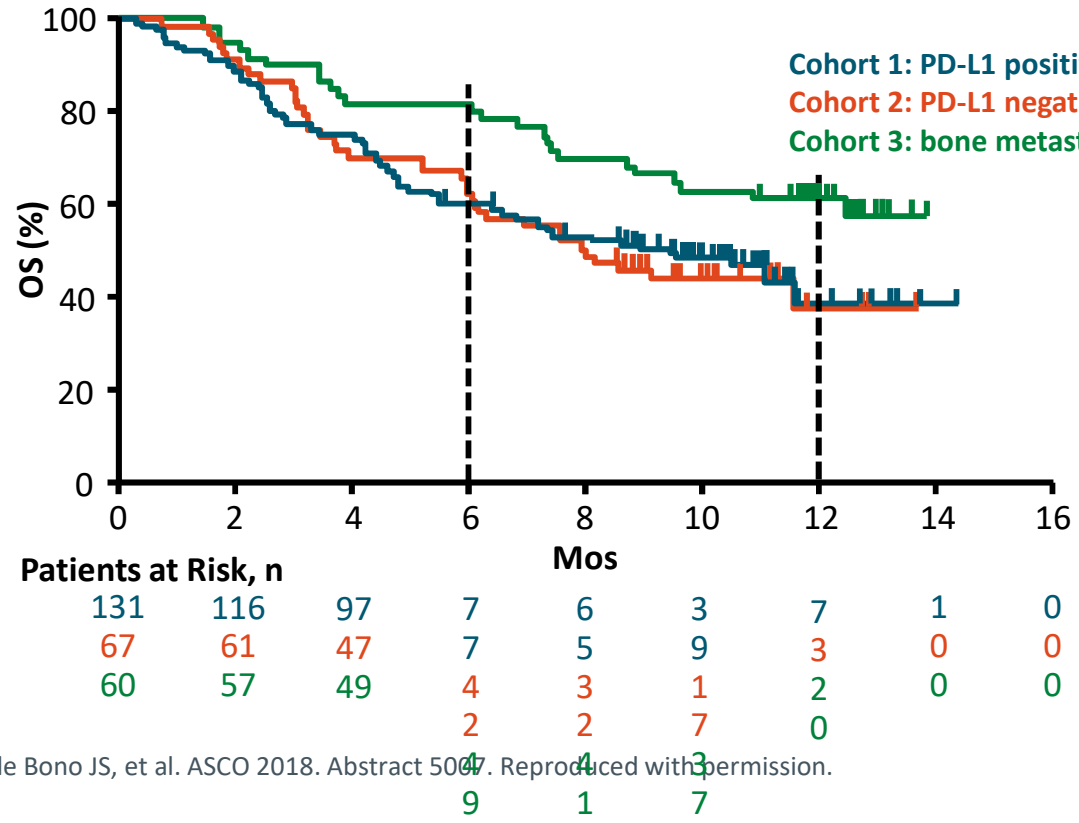
KEYNOTE-199: Response

Response Outcome	Cohort 1: PD-L1 Positive (n = 131)	Cohort 2: PD-L1 Negative (n = 67)	Cohort 3: Bone Metastases (n = 60)	Cohorts 1 + 2 (n = 198)	Cohorts 1 + 2 + 3 (n = 258)
ORR,* n (%)	7 (5)¶	2 (3)¶	--	9 (5)¶	9 (4)
▪ CR	2 (2)	0	--	2 (1)	2 (< 1)
▪ PR	5 (4)	2 (3)	--	7 (4)	7 (3)
▪ SD (any duration)	22 (17)	14 (21)	--	36 (18)	36 (14)
▪ SD ≥ 6 mos	5 (4)	2 (3)	--	7 (4)	7 (3)
▪ Non-CR/non-PD†	0	0	22 (37)	0	22 (9)
▪ PD	76 (58)	42 (63)	33 (55)	118 (60)	151 (59)
▪ NE	4 (3)	1 (1)	1 (2)	5 (3)	6 (2)
▪ NA‡	22 (17)	8 (12)	4 (7)	30 (15)	34 (13)
DCR ≥ 6 mos,§ n (%)	12 (9)	4 (6)	13 (22)	16 (8)	29 (11)
mDoR, mos (range)	8.4 (1.9-10.6+)	NR (4.4-7.2+)	--	8.4 (1.9-10.6+)	--
Median follow-up, mos	8.1	7.9	11.8	--	--
Ongoing responses, %	11	9	12	--	--

*CR + PR by RECIST v1.1. †Patients with persistent existing lesions or who developed new lesions. ‡Patients with 1 post-BL assessment. §Patients with CR or PR of any duration, SD or non-CR/non-PR for ≥ 6 mos by RECIST v1.1. ¶Primary endpoint.

de Bono JS, et al. ASCO 2018. Abstract 5007.

KEYNOTE-199: OS by Cohort*



	Events, %	Median OS, Mos (95% CI)	6-Mo OS, %	12-Mo OS, %
Cohort 1: PD-L1 positive	53	9.5 (6.6-NR)	60	39
Cohort 2: PD-L1 negative	57	8.0 (5.9-NR)	63	38
Cohort 3: bone metastases	40	NR (9.6-NR)	82	61

*Distinct cohorts, not a randomized comparison.

de Bono JS, et al. ASCO 2018. Abstract 5007. Reproduced with permission.

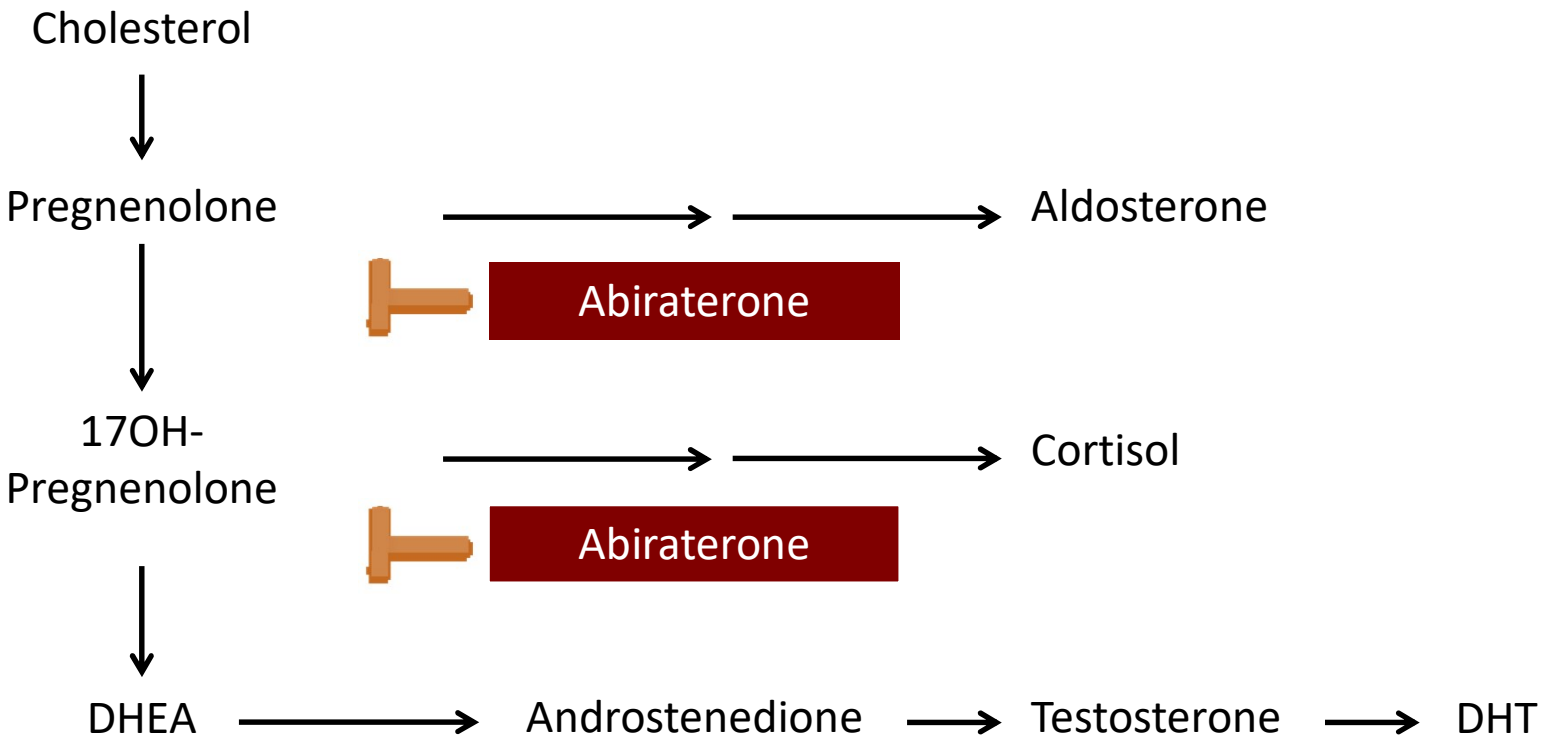
KEYNOTE-199: Response by Somatic DNA Aberration (Cohorts 1 + 2 + 3)

Response Outcome, n (%)	*BRCA1/2* or *ATM* (n = 19)	Other DDR Genes* (n = 10)	Negative (n = 124)
ORR	2 (11)	0	4 (3)
▪ CR	0	0	2 (2)
▪ PR	2 (11)	0	2 (2)
▪ SD (any duration)	2 (11)	2 (20)	18 (15)
▪ PD	12 (63)	5 (50)	80 (65)
DCR (any duration)	4 (22)	0	22 (18)
PSA responders	2 (11)	1 (10)	4 (3)

**BARD1, BRIP1, CDK12, CHEK1, CHEK1, FANCL, PALB2, PPP2R2A, RAD51C, RAD51B, AD51D, RAD54L.*

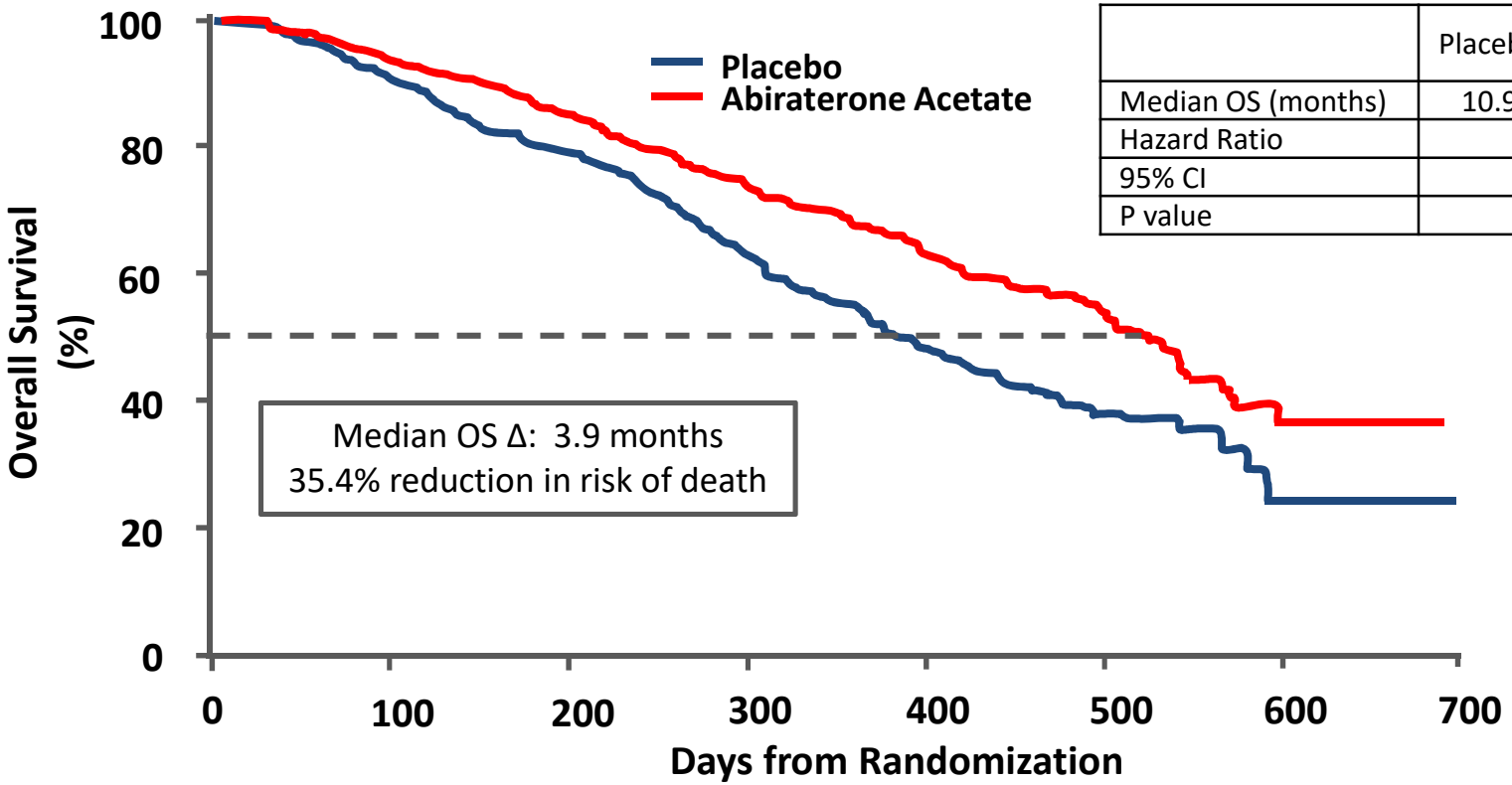
de Bono JS, et al. ASCO 2018. Abstract 5007.

Abiraterone Acetate: Androgen Biosynthesis Inhibitor



Androgens

COU 301: Overall Survival



	Placebo	Abiraterone Acetate
Median OS (months)	10.9	14.8
Hazard Ratio	0.65	
95% CI	0.54-0.77	
P value	<0.001	

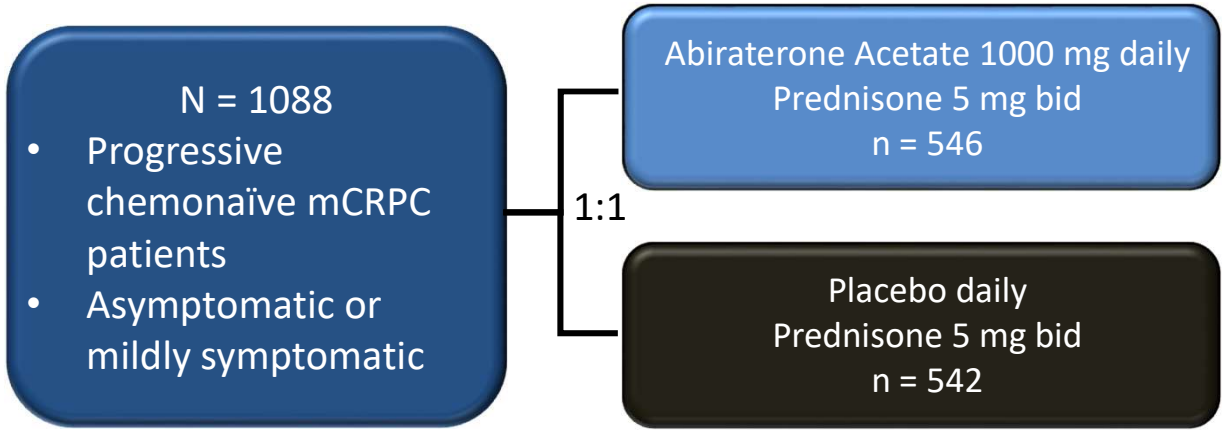
2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo[1]

1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo[1]

Updated results: 4.6-month difference in median survival with abiraterone acetate[2]

1. de Bono JS, et al. *N Engl J Med.* 2011;364(21):1995-2005. 2. Fizazi K, et al. European Multidisciplinary Cancer Congress; 2011. Abstract 7000.

COU 302: Abiraterone Acetate Phase III Trial in Chemonaïve mCRPC



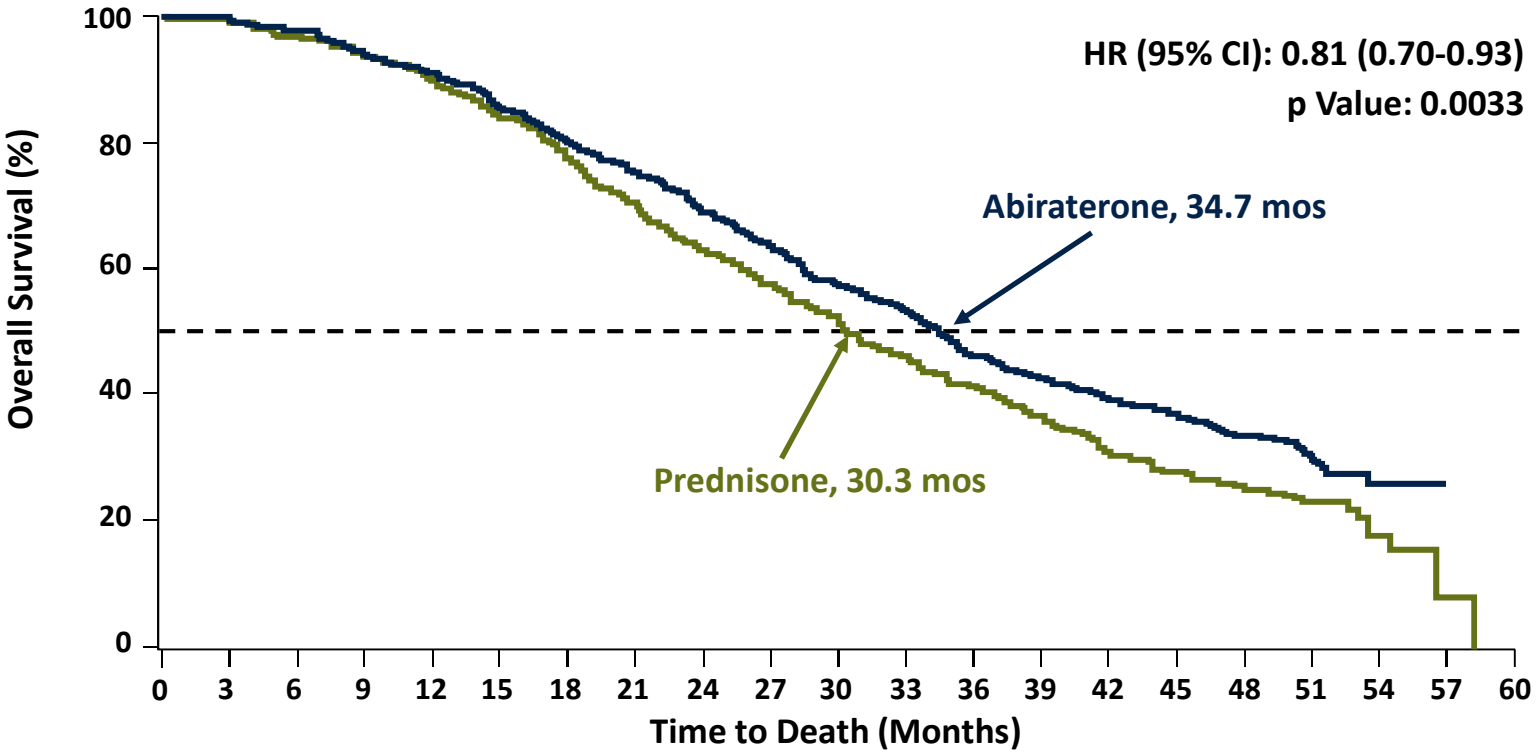
Primary Endpoints:
- Radiographic progression-free survival (rPFS) by central review
- OS

Secondary:
- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG PS deterioration
- Time to PSA progression

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

Saad F, et al. AUA 2013. Abstract 713

Ryan et al. Final Overall Survival Analysis of COU-AA-302, a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy

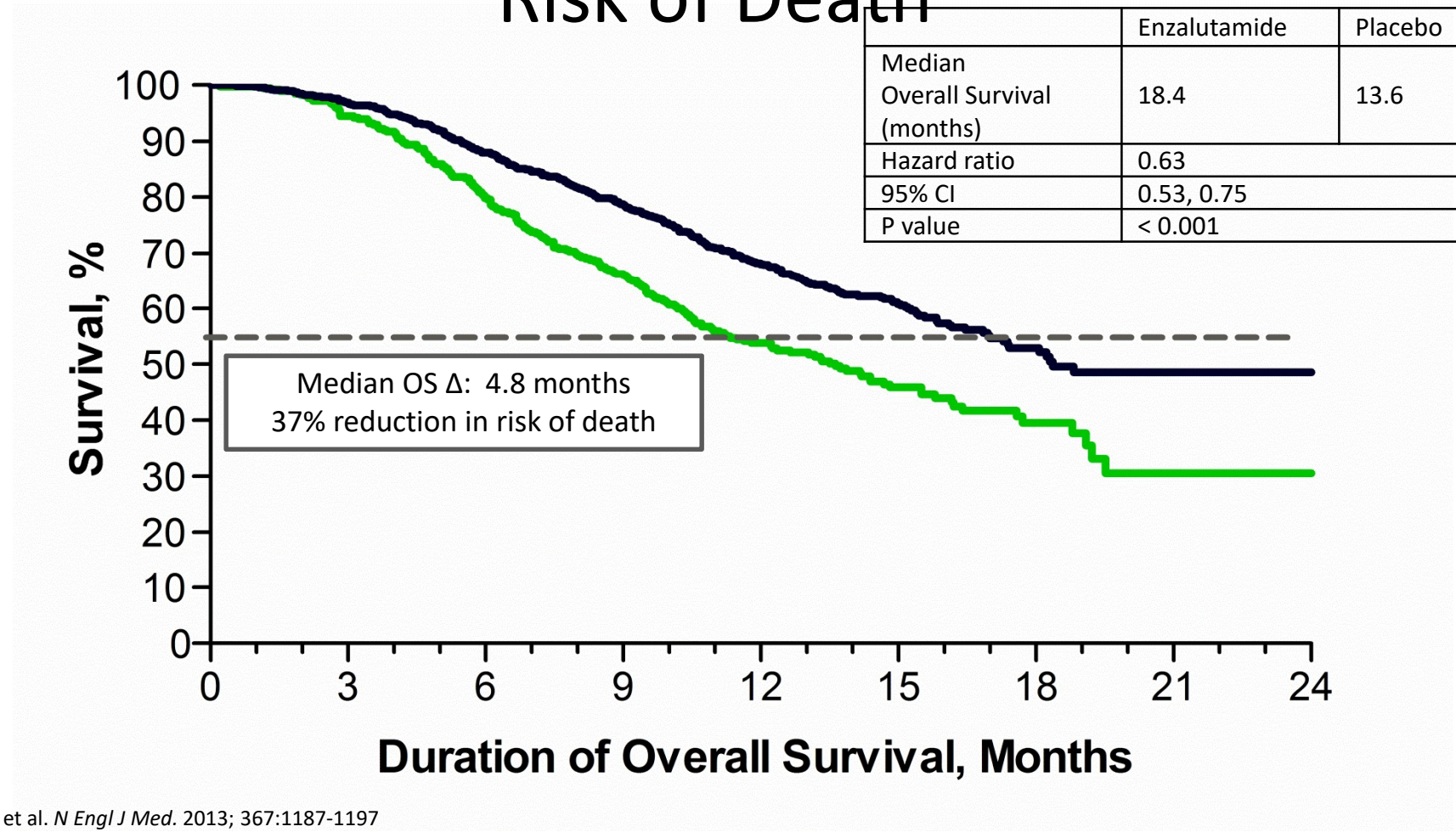


Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- Median follow-up of 49.2 mos
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

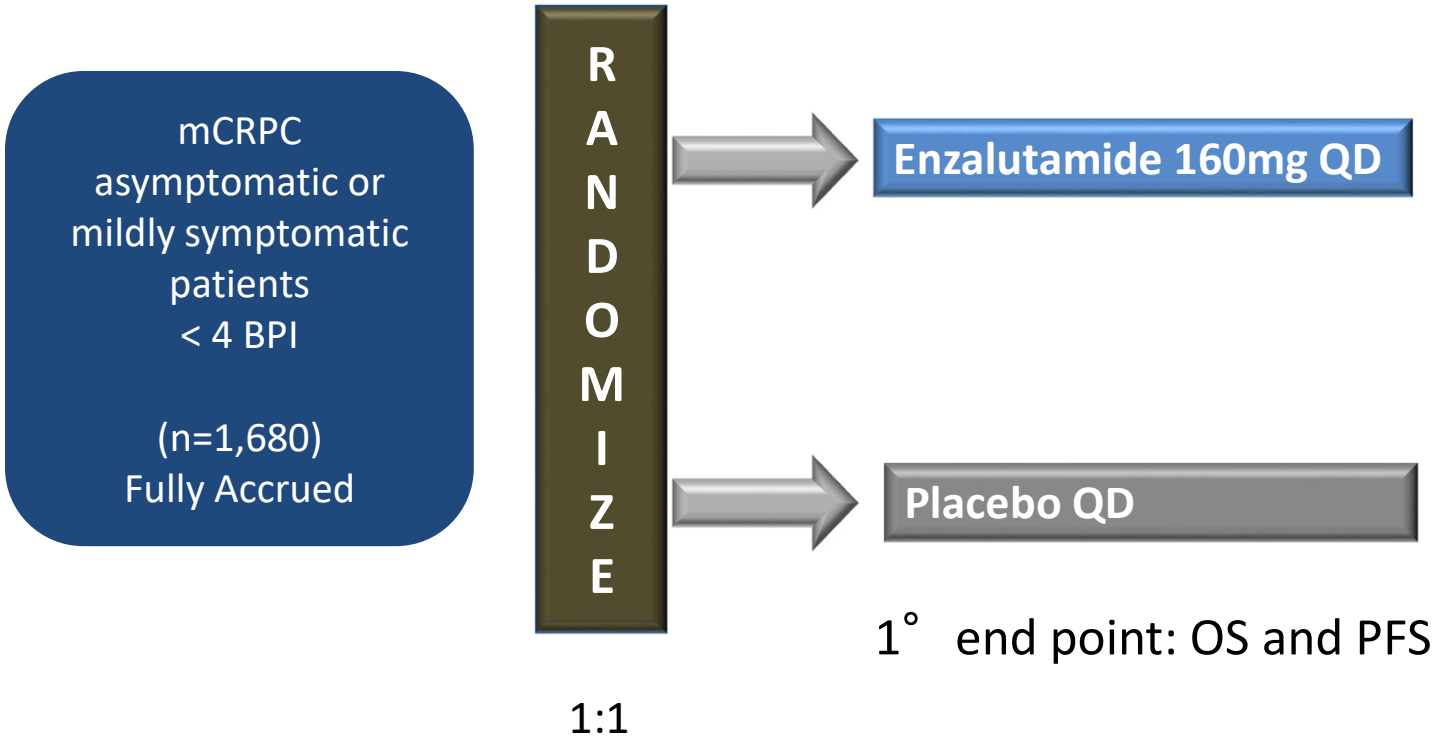
Enzalutamide Prolonged Survival, Reducing Risk of Death

	Enzalutamide	Placebo
Median Overall Survival (months)	18.4	13.6
Hazard ratio	0.63	
95% CI	0.53, 0.75	
P value	< 0.001	



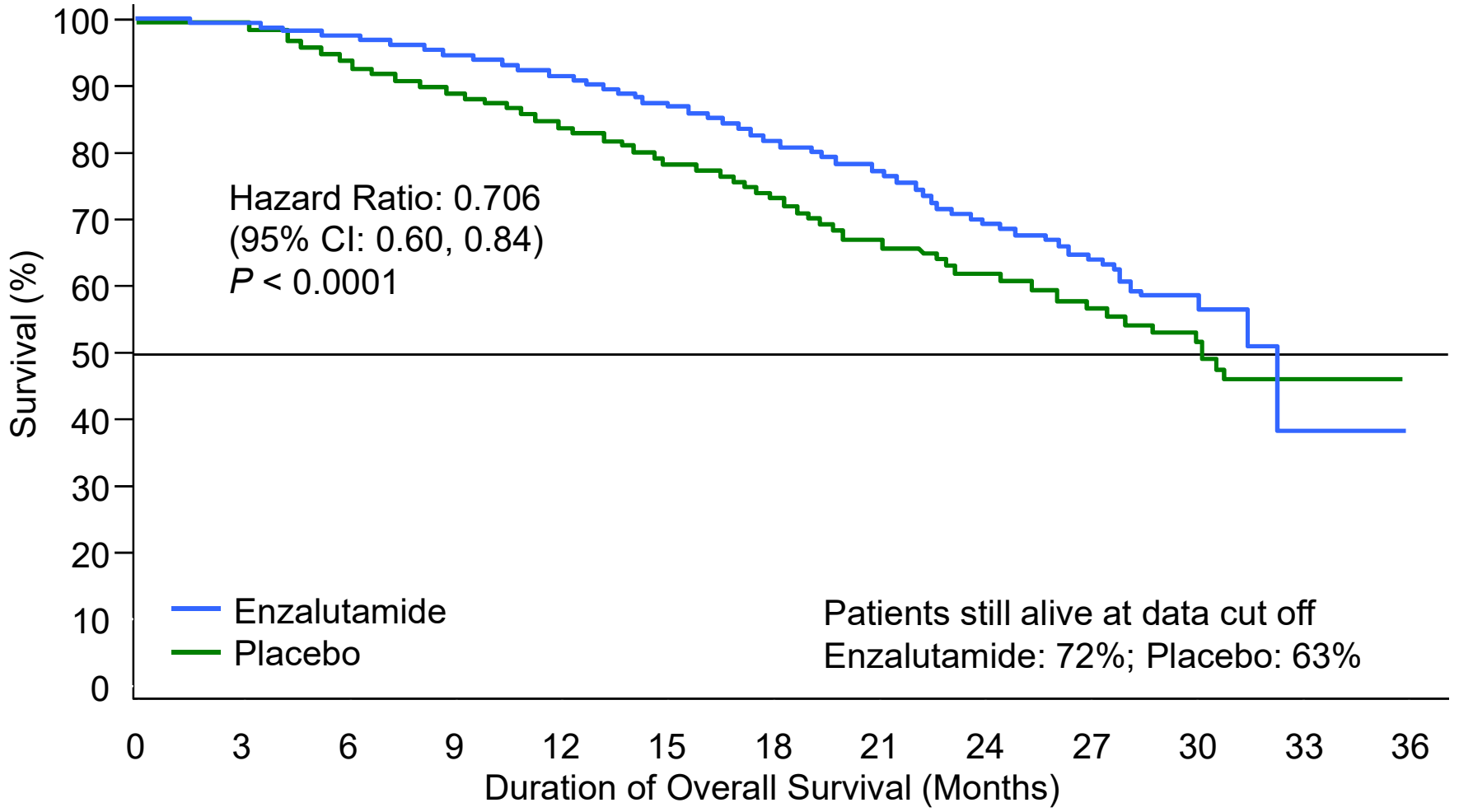
Scher HI, et al. *N Engl J Med*. 2013; 367:1187-1197

PREVAIL Phase III Trial of Enzalutamide in Asymptomatic or Mildly Symptomatic mCRPC Pre Chemotherapy



A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL) (NCT01212991). Available at www.clinicaltrials.gov. Accessed August 21, 2013.

PREVAIL: Overall Survival



Median OS: Enzalutamide, 32.4 Months; Placebo, 30.2 months

Beer T, et al. *J Clin Oncol*. 2014;32(suppl 4). Abstract LBA 1.

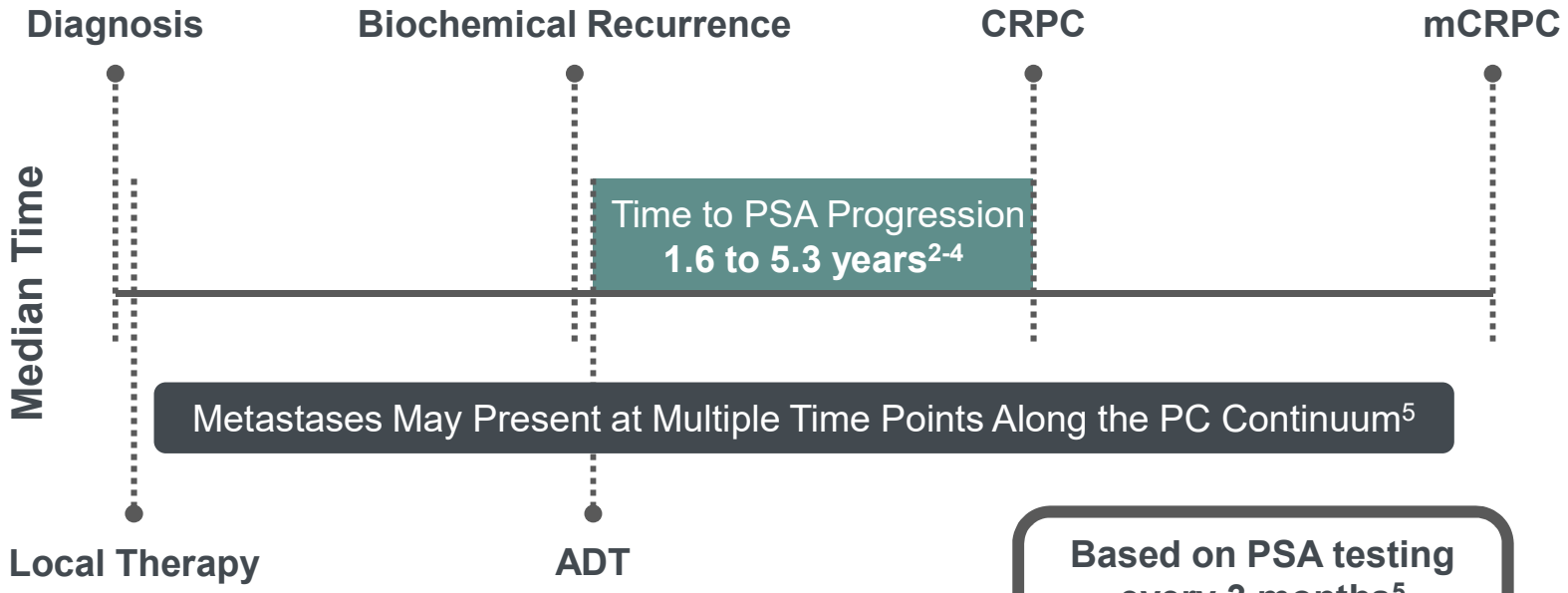
Antonarakis, et al **AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer**

AR-V7, the most important AR transcriptional variant, is expressed at detectable levels in CTCs in a significant proportion of CRPC patients

Outcome	AR-V7[–] → AR-V7[–] (n=36)	AR-V7[–] → AR-V7[+] (n=6)	AR-V7[+] → AR-V7[+] (n=16)
PSA Response	68% (95%CI, 52 – 81%)	**17%** (95%CI, 4 – 58%)	0% (95%CI, 0 – 19%)
PSA Progression-Free Survival	6.1 months (95%CI, 5.9 mo – NR)	**3.0 months** (95%CI, 2.3 mo – NR)	1.4 months (95%CI, 0.9 – 2.6 mo)
Progression-Free Survival	6.5 months (95%CI, 6.1 mo – NR)	**3.2 months** (95%CI, 3.1 mo – NR)	2.1 months (95%CI, 1.9 – 3.1 mo)

Biochemical Recurrence to CRPC

- Based on data from three retrospective studies involving >68,000 men with PC, 10% to 20% developed CRPC within 5 years of surgical or medical castration[1]



RADAR Recommendation for the Early Identification of Metastatic Disease[5]

For Biochemical Recurrent Patients:
Scan patients when their PSA is 5-10 ng/mL; if negative, re-scan when their PSA is 20 ng/mL and every doubling of PSA thereafter

1. Kirby M et al. Int J Clin Pract 2011;65(11):1180-92. **2.** Sharifi N et al. BJU Int 2005;96(7):985-9. **3.** Ross RW et al. Cancer 2008;112(6):1247-53. **4.** Oefelein MG et al. Urology 2002;60(1):120-4. **5.** Crawford ED et al. Urology 2014;83(8):664-9.

076-2170-PM 04/17

Characterization of CRPC population Based on a Systematic Review

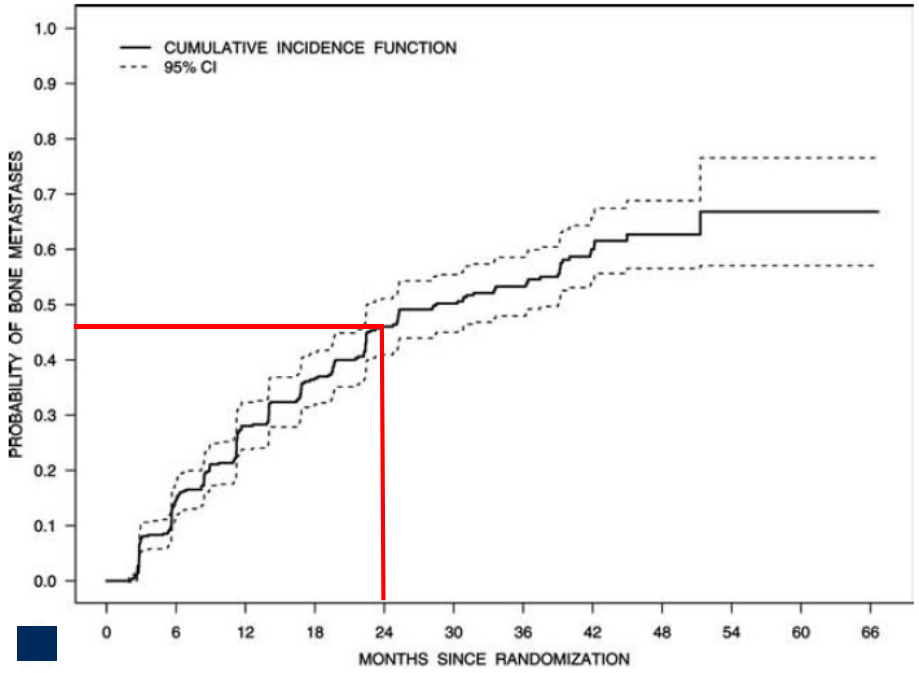
- CRPC is an advanced form of prostate cancer associated with frequent metastases, poor survival rates, poor quality of life, few therapeutic options

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.

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

Figure 1: IMAAGEN Study Design

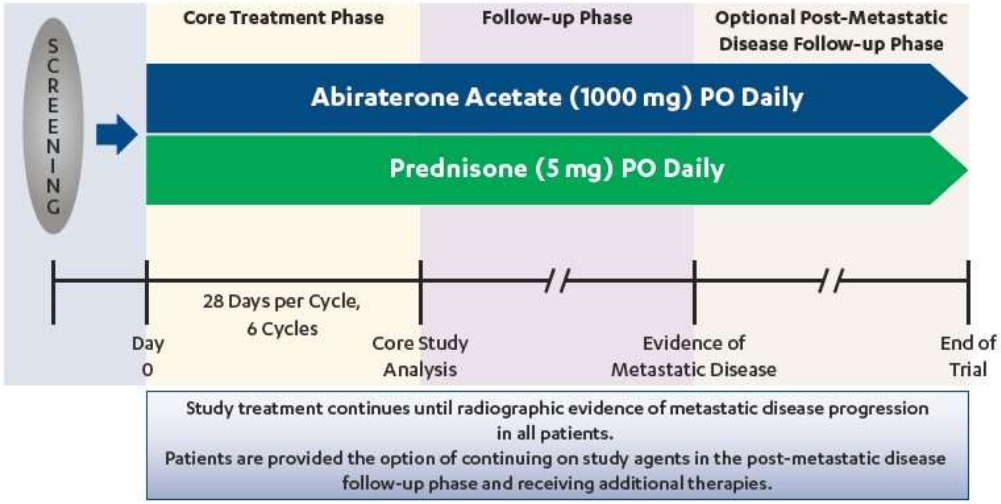


Table 2: PSA and PSADT at Screening

	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

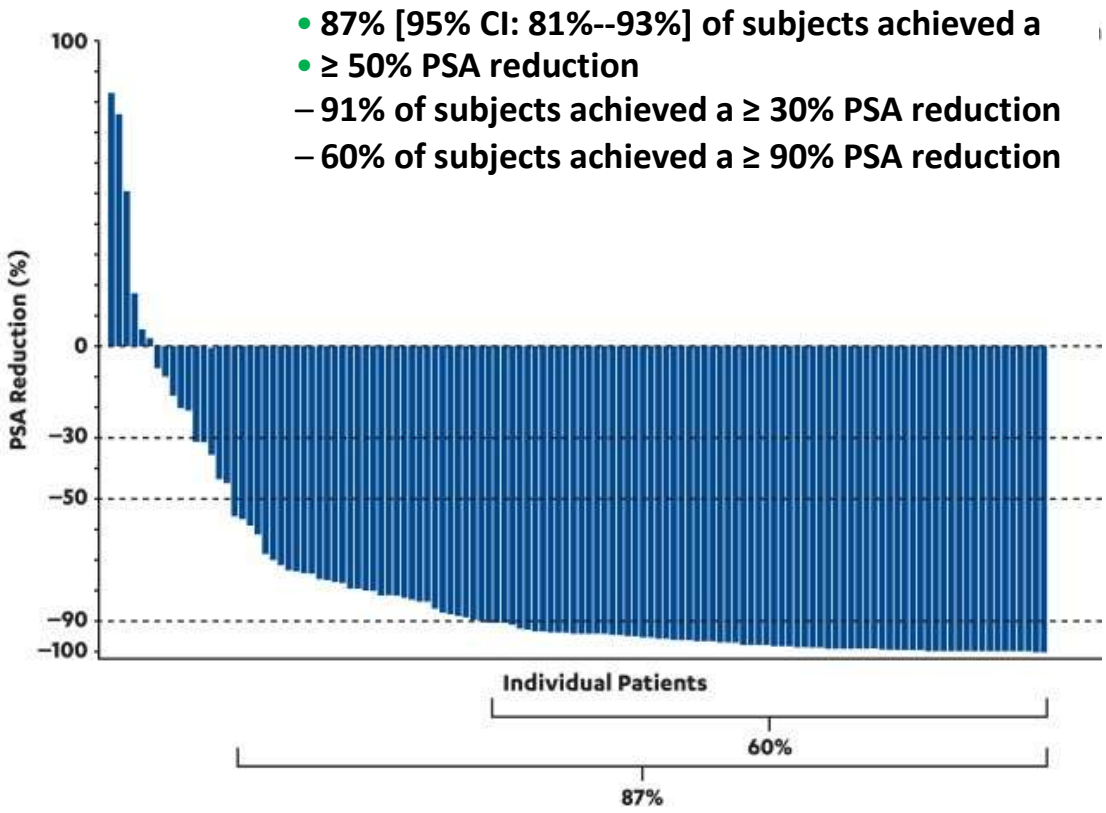
	Abiraterone Acetate Plus Prednisone (n=131)
Age, years	71.2 (48.0--90.0)
Mean, range	
Race, n (%)	108 (82.4)
White	19 (14.5)
Black or African American	2 (1.5)
Asian Other	1 (0.8)
Not Reported	1 (0.8)
Calculated Gleason Score, n (%)	
n*	125
< 7	17 (13.6)
7	59 (47.2)
> 8	49 (39.2)
Mean, SD Median Range	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

*n = Data for 6 subjects were not available at the Tme of the data base lock, 31Dec2013

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

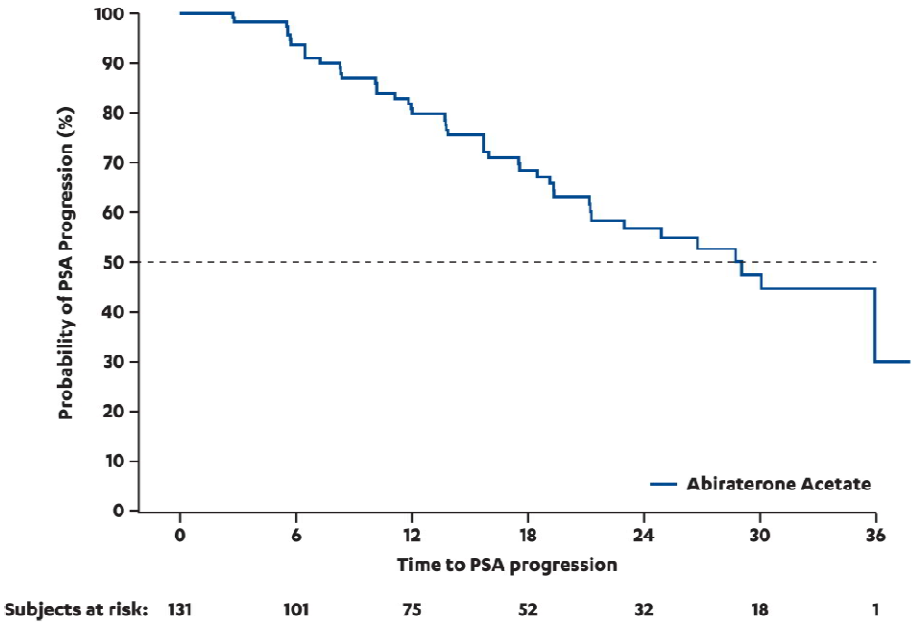
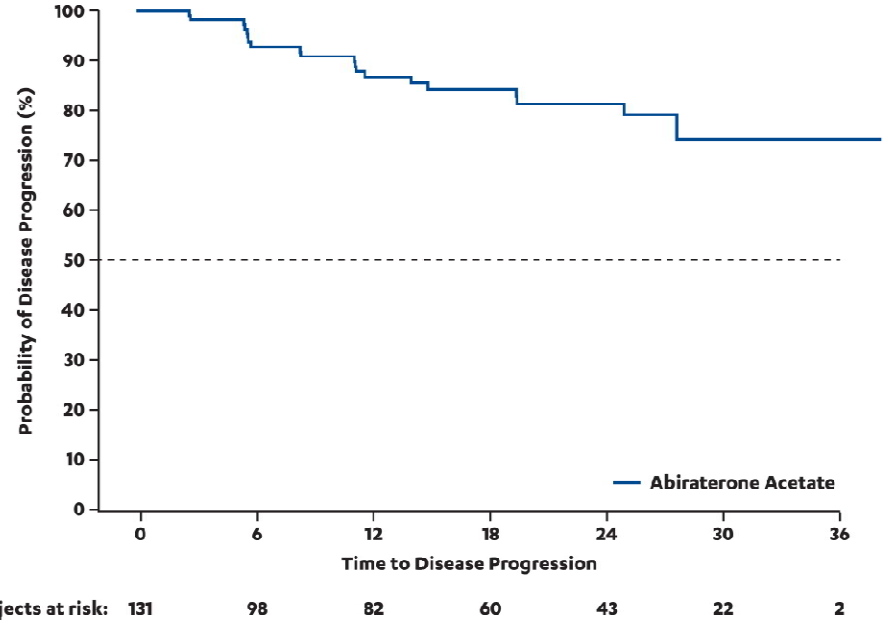
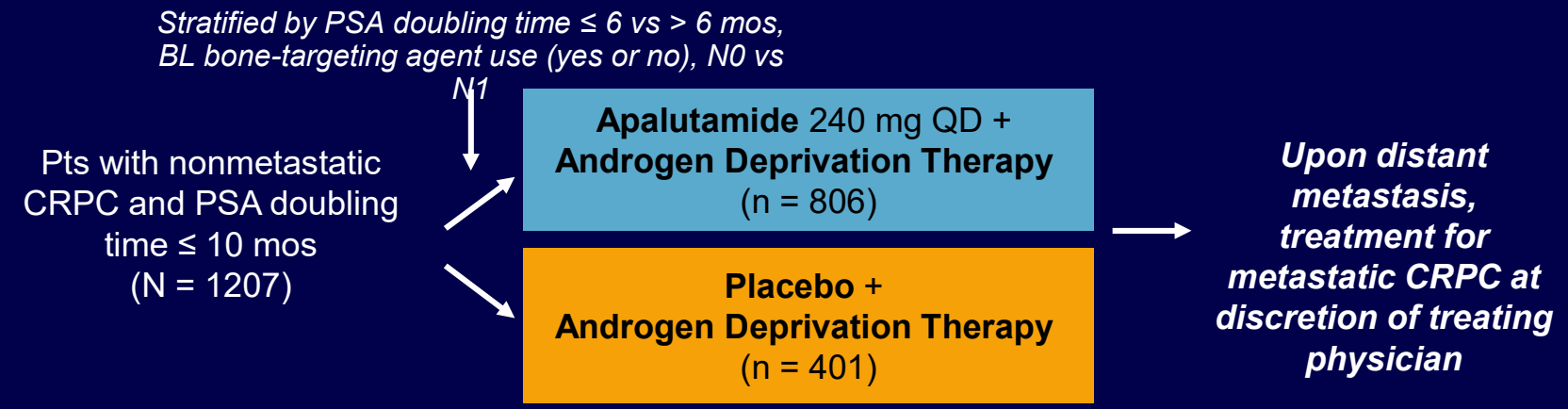


Figure 4: Radiographic Evidence of Disease Progression



Apalutamide vs Placebo in Nonmetastatic CRPC (SPARTAN): Phase III Study Design



- Primary endpoint: metastasis-free survival
- Secondary endpoints including: time to metastasis, PFS, time to symptomatic progression, OS, time to chemotherapy
- Exploratory endpoints: time to PSA progression, PSA response rate, PFS2, PRO

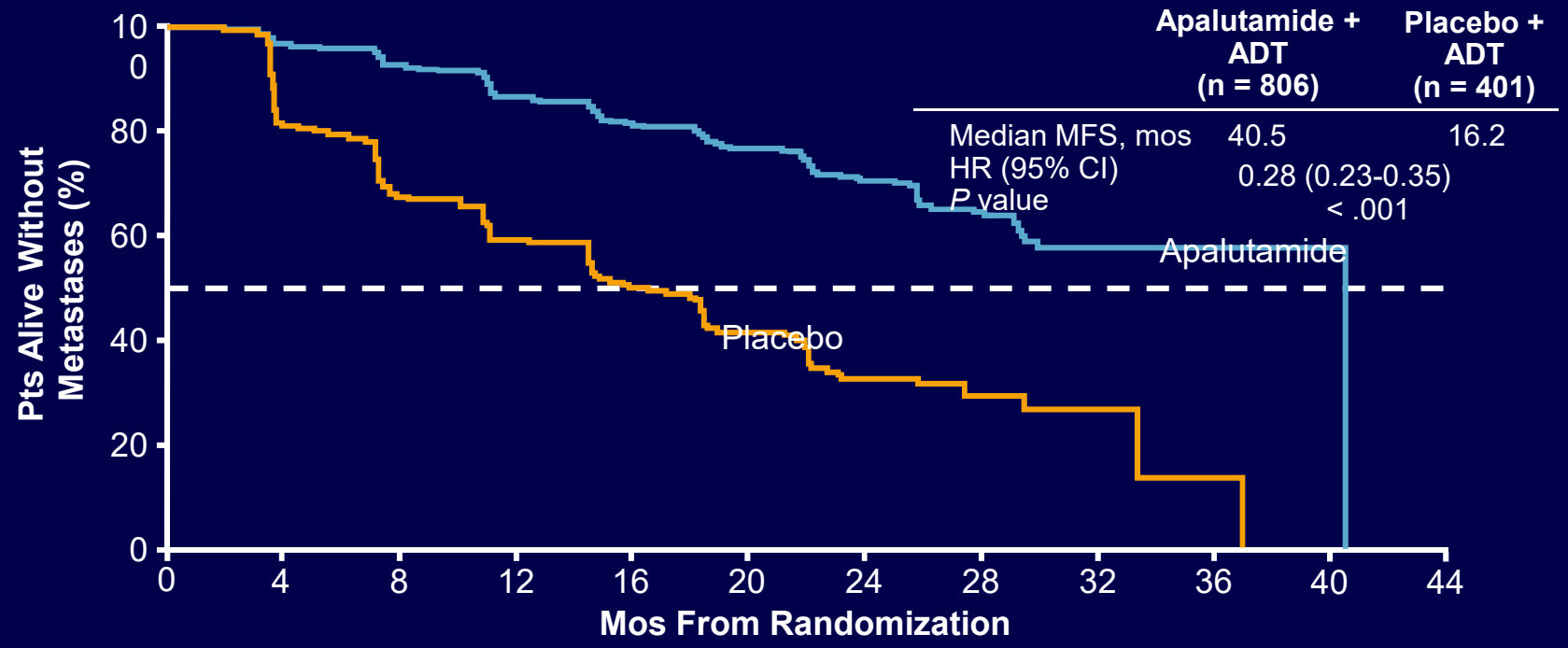
Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

SPARTAN: Baseline Characteristics

Characteristic	Apalutamide + ADT (n = 806)	Placebo + ADT (n = 401)
Median age, yrs (range)	74 (48-94)	74 (52-97)
Median time from diagnosis to randomization, yrs	7.95	7.85
Median PSA doubling time, mos	4.40	4.50
PSA doubling time, %		
▪ ≤ 6 mos	71.5	70.8
▪ > 6 mos	28.5	29.2
Baseline use of bone-targeting agent, %	10.2	9.7
Nodal status at entry, %		
▪ N0	83.5	83.8
▪ N1	16.5	16.2
Prior therapy, %		
▪ Definitive local therapy	76.6	76.6
▪ GnRH antagonist	96.8	96.5
▪ First-generation ADT	73.4	72.3

Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

SPARTAN: Metastasis-Free Survival (Primary Endpoint)



- MFS benefit with apalutamide observed for all pt subgroups analyzed

Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

SPARTAN: Subsequent Treatment Following Discontinuation

Treatment	Apalutamide + ADT (n = 803*)	Placebo + ADT (n = 398*)
Discontinued study treatment, n (%)	314 (39.1)	279 (70.1)
Received approved therapy† for mCRPC, n/N (%)	165/314 (52.5)	217/279 (77.8)
First subsequent approved treatment, n		
▪ Abiraterone acetate + prednisone	125	161
▪ Enzalutamide	20	28
▪ Docetaxel	15	18
▪ Cabazitaxel	0	1
▪ Sipuleucel-T	4	9
▪ Radium-223	1	0

*3 pts did not receive study treatment. †Agents associated with improved OS.

- Of pts who discontinued study treatment, 46% (145/314) in apalutamide arm and 68% (189/279) in placebo arm received an androgen signaling inhibitor

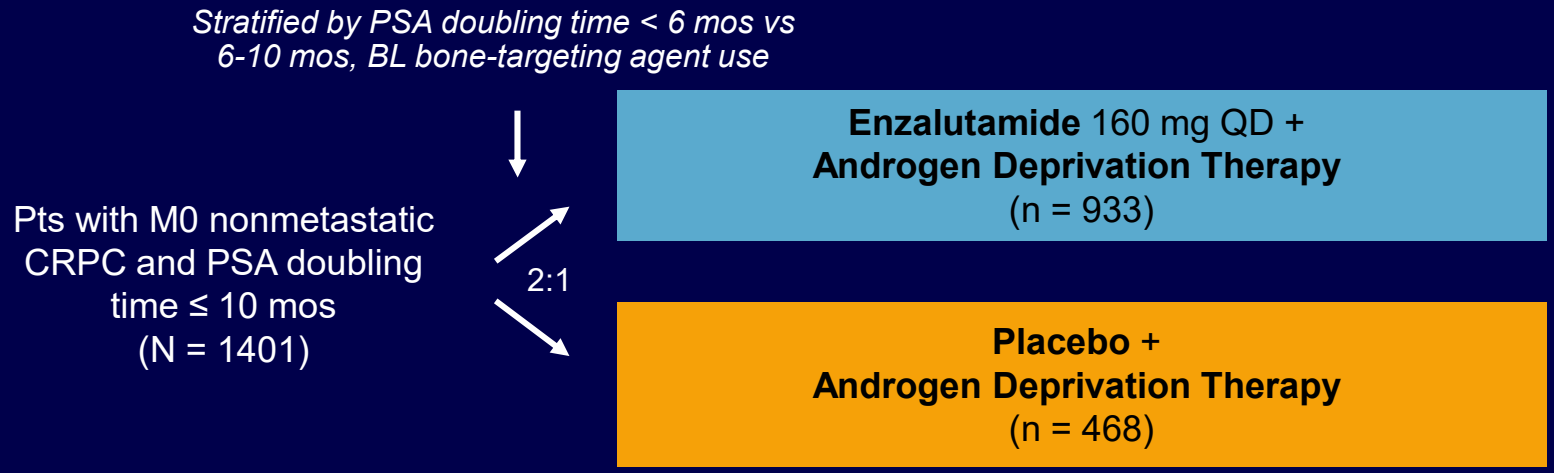
Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

SPARTAN: Conclusions

- In men with high-risk nonmetastatic CRPC, apalutamide prolonged metastasis-free survival by just over 2 yrs compared with placebo
  - MFS benefit with apalutamide observed for all pt subgroups tested
- Apalutamide also improved time to metastasis, PFS, time to symptomatic progression, time to PSA progression, and PSA response rate as compared with placebo
- Apalutamide with ADT was well tolerated
- Apalutamide is FDA approved for pts with nonmetastatic CRPC based on these results

Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

Enzalutamide vs Placebo in Nonmetastatic CRPC (PROSPER): Phase III Study Design



- Primary endpoint: metastasis-free survival
- Secondary endpoints including: safety, time to PSA progression, time to next therapy, OS, PSA response, QoL

Hussain M, et al. ASCO GU 2018. Abstract 3.

Slide credit: clinicaloptions.com

PROSPER: Baseline Characteristics

Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age, yrs (range)	74 (50-95)	73 (53-92)
ECOG PS, %		
▪ 0	80	82
▪ 1	20	18
Median serum PSA, ng/mL (range)	11.1 (0.8-1071.1)	10.2 (0.2-467.5)
Median PSA doubling time, mos (range)	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time, %		
▪ < 6 mos	77	77
▪ ≥ 6 mos	23	23
Baseline use of bone-targeting agent, %	11	10

Hussain M, et al. ASCO GU 2018. Abstract 3.

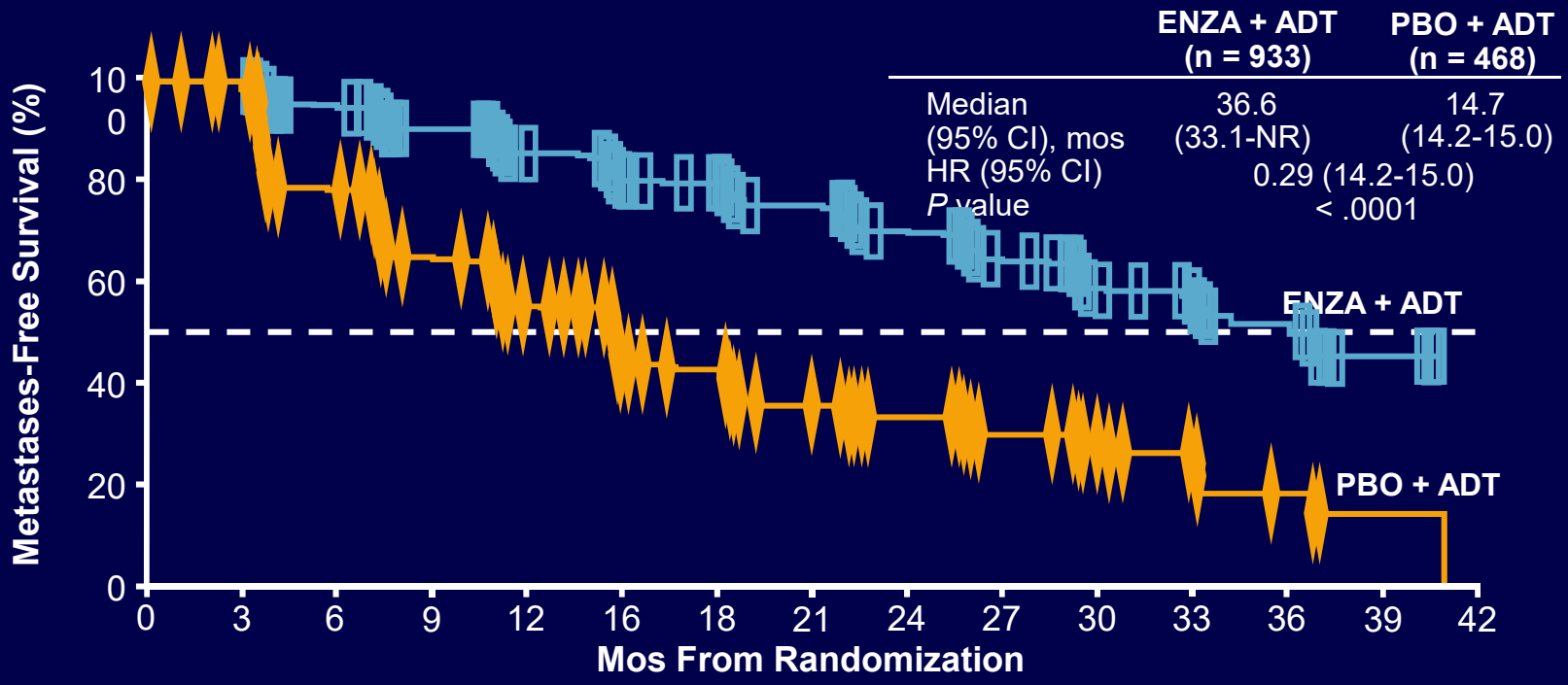
PROSPER: Progression Events

Progression Event, %	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Any progression event	23	49
Radiographic progression*	85	98
▪ New bone metastases	32	35
▪ New soft tissue metastases	50	58
▪ Concurrent new bone and soft tissue metastases	3	6
Death without documented radiographic progression within 112 days of treatment discontinuation	15	2

*Based on total number of progression events in each arm (enzalutamide + ADT, n = 219; placebo + ADT, n = 228)

Hussain M, et al. ASCO GU 2018. Abstract 3.

PROSPER: Metastasis-Free Survival



- MFS favored enzalutamide + ADT over placebo + ADT in all pt subgroups analyzed

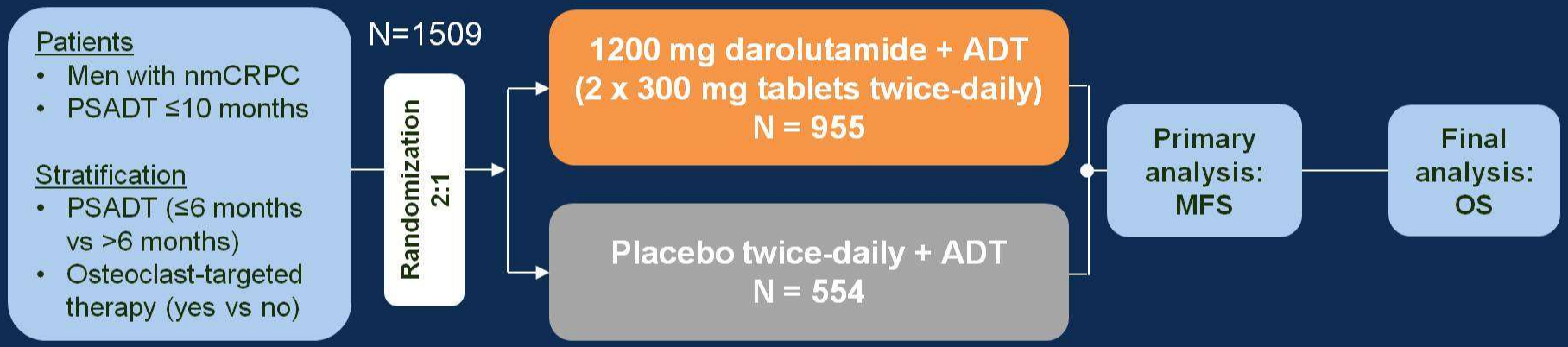
Hussain M, et al. ASCO GU 2018. Abstract 3.

PROSPER: Conclusions

- Enzalutamide + ADT reduced the risk of progression to metastatic CRPC by 71% compared with placebo + ADT in M0 CRPC pts with rapid PSA doubling time
  - Median MFS: 36.6 vs 14.7 mos with enzalutamide + ADT vs placebo + ADT (HR: 0.29; *P* < .0001)
- Treatment was generally well tolerated with toxicities as expected
- Enzalutamide also significantly prolonged time to PSA progression and time to first use of new antineoplastic therapy compared with placebo
- Median OS not reached in either treatment group with median follow-up of 22 mos

Hussain M, et al. ASCO GU 2018. Abstract 3.

ARAMIS trial design

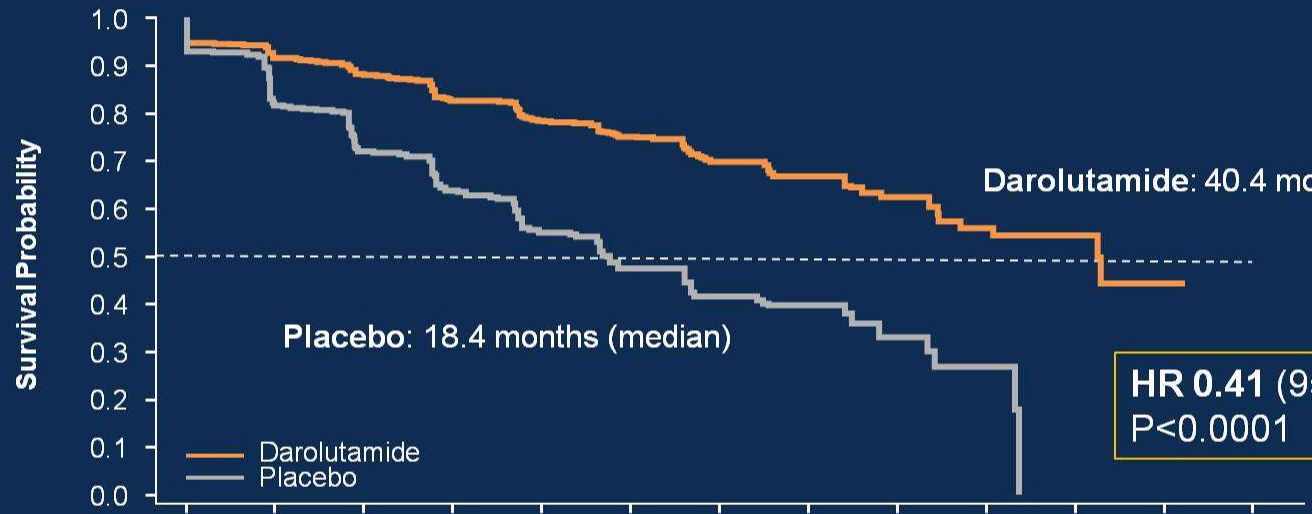


ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time.

Presented by: Karim Fizazi

Primary endpoint: Metastasis-free survival

59% risk reduction of distant metastases or death



HR 0.41 (95% CI 0.34–0.50)
P<0.0001

Number of subjects at risk

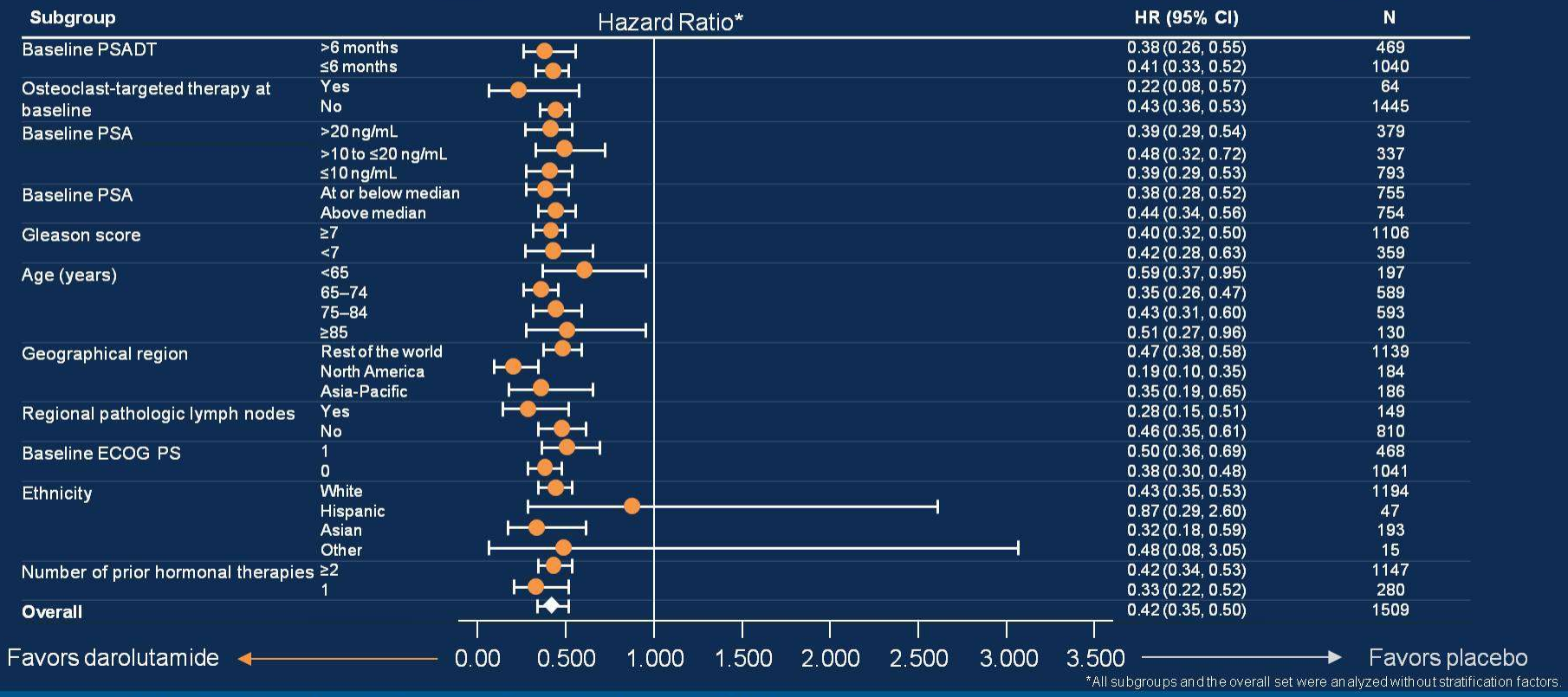
Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

Median follow-up time at primary analysis was 17.9 months

CI, confidence interval; HR, hazard ratio.

Presented by: Karim Fizazi

MFS benefit was consistent across subgroups



*All subgroups and the overall set were analyzed without stratification factors.

Presented by: Karim Fizazi

Secondary endpoints

Endpoint, median months	Darolutamide (N = 955)	Placebo (N = 554)	Hazard ratio (95% CI)	*P* value
Overall survival	NR (78)	NR (58)	0.71 (0.50–0.99)	0.0452
Time to pain progression	40.3 (251)	25.4 (178)	0.65 (0.53–0.79)	<0.0001
Time to cytotoxic chemotherapy	NR (73)	38.2 (79)	0.43 (0.31–0.60)	<0.0001
Time to first SSE	NR (16)	NR (18)	0.43 (0.22–0.84)	0.0113

CI, confidence interval; NR, not reached; SSE, symptomatic skeletal event.

Incidence of TEAEs

	Darolutamide (N = 954)		Placebo (N = 554)	
Adverse event, n (%)	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Any	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious	237 (24.8)	151 (15.8)	111 (20)	70 (12.6)
Discontinuation	85 (8.9)	32 (3.3)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0 (0)	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0 (0)	34 (6.1)	0 (0)
Pain in extremity	55 (5.8)	0 (0)	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0 (0)	23 (4.2)	0 (0)
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0 (0)
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

TEAE, treatment-emergent adverse event.

Presented by: Karim Fizazi

TEAEs of interest

Adverse event, all grades, n (%)	Darolutamide (N = 954)	Placebo (N = 554)
Fatigue/asthenic conditions	151 (15.8)	63 (11.4)
Dizziness (including vertigo)	43 (4.5)	22 (4.0)
Cognitive disorder	4 (0.4)	1 (0.2)
Memory impairment	5 (0.5)	7 (1.3)
Seizure (any event)	2 (0.2)	1 (0.2)
Bone fracture	40 (4.2)	20 (3.6)
Falls (including accident)	40 (4.2)	26 (4.7)
Hypertension	63 (6.6)	29 (5.2)
Coronary artery disorders	31 (3.2)	14 (2.5)
Heart failure	18 (1.9)	5 (0.9)
Rash	28 (2.9)	5 (0.9)
Weight decreased (any event)	34 (3.6)	12 (2.2)
Hypothyroidism	2 (0.2)	1 (0.2)

TEAE, treatment-emergent adverse event.

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

Chemohormonal 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)

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

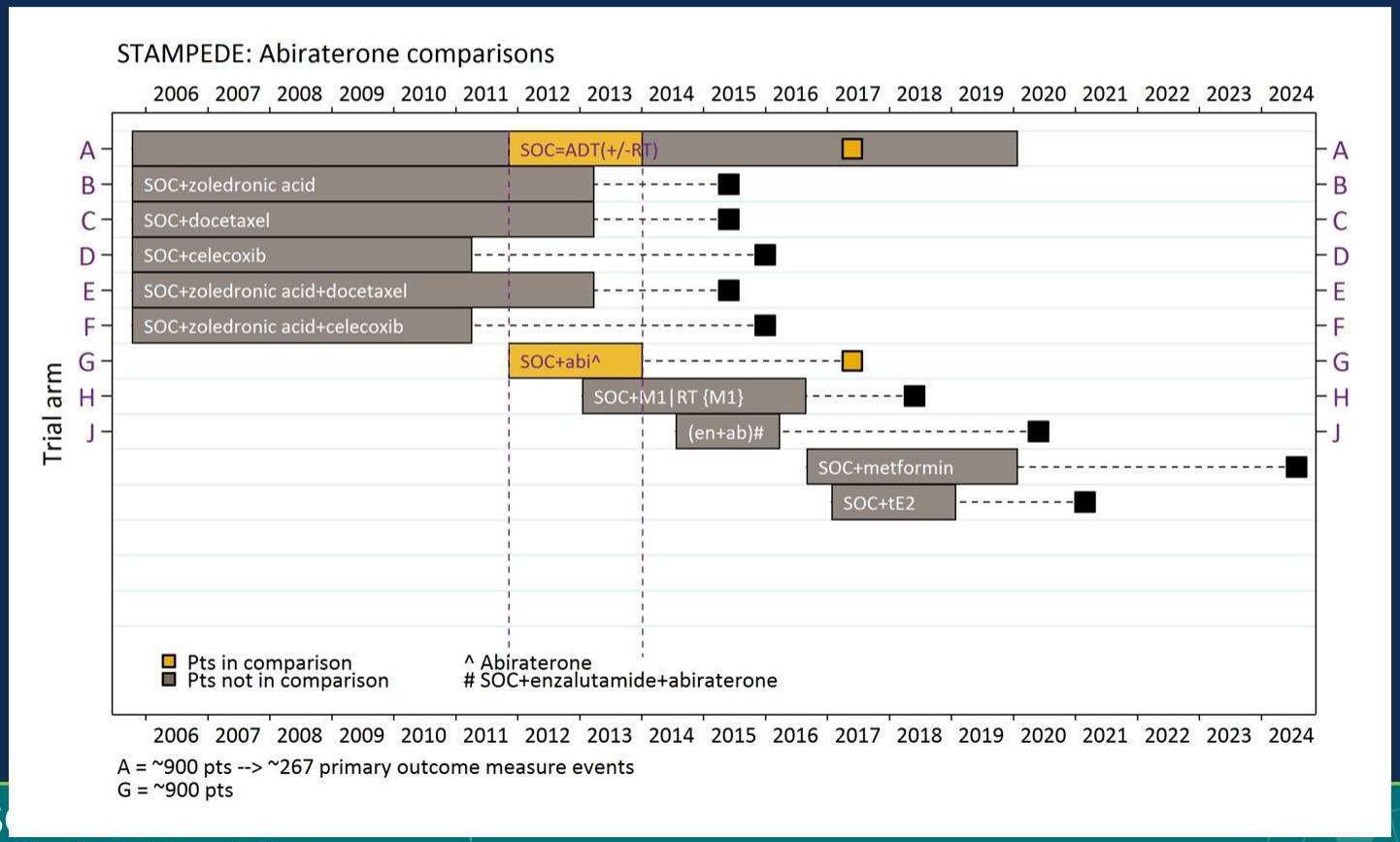
Nicholas James
University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

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

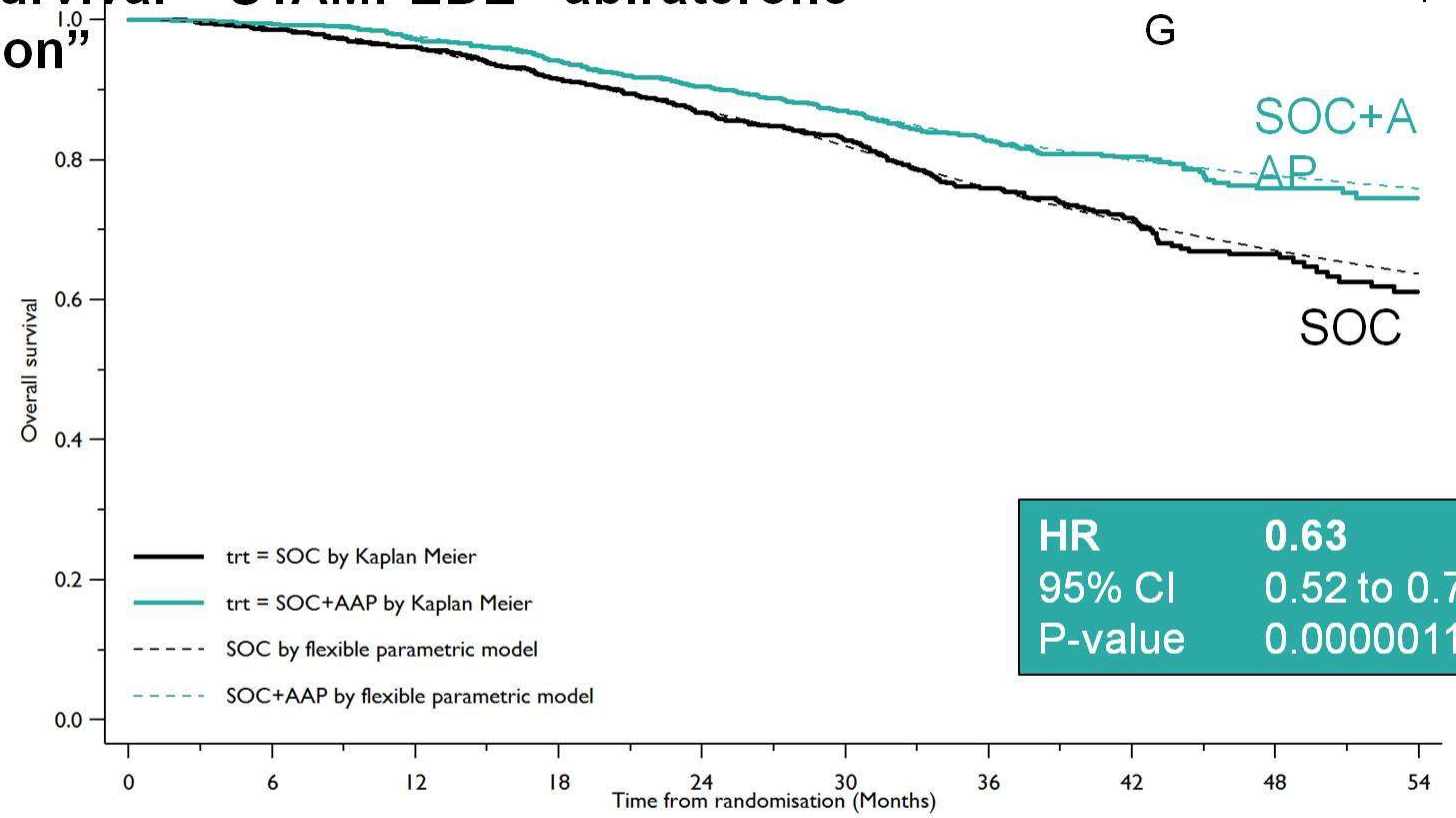
Presented By Charles Ryan at 2017 ASCO Annual Meeting

Abiraterone comparison: patients



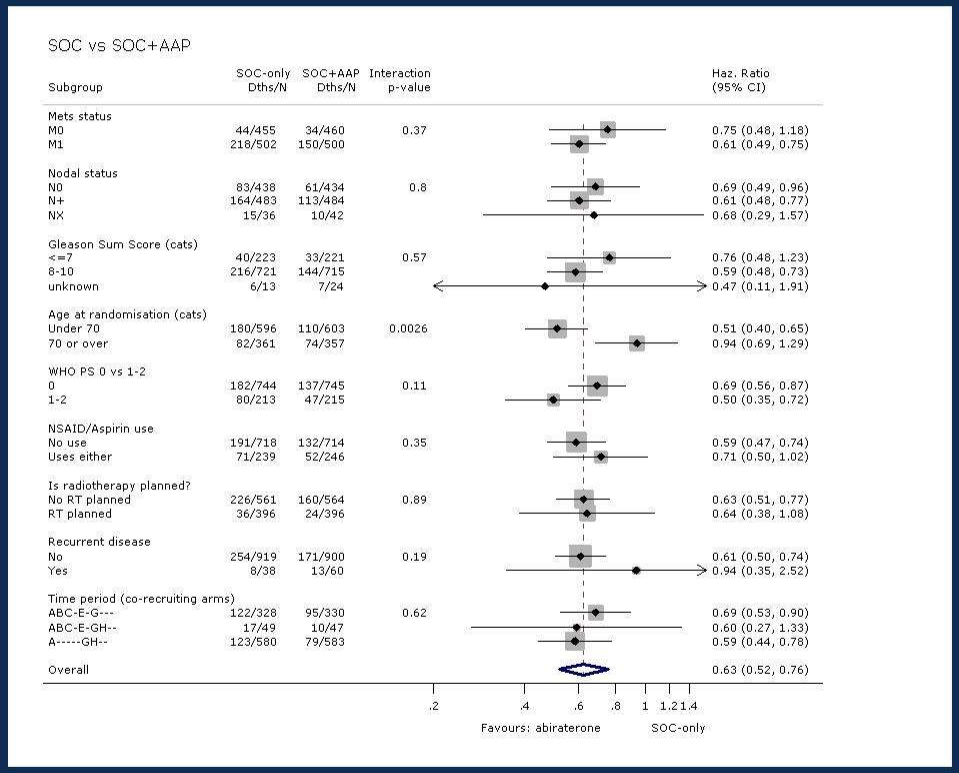
Overall Survival – STAMPEDE "abiraterone comparison"

Events 262 A | 184 G



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

Overall Survival – STAMPEDE "abiraterone comparison"



No good evidence of heterogeneity by stratification factors

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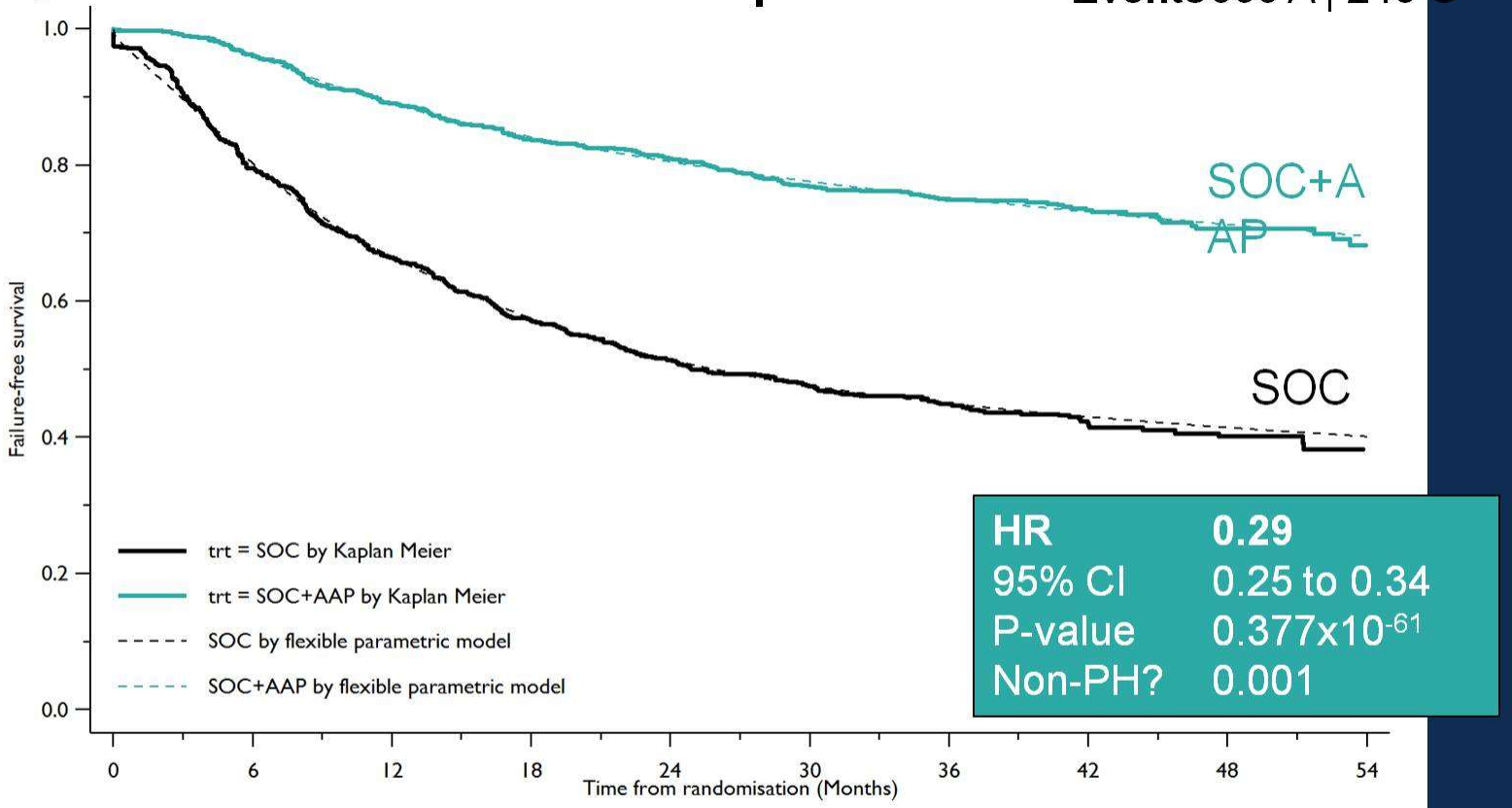
FFS – STAMPEDE "abiraterone comparison"

Events 535 A | 248 G



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

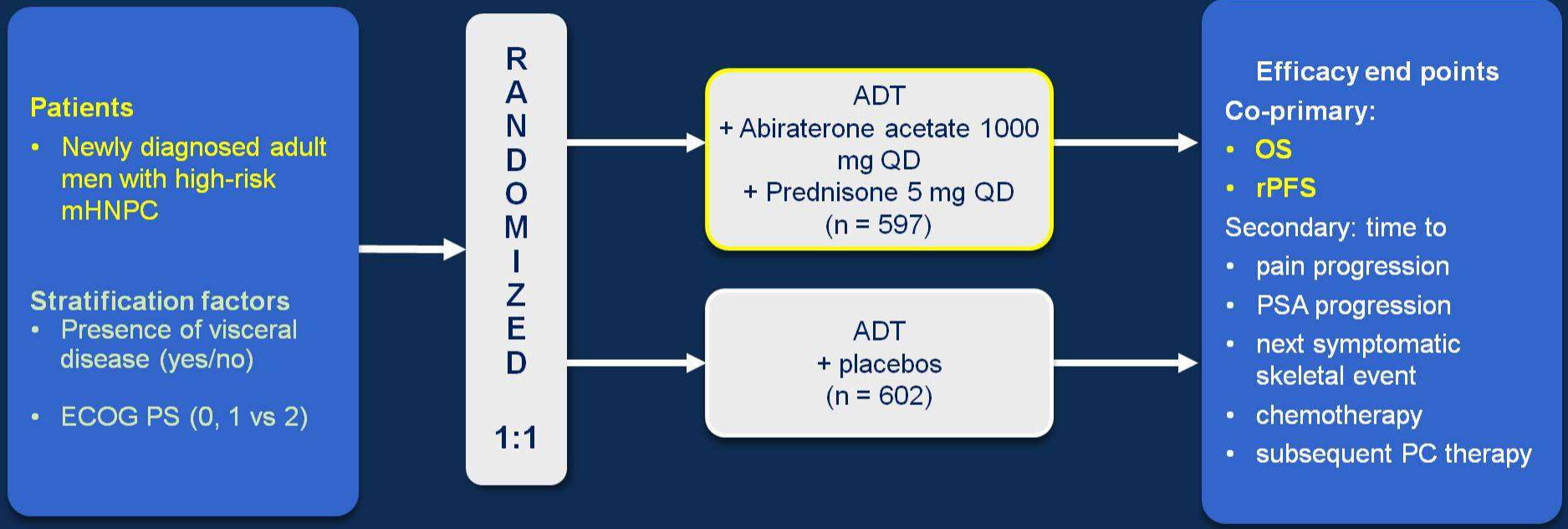
The administration of abiraterone is expected to be as follows:

- **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

Overall study design of LATITUDE



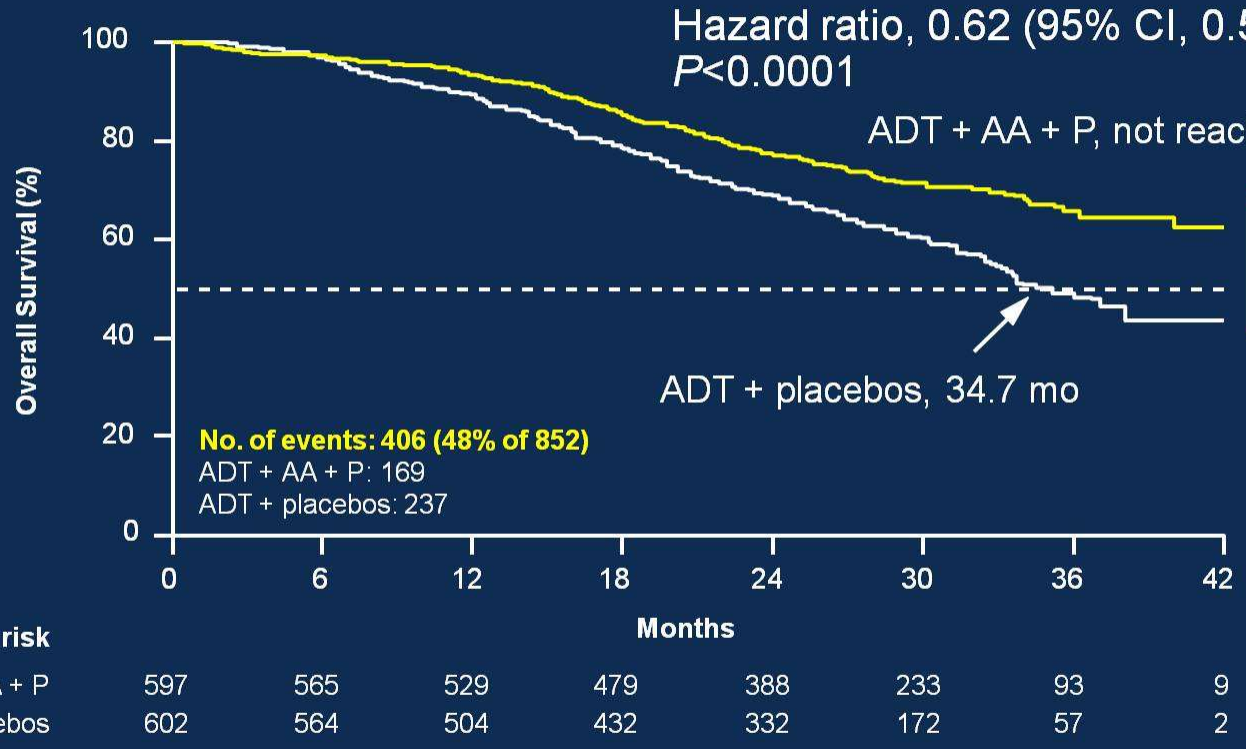
- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

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%

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

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

Presented By Karim Fizazi at 2017 ASCO Annual Meeting

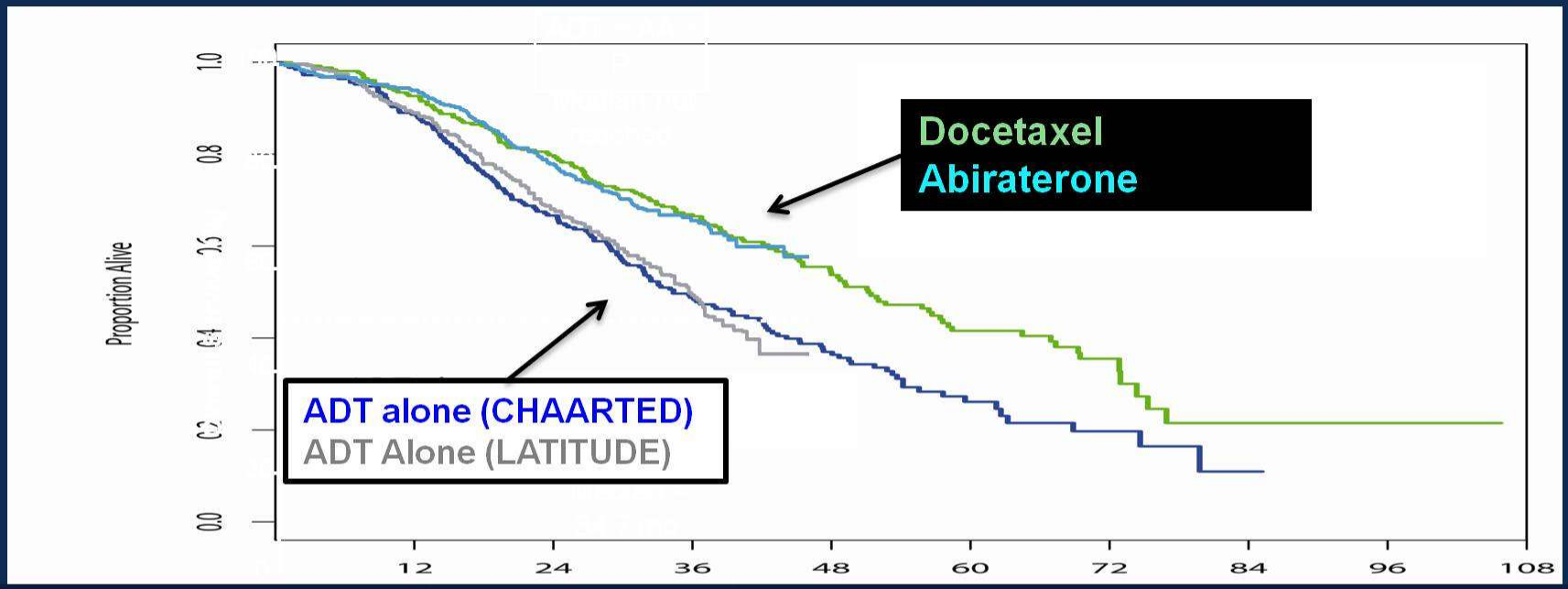
Docetaxel vs. Abiraterone

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%*

Presented By Eric Small at 2017 ASCO Annual Meeting

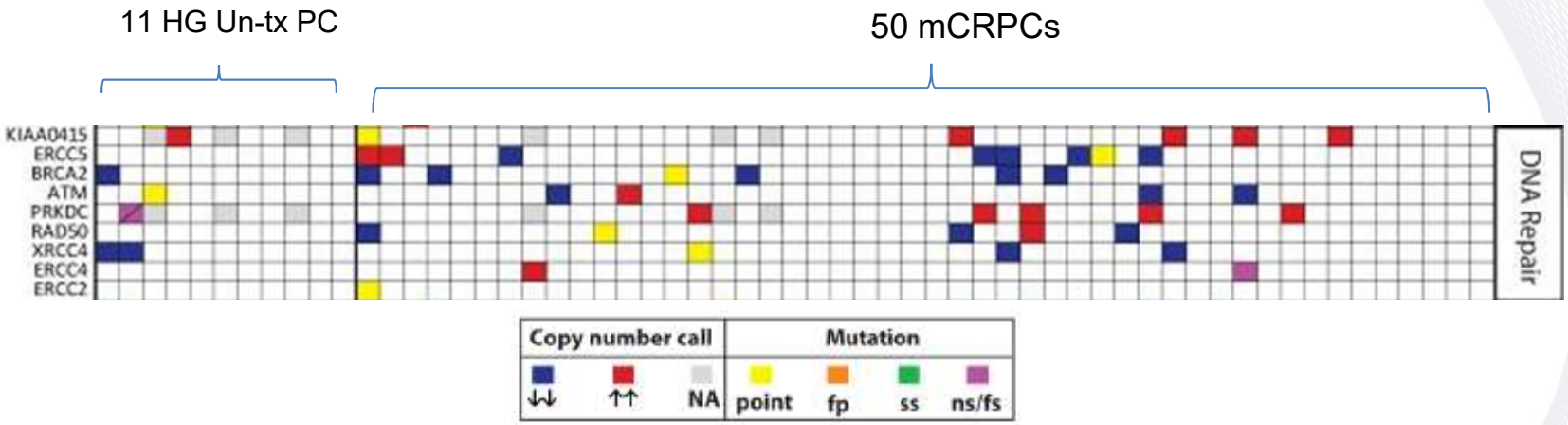
Docetaxel vs. Abiraterone



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

Selection of Treatment

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



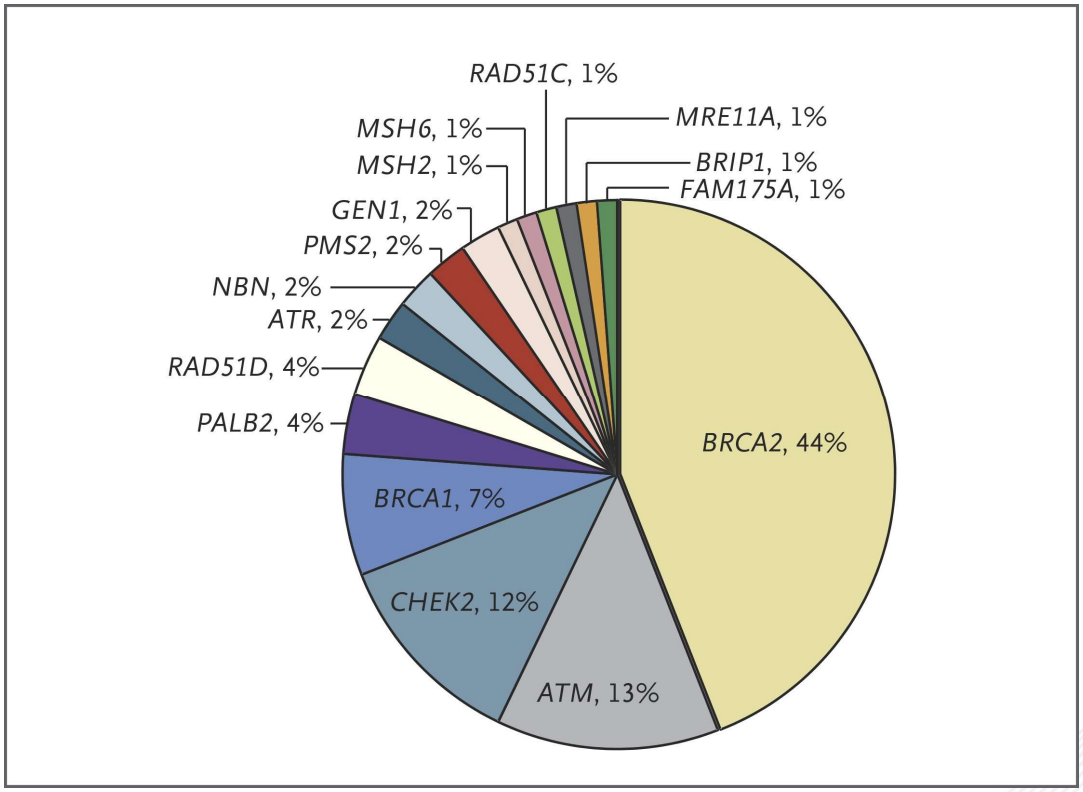
Approximately 50% (24 cases of mCRPC) with aberration in DNA repair genes

Grosso 2012. Nature

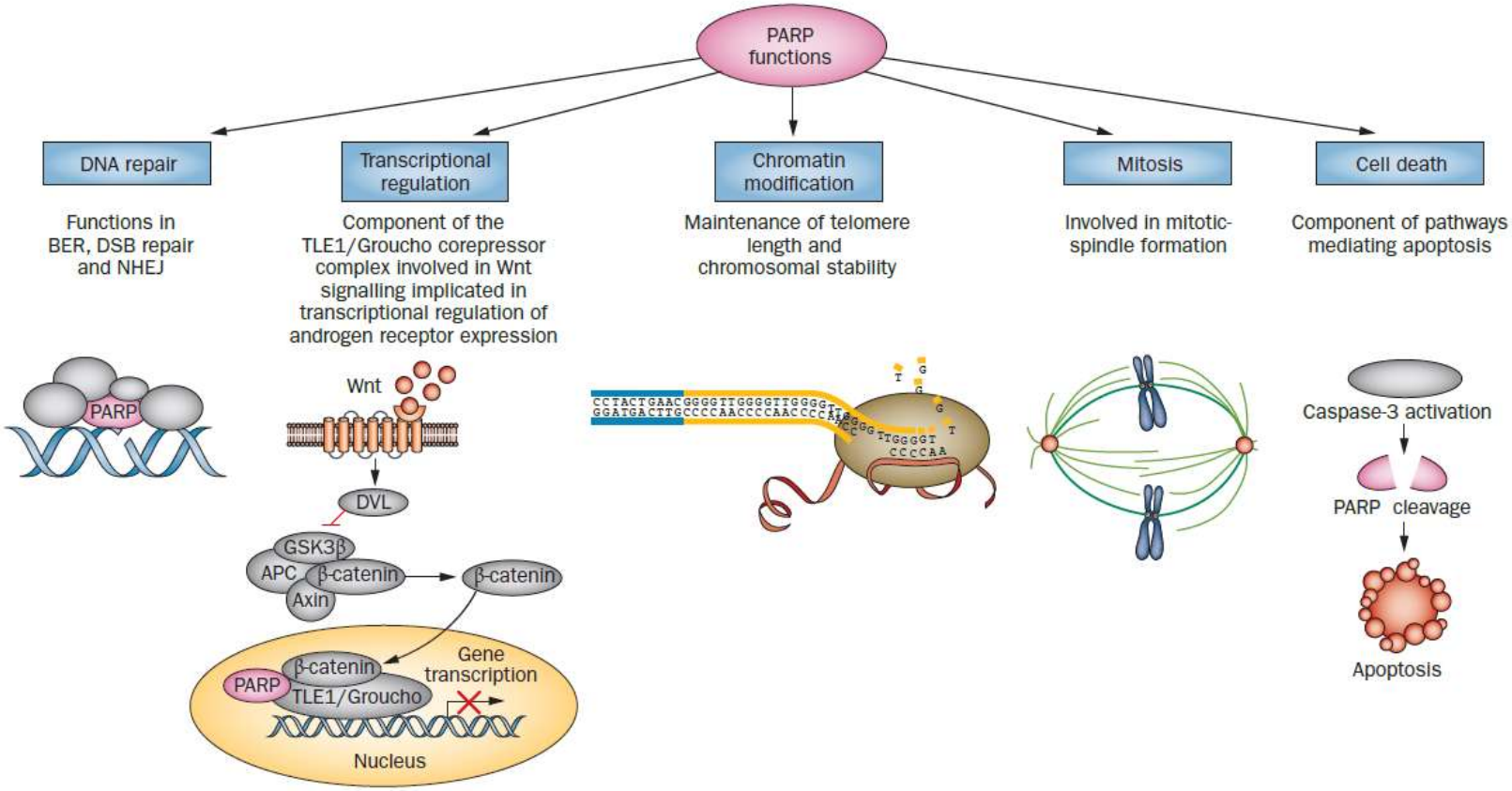
Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)

The NEW ENGLAND JOURNAL of MEDICINE

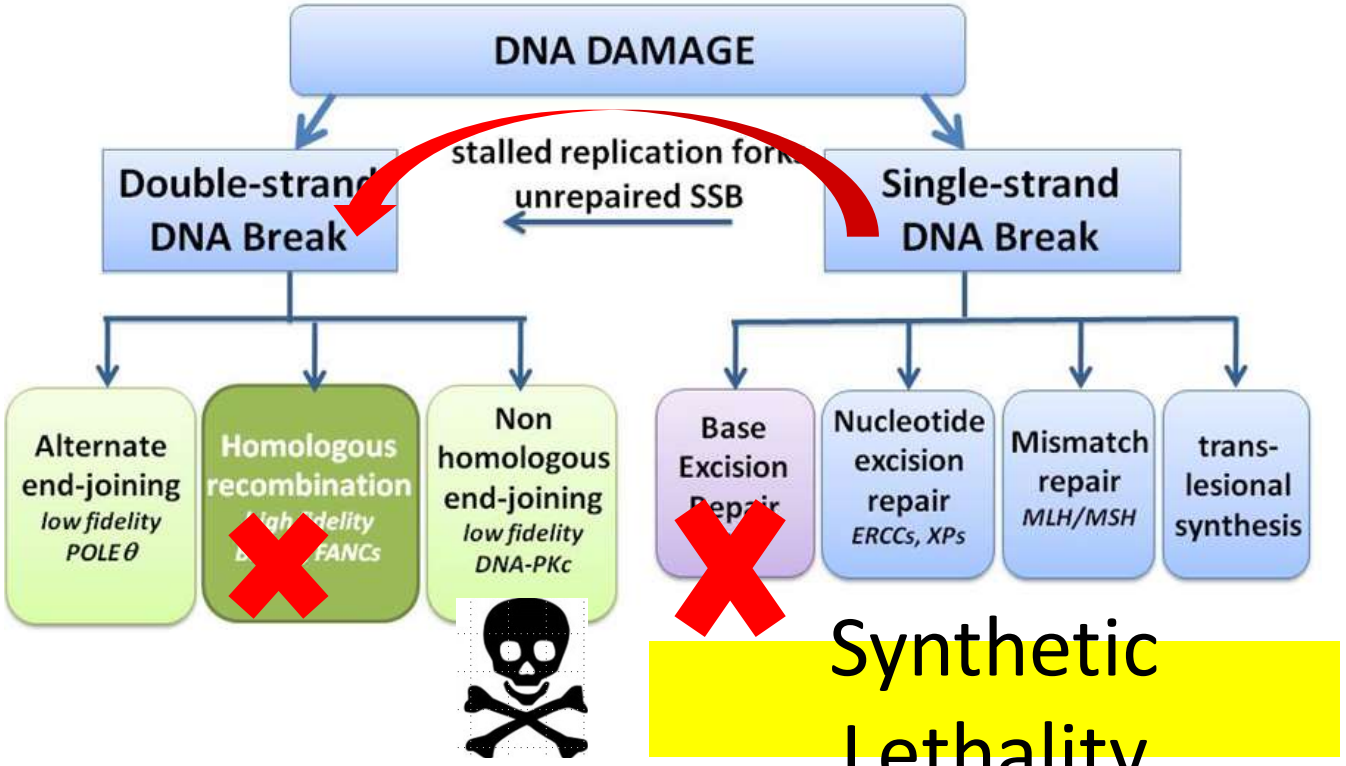


The NEW ENGLAND JOURNAL of MEDICINE



Sonnenblick. Nature Review 2015

Synthetic Lethality: PARP inhibition in HRD cancer



Olaparib in Prostate Cancer

- **TOPARP study: n=49 patients with mCRPC, who are docetaxel-pre-treated.** (Mateo et al. 2015)
  - **32.7 % (16/49**) response rate in "unselected" mCRPC patients.
  - A post-hoc analysis of their prospectively obtained tumor tissue:
    - **16 (33%)** had mutations in DNA repair pathway (*ATM, BRCA2* and others*)* (biomarker positive)
      - **14 of these patient responded**
    - **33 (67%)** had no such mutations (biomarker negative)
      - **2 o**f these patients responded.

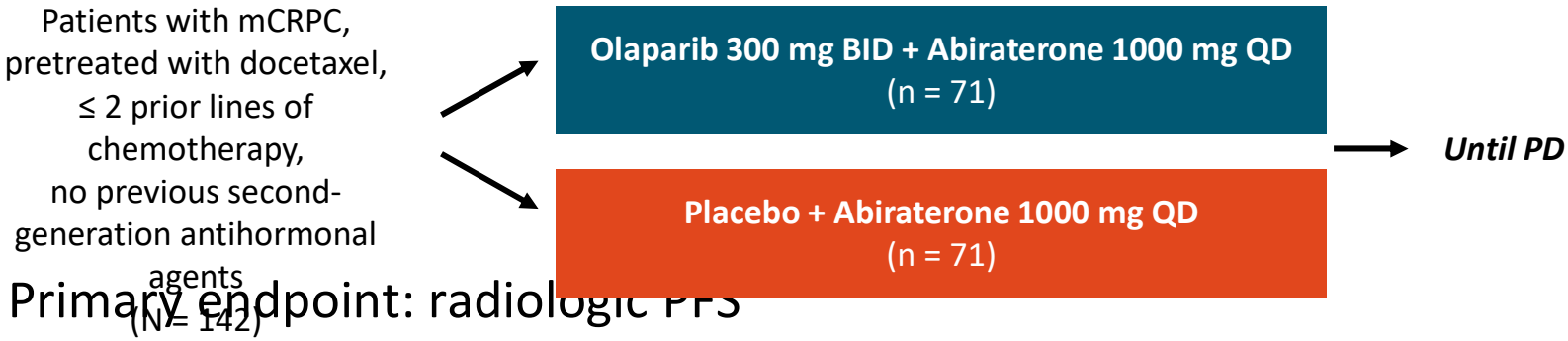
Olaparib + Abiraterone in mCRPC: Background

- Olaparib: PARP inhibitor approved by FDA for treatment of recurrent ovarian cancer and previously treated, germline *BRCA*-mutated advanced ovarian cancer or metastatic breast cancer[1]
- In phase II TOPARP-A trial, olaparib monotherapy demonstrated antitumor activity in patients with previously treated mCRPC, particularly those with DNA-repair defects[2]
- Combination of olaparib + abiraterone may provide synergistic antitumor activity due to increased sensitivity to PARP inhibition resulting from functional HRR impairment via ADT[3-5]
- Current study evaluated efficacy, safety of olaparib + abiraterone in patients with mCRPC following chemotherapy regardless of HRR mutation status[6]

1. Olaparib [package insert]. 2. Mateo J, et al. N Engl J Med. 2015;373:1697-1708. 3. Schiewer MJ, et al. Cancer Discov. 2012;2:1134-1149. 4. Polinghorn WR, et al. Cancer Discov. 2013;3:1245-1253. 5. Asim M, et al. Nat Commun. 2017;8:374. 6. Clarke N, et al. ASCO 2018. Abstract 5003.

Olaparib + Abiraterone in mCRPC: Study Design

- Randomized, double-blind, placebo-controlled phase II trial



- Primary endpoint: radiologic PFS
- Secondary endpoints: rPFS by HRRm status, PFS2, OS, ORR, TFST/TSST, CTC-conversion rate, HRQoL, safety/tolerability

Clarke N, et al. ASCO 2018. Abstract 5003.

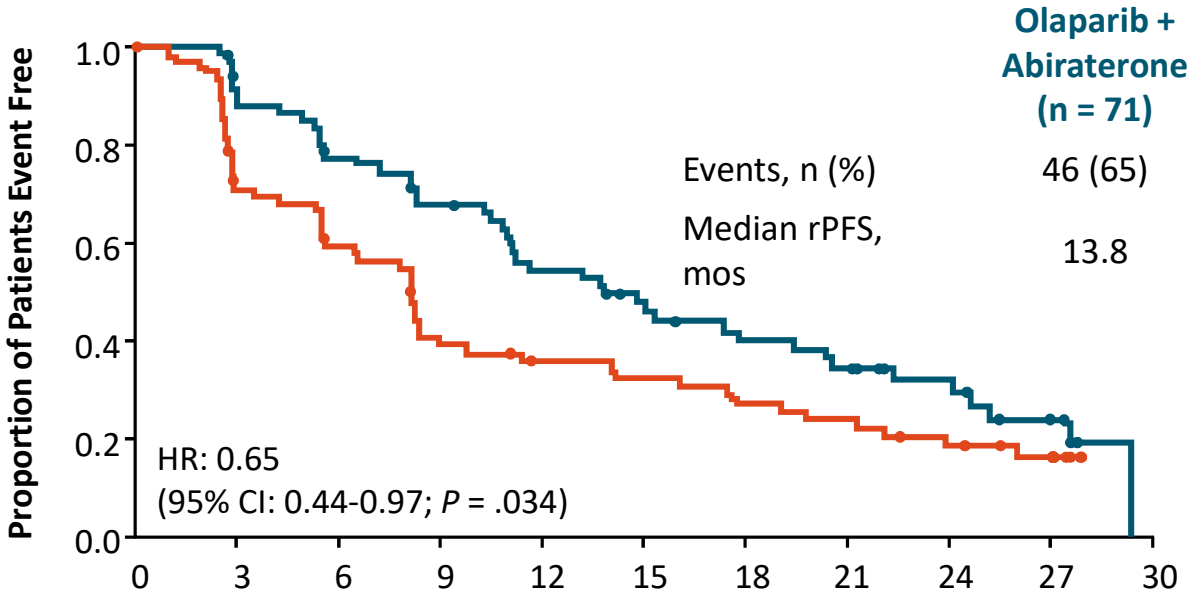
Olaparib + Abiraterone in mCRPC: Patient Population

Characteristic	Olaparib + Abiraterone (n = 71)	Abiraterone (n = 71)
Median age, yrs (IQR)	70 (65-75)	67 (62-74)
White race, n (%)	67 (94)	67 (94)
ECOG PS, n (%) ▪0 ▪1 ▪2	 34 (48) 36 (51) 1 (1)	 38 (54) 30 (42) 1 (1)
Median PSA concentration, µg/L (IQR)	86 (23-194)	47 (21-199)
Median time from diagnosis to first dose, mos (IQR)	62 (38-93)	48 (32-76)

Characteristic	Olaparib + Abiraterone (n = 71)	Abiraterone (n = 71)
Extent of disease, n (%) ▪ Bone only ▪ Soft tissue only ▪ Bone and soft tissue	 33 (46) 8 (11) 30 (42)	 33 (46) 11 (15) 27 (38)
Number of bone metastases, n (%) ▪ 0-4 ▪ 5-9	 32 (45) 39 (55)	 46 (65) 25 (35)
Prior cabazitaxel treatment, n (%)	10 (14)	9 (13)
Median duration of prior LHRH agonist, mos (IQR)	53 (32-84)	37 (28-59)

Clarke N, et al. ASCO 2018. Abstract 5003.

Olaparib + Abiraterone in mCRPC: Investigator-Assessed Radiologic PFS (Primary Endpoint)

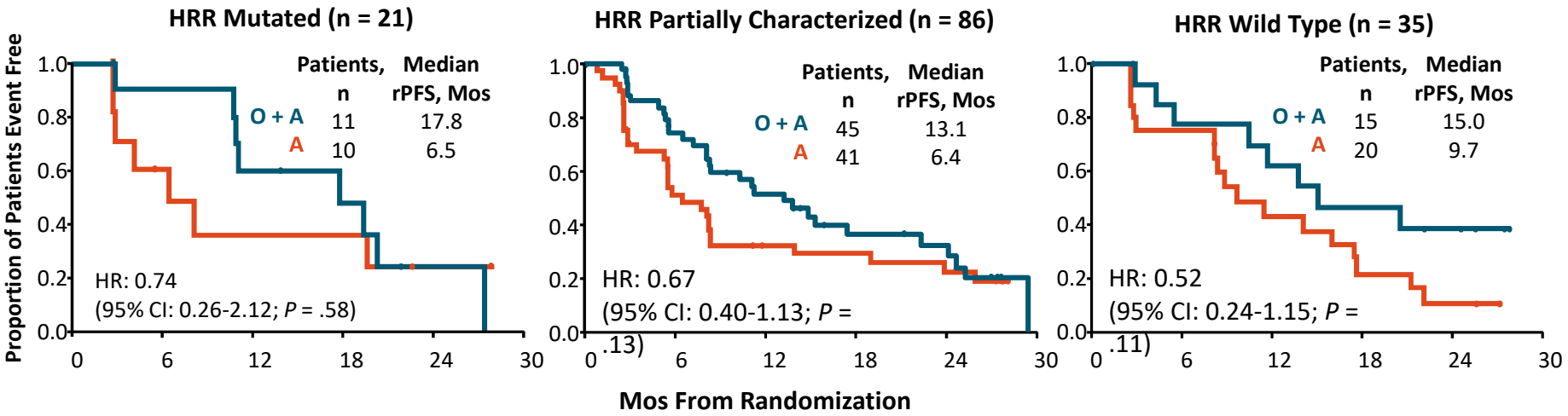


	Olaparib + Abiraterone (n = 71)	Abiraterone (n = 71)
Events, n (%)	46 (65)	54 (76)
Median rPFS, mos	13.8	8.2

Patients at Risk, n											
Olaparib + abiraterone	71	58	50	42	33	26	21	18	13	8	0
Abiraterone	71	48	39	25	21	19	16	14	10	7	0

Clarke N, et al. ASCO 2018. Abstract 5003. Reproduced with permission.

Olaparib + Abiraterone in mCRPC: Radiologic PFS by HRR Mutation Status



- HRR mutation testing completed on 142 patients with tumor, germline, or plasma samples
  - Biomarker data obtained for 136 patients (96%), 21 (15%) of which were HRR mutation positive
  - HRR mutations included *BRCA2, ATM, CHEK1, CHEK2, PALB2, BRIP1, CDK12*

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Olaparib + Abiraterone in mCRPC: Conclusions

- In patients with mCRPC previously treated with docetaxel, addition of olaparib to abiraterone significantly increased radiologic PFS vs abiraterone alone
  - HR: 0.65 (95% CI: 0.44-0.97; *P* = .034)
  - Benefit seen regardless of HRR mutation status
- Increased toxicity with combination, including serious cardiovascular AEs
- Phase III trial planned, starting in 2018

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Slide credit: clinicaloptions.com

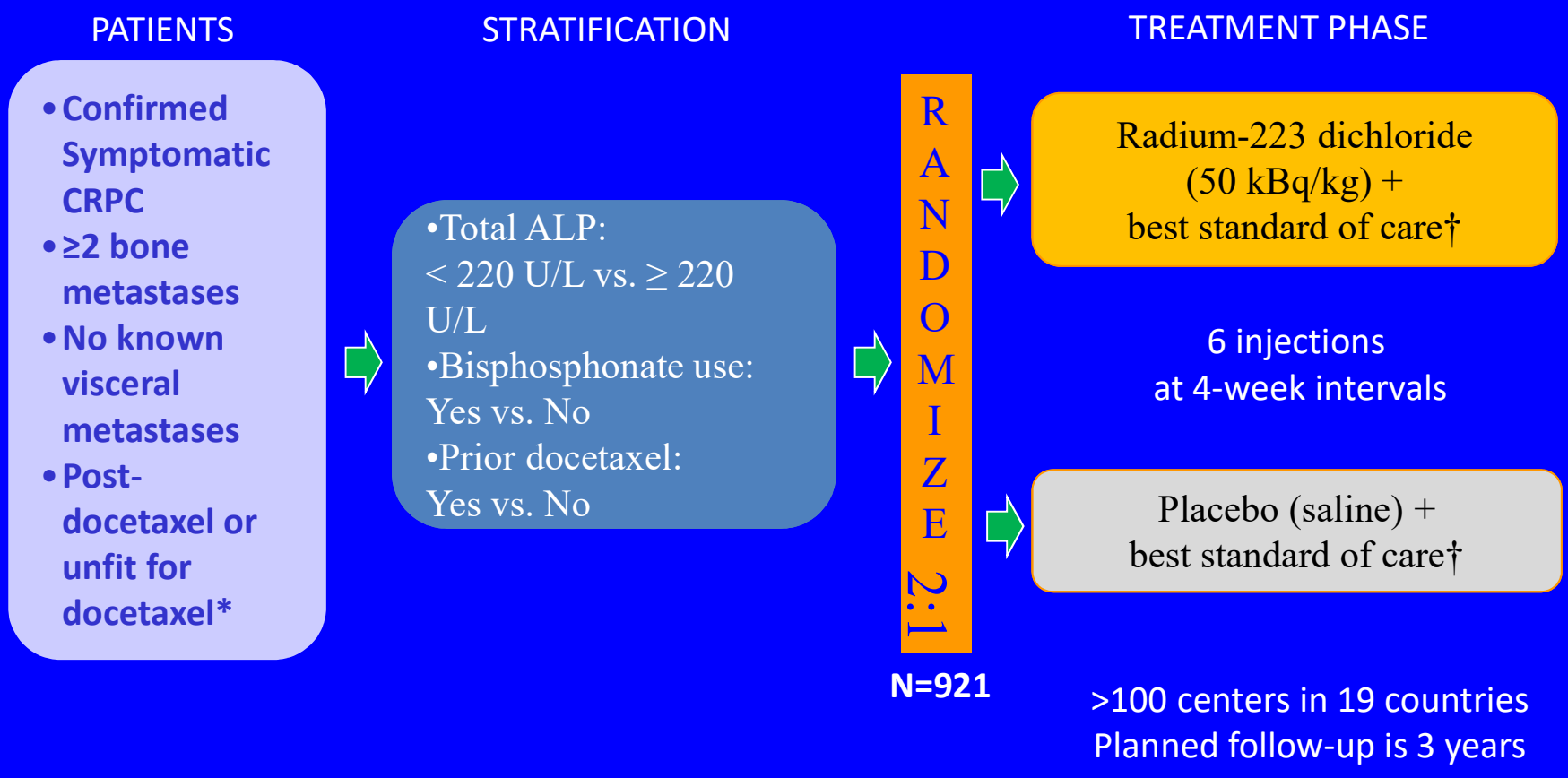
Ongoing Trials of PARP inhibitor

Ph	Agent	Setting	Tx Arms	Primary Endpoint	NCT
1	Olaparib	**Intermediate/High Risk Prostate Cancer Before Radical Prostatectomy (CaNCaP03)**	Olaparib +Degarelix vs Olaparib alone	Biomarker endpoint (PARP Inhibition)	NCT02324998 (Not Yet Open)
2	Rucaparib (Clovis)	HR Deficient mCRPC (deleterious mt inBRCA1/2 or ATM or other HR genes	Rucaparib	ORR and PSA response	TRITON2 NCT02952534
3	Rucaparib (Clovis)	mCRPC, HR deficient (BRCA1/2 or ATM)	Rucaparib vs Investigator choice (Doc, Abi, Enz)	rPFS	TRITON3 NCT02975934 (not yet open)
2	Niraparib	mCRPC (taxaned and AR pre-treated) (Biomarker positive for HR deficient)	Neraparib	Response Rate	NCT02854436 (OPEN)

Combination Trials

Ph	Agent	Setting	Tx Arms/Cohort	Primary Endpoint	NCT
1b/II	Olaparib	mCRPC A: post-docet B: post Ai/Enz C: Post-Abi / naïve to Enz and cheo	A: pembro +Olaparib B: Pembro + Docet/Pred C: Pembro+Enzalutamide	PSA response and toxcity	KEYNOTE-365
R-II	Olaparib	mCRPC (≥ 2 prior lines)	Cediranib plus Olaparib vs Olaparb	rPFS	NCT02893917
I / II	Olapariib	mCRPC, (lung , breast, Ov, CRC)	Durva+Ced Durva+Ola Durva+CO	Safety an dose finding	NCT02484404

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design[1]

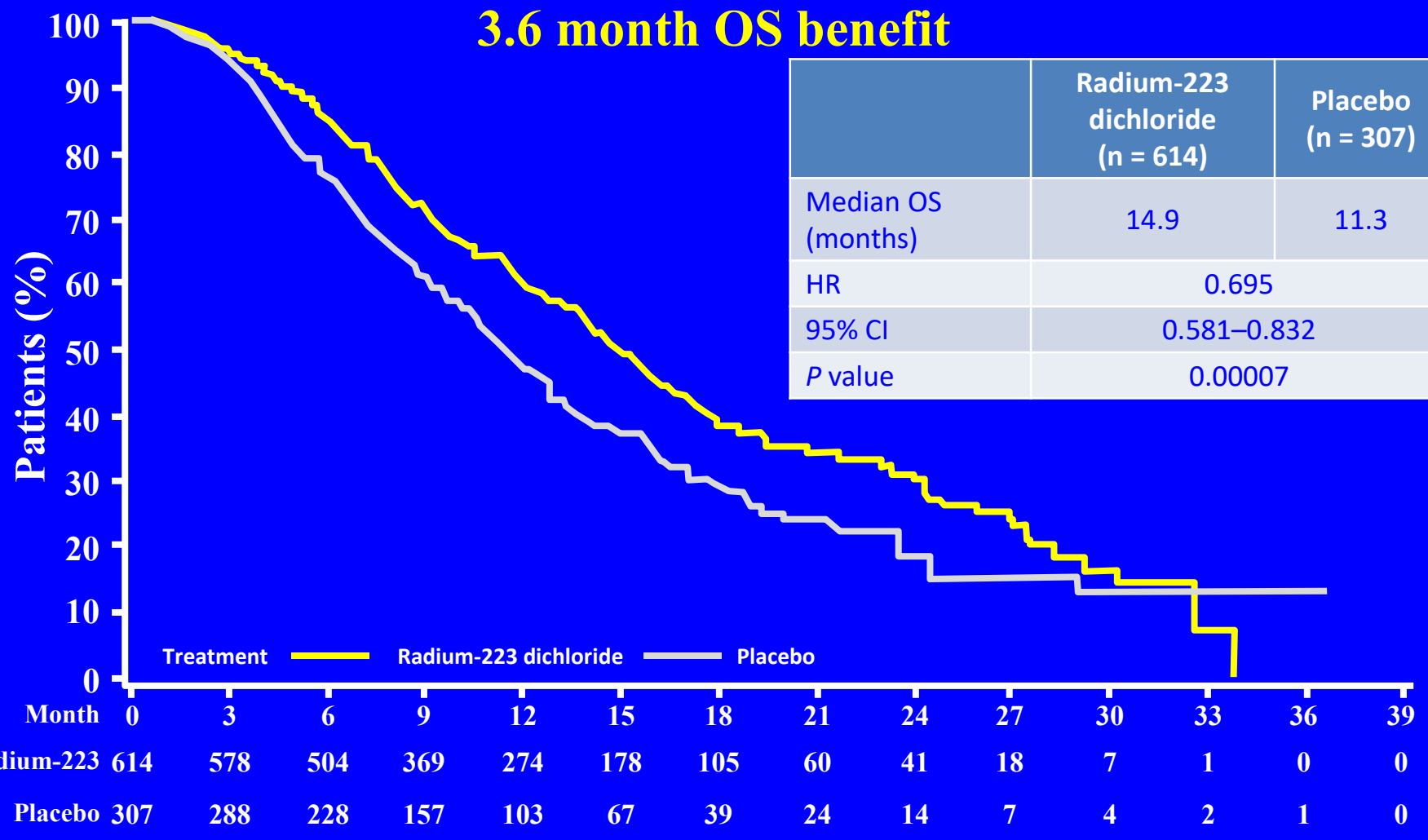


*Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable

†Best standard of care defined as a routine standard of care at each center, eg. local external beam radiotherapy, corticosteroids, anti-androgens, estrogens (e.g., stilbestrol), estramustine, or ketaconazole

Reference: 1. Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

ALSYMPCA Updated Analysis: Overall Survival



	Radium-223 dichloride (n = 614)	Placebo (n = 307)
Median OS (months)	14.9	11.3
HR	0.695	
95% CI	0.581–0.832	
P value	0.00007	

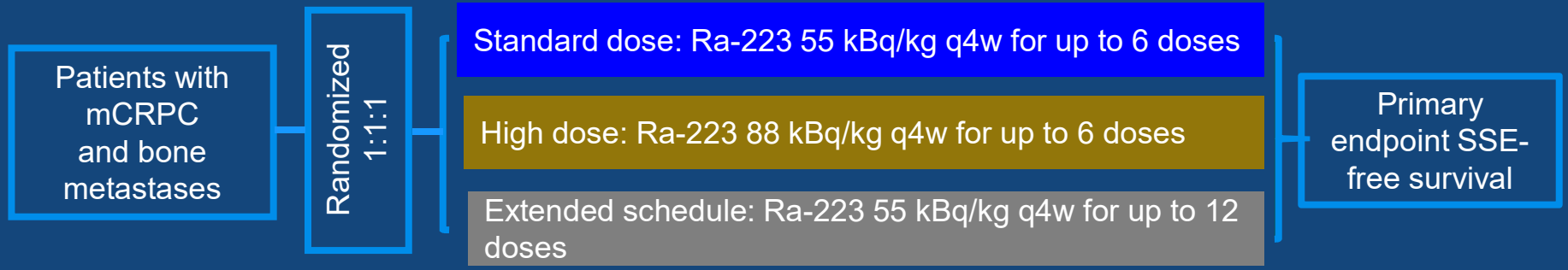
Reference: Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

A randomized phase 2 study investigating 3 dosing regimens of radium-223 dichloride (Ra-223) in bone metastatic castration-resistant prostate cancer (mCRPC)

Cora N. Sternberg, Fred Saad, Julie N. Graff, Avivit Peer, Ulka N. Vaishampayan, Eugene Leung, Eli Rosenbaum, Howard Gurney, Richard Epstein, Ian D. Davis, Bingyan Wu, Lucia Trandafir, Volker Jean Wagner, Maha Hussain

Cora N. Sternberg

Study design (n=391)



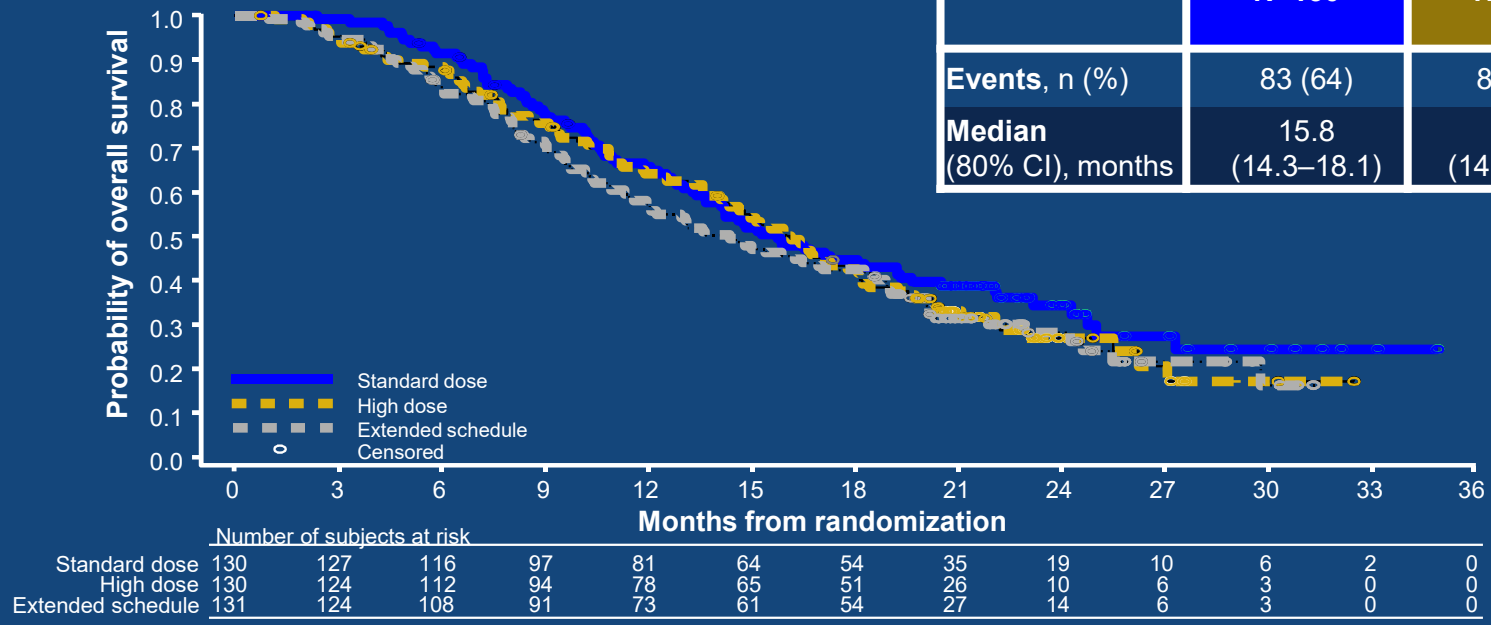
- Stratification:
  - Prior chemotherapy: ≤1 prior regimen vs >1 prior regimen
  - Total ALP: <220 U/L vs ≥220 U/L
  - Worst pain score by BPI: ≤4 vs >4
- Concomitant therapy allowed: hormonal, bisphosphonates, RANK ligand inhibitors

ALP, alkaline phosphatase; BPI, brief pain inventory; SSE-free survival, symptomatic skeletal event-free survival

Cora N. Sternberg

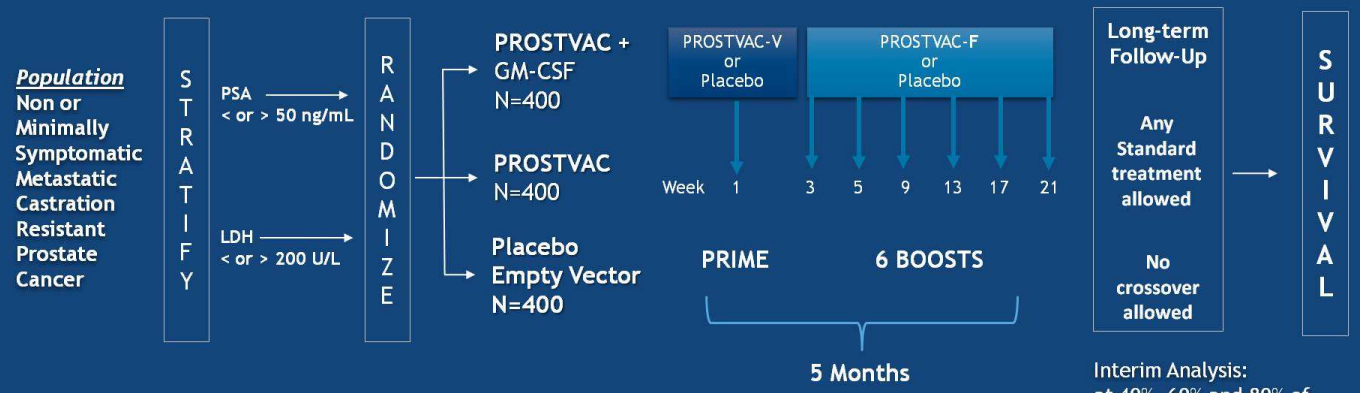
Overall survival

	Standard dose N=130	High dose N=130	Extended schedule N=131
Events, n (%)	83 (64)	89 (68)	93 (71)
Median (80% CI), months	15.8 (14.3–18.1)	16.0 (14.7– 17.2)	14.4 (12.1–16.5)



Cora N. Sternberg

PROSPECT Phase 3 Design



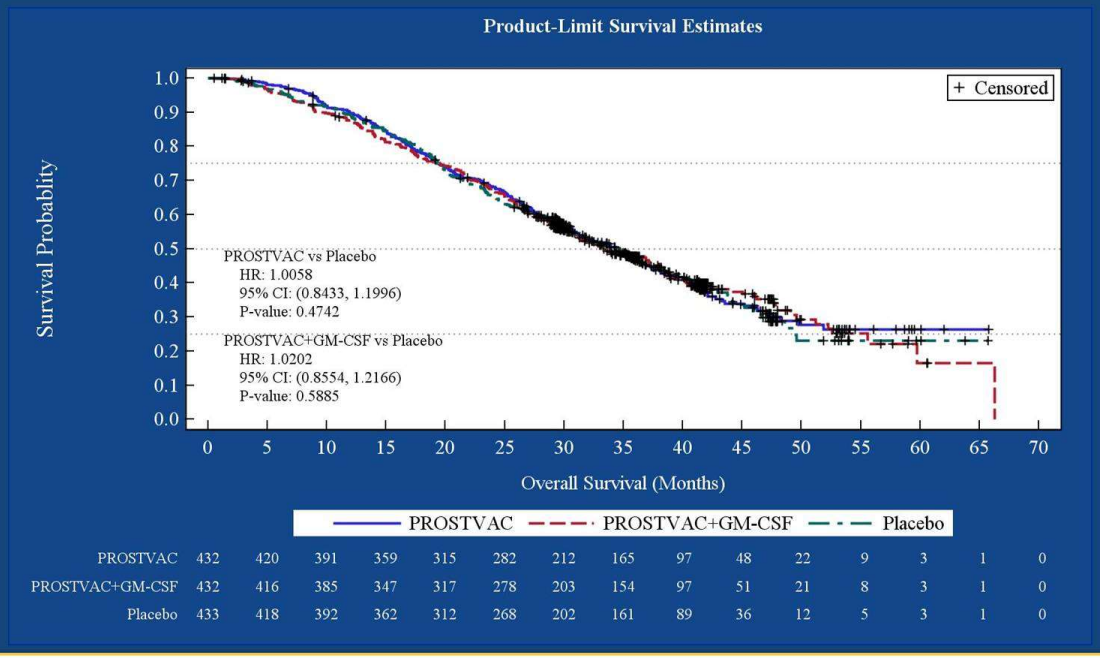
- **Primary Endpoint:** **Overall Survival**
- Secondary Endpoint: Event-Free Survival at 6 Months

Interim Analysis:
at 40%, 60% and 80% of the expected events

Two comparisons:
PROSTVAC vs Pbo
PROS + GM vs Pbo

Presented By James Gulley at 2018 ASCO Annual Meeting

Overall Survival ITT



Sep 2017
Interim Analysis #3
DMC recommended closure of the study on grounds of futility

Median OS	
PROSTVAC	34.4
PROSTVAC+ GM-CSF	33.2
Placebo	34.3

Presented By James Gulley at 2018 ASCO Annual Meeting

Conclusions

- The optimal sequence of agents is yet to be determined
- Docetaxel chemotherapy for hormone sensitive patients should be offered to high disease volume patients
- Immune therapy should be given early in asymptomatic non visceral patients
- The effect of lyase inhibitors on chemotherapy is unknown.

Conclusions

- ArV7 is promising biomarker for sensitivity to enzalutamide and abiraterone
- PARP inhibition is a promising therapeutic target in patients with BRCA mutations