

DANIEL PETRYLAK, MD

SURFING BETWEEN THERAPEUTIC OPTIONS FOR HRPC

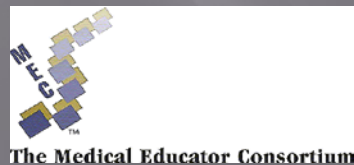
RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

GRANT/RESEARCH SUPPORT: AGENSYS, ASTRAZENECA, BAYER, CLOVIS, DENDREON, ELI LILLY, ENDOCYTE,
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CONSULTANT: ASTRAZENECA, BAYER, BELLICUM, DENDREON, EXELIXIS, FERRING,
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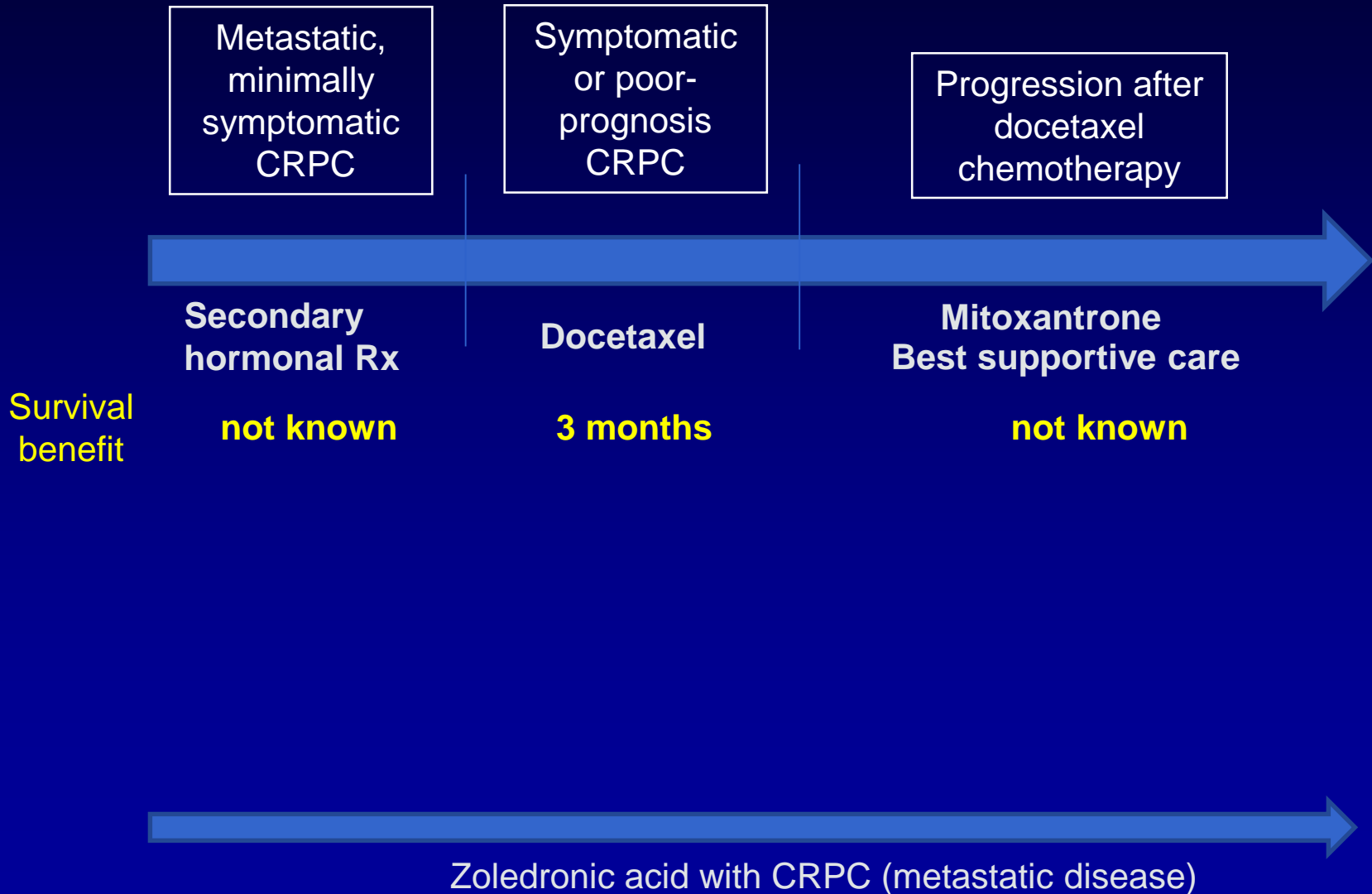
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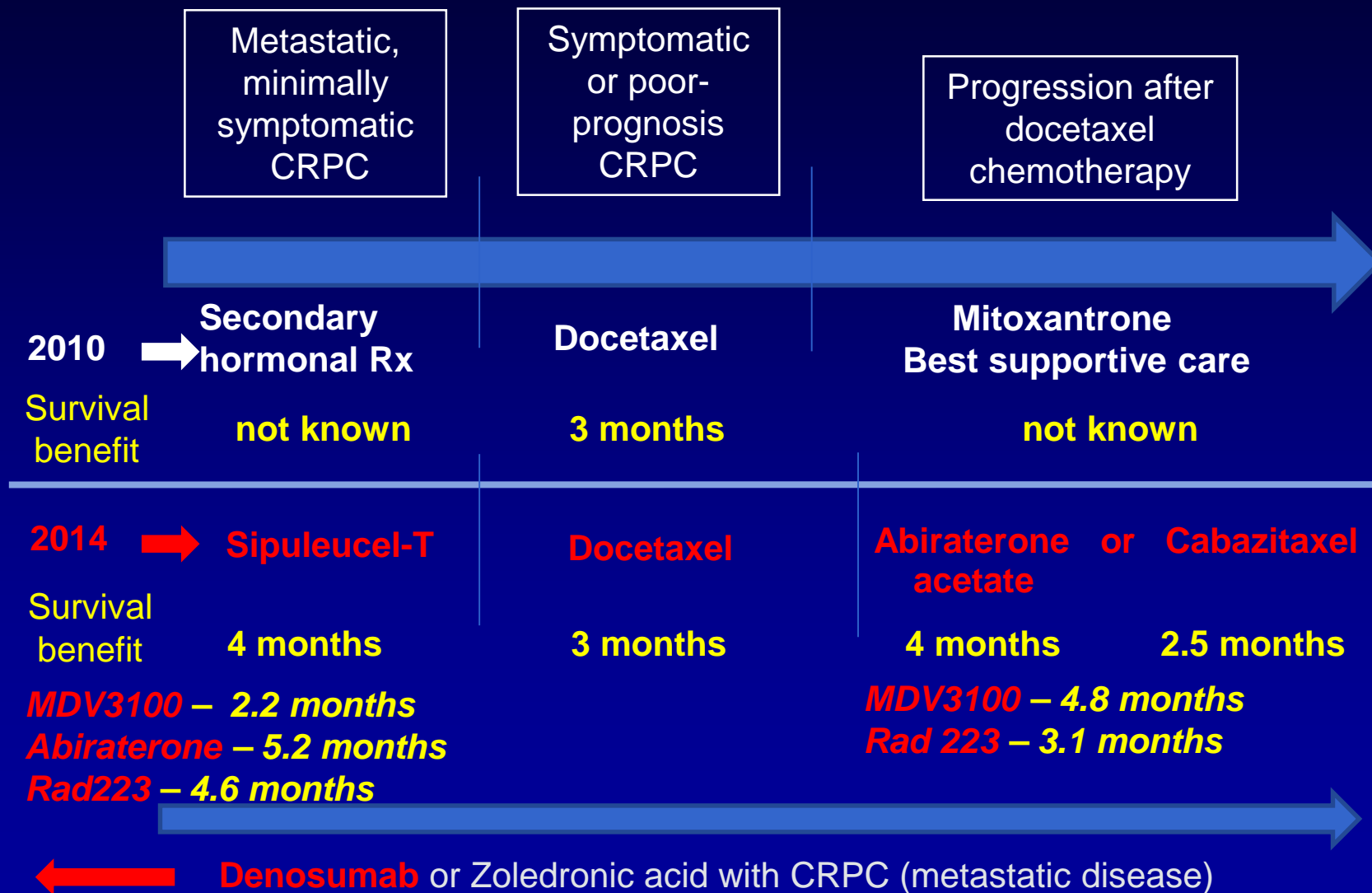


13th Annual New Orleans Summer Cancer Meeting
July 20-22, 2018

Sequencing CRPC therapy – 2010



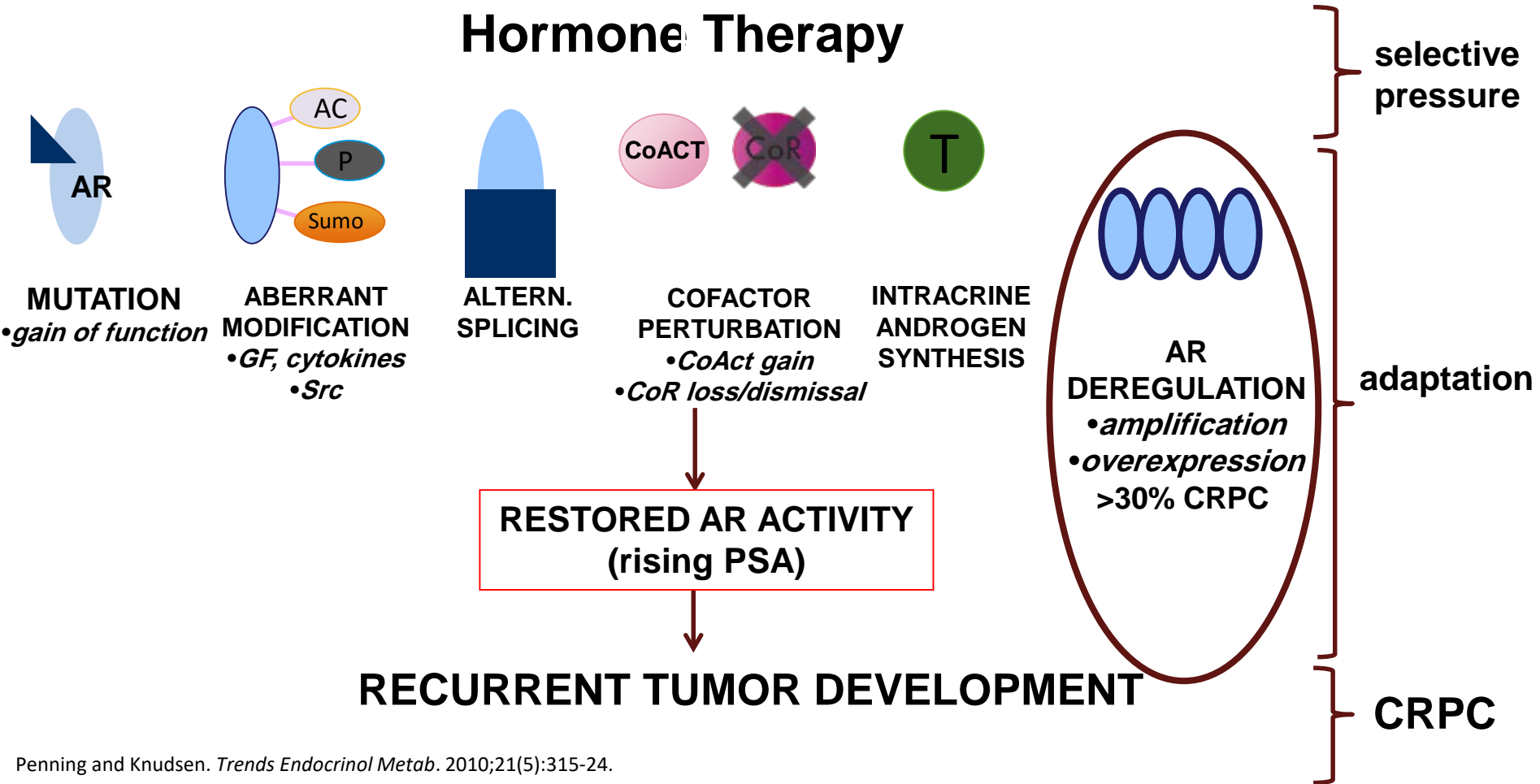
Sequencing CRPC therapy – 2018



Classes of Agents

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

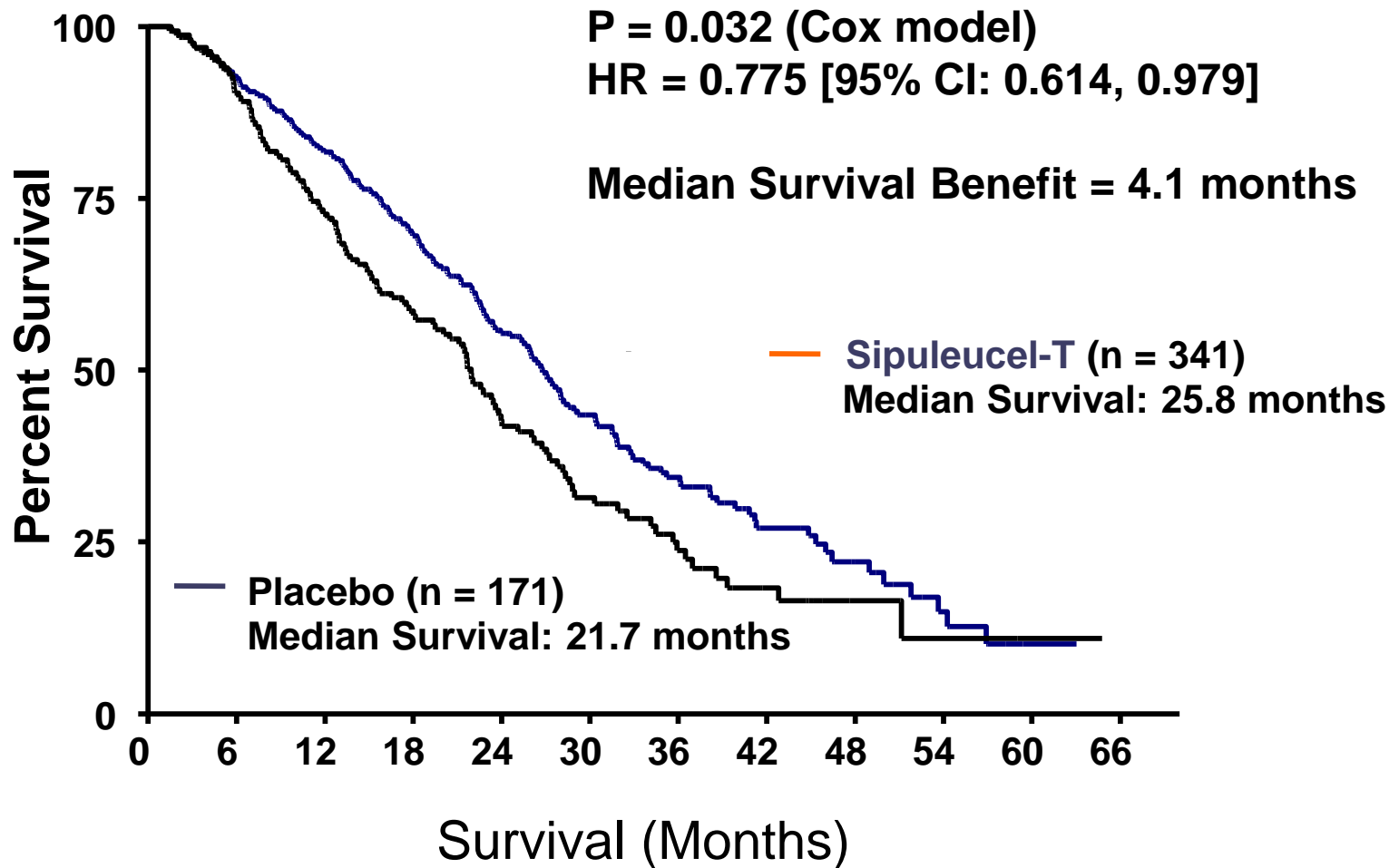
Development of Castrate Resistant Prostate Cancer



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

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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, months	13.0	7.1	5.4	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)

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

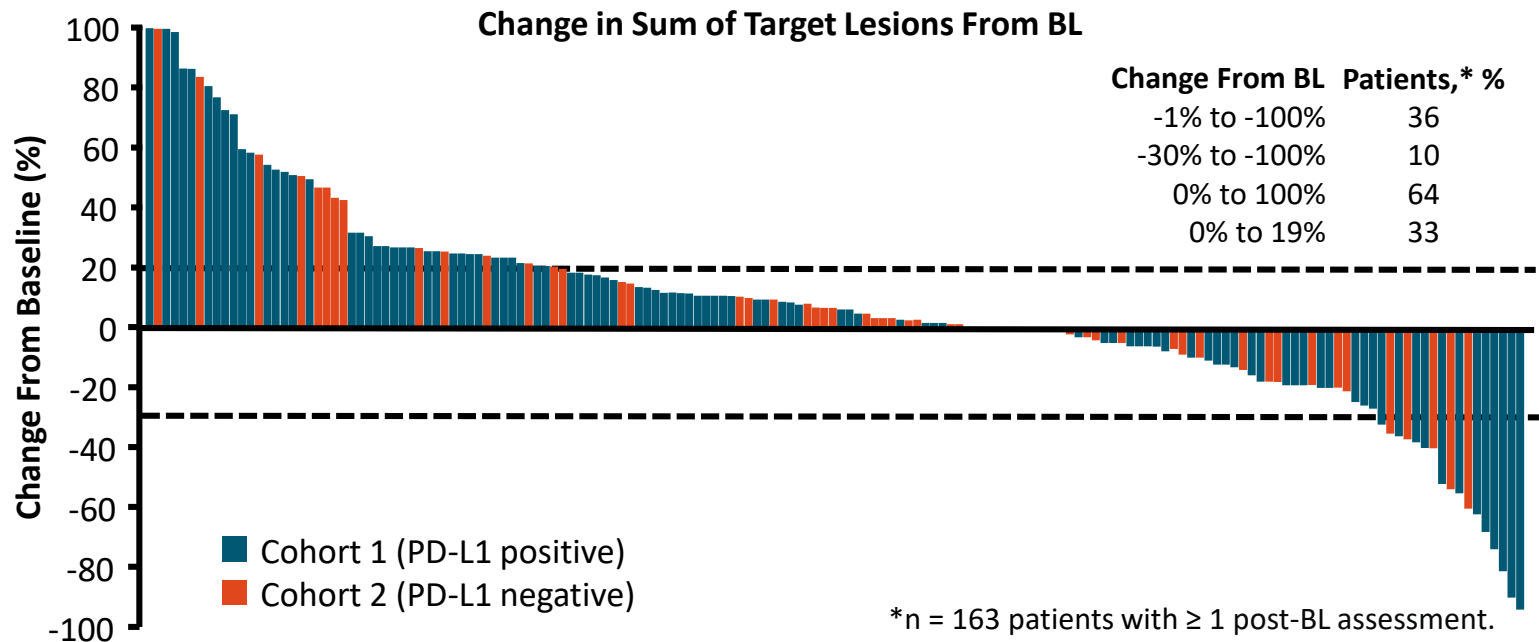
- Primary endpoint: ORR per RECIST v1.1 by BICR in cohorts 1 and 2 (separately and combined)
- Secondary endpoints: DCR, DoR per RECIST v1.1, PCWG3-modified RECIST; OS, safety
- Exploratory endpoints: biomarker signature for benefit with PD-1 blockade

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			
▪ ≥ 2 antiendocrine therapies	32	27	25
▪ Enzalutamide only	26	22	25
▪ Abiraterone only	30	40	30
▪ Enzalutamide + abiraterone	44	37	45
	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 $\geq 50\%$ PSA reduction from BL

KEYNOTE-199: Response

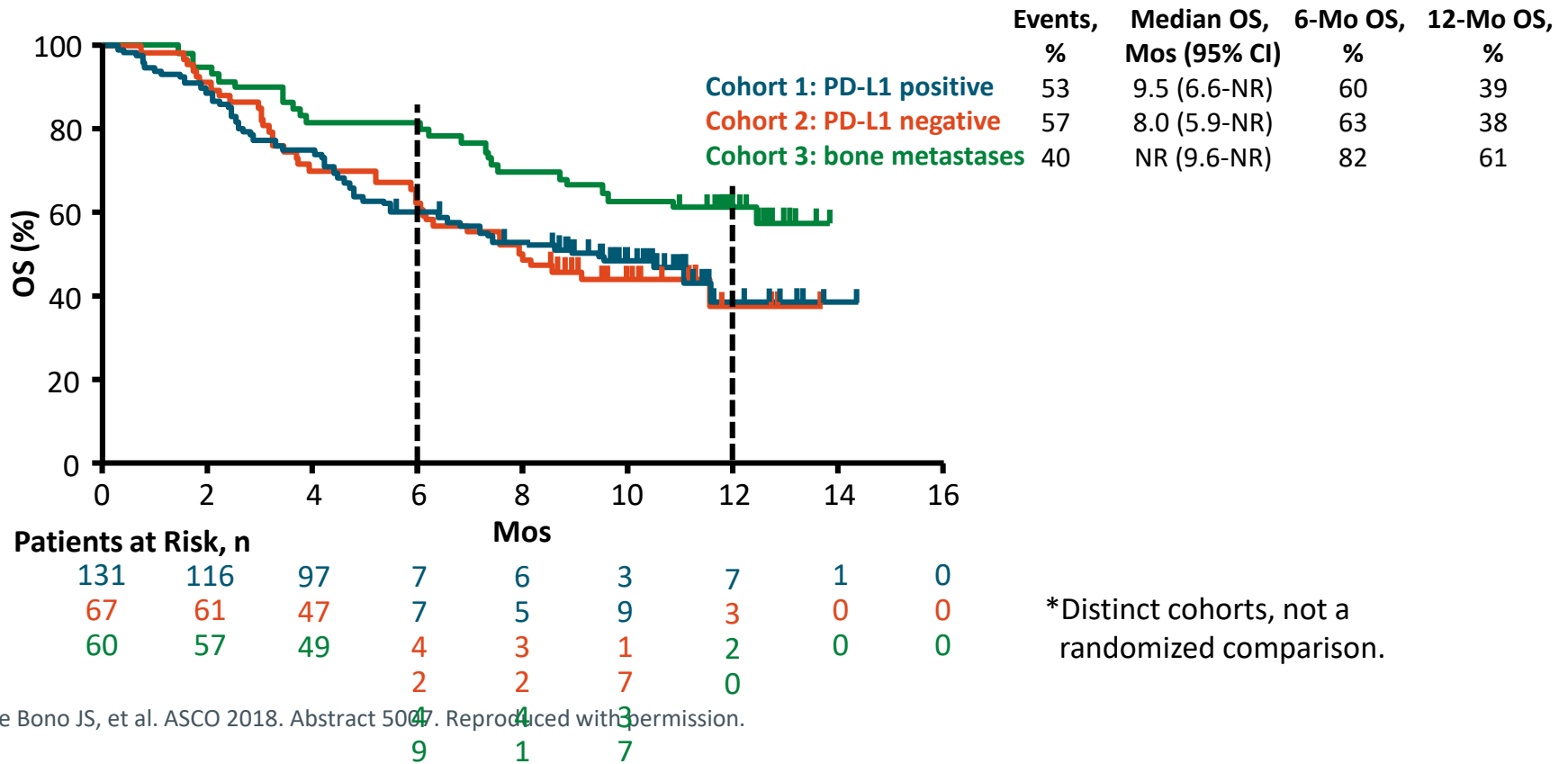
Response Outcome	Cohort 1: PD-L1 Positive (n = 131)	Cohort 2: PD-L1 Negative (n = 67)	Cohort 3: Bone Metastases (n = 60)	Cohorts 1 + 2 (n = 198)	Cohorts 1 + 2 + 3 (n = 258)
ORR,* n (%)	7 (5) [¶]	2 (3) [¶]	--	9 (5) [¶]	9 (4)
▪ CR	2 (2)	0	--	2 (1)	2 (< 1)
▪ PR	5 (4)	2 (3)	--	7 (4)	7 (3)
▪ SD (any duration)	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*



*Distinct cohorts, not a randomized comparison.

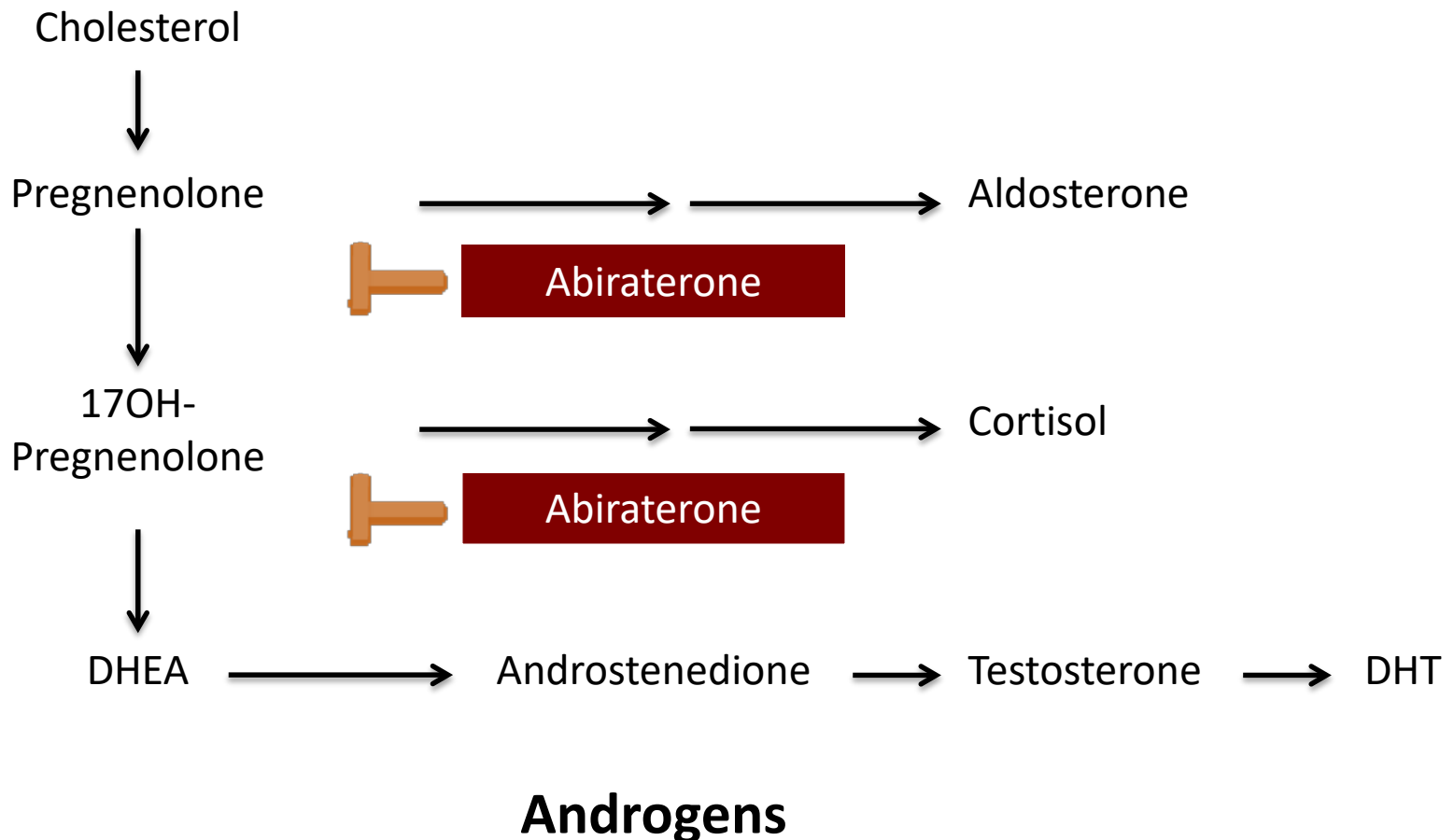
de Bono JS, et al. ASCO 2018. Abstract 5007. Reproduced with permission.

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

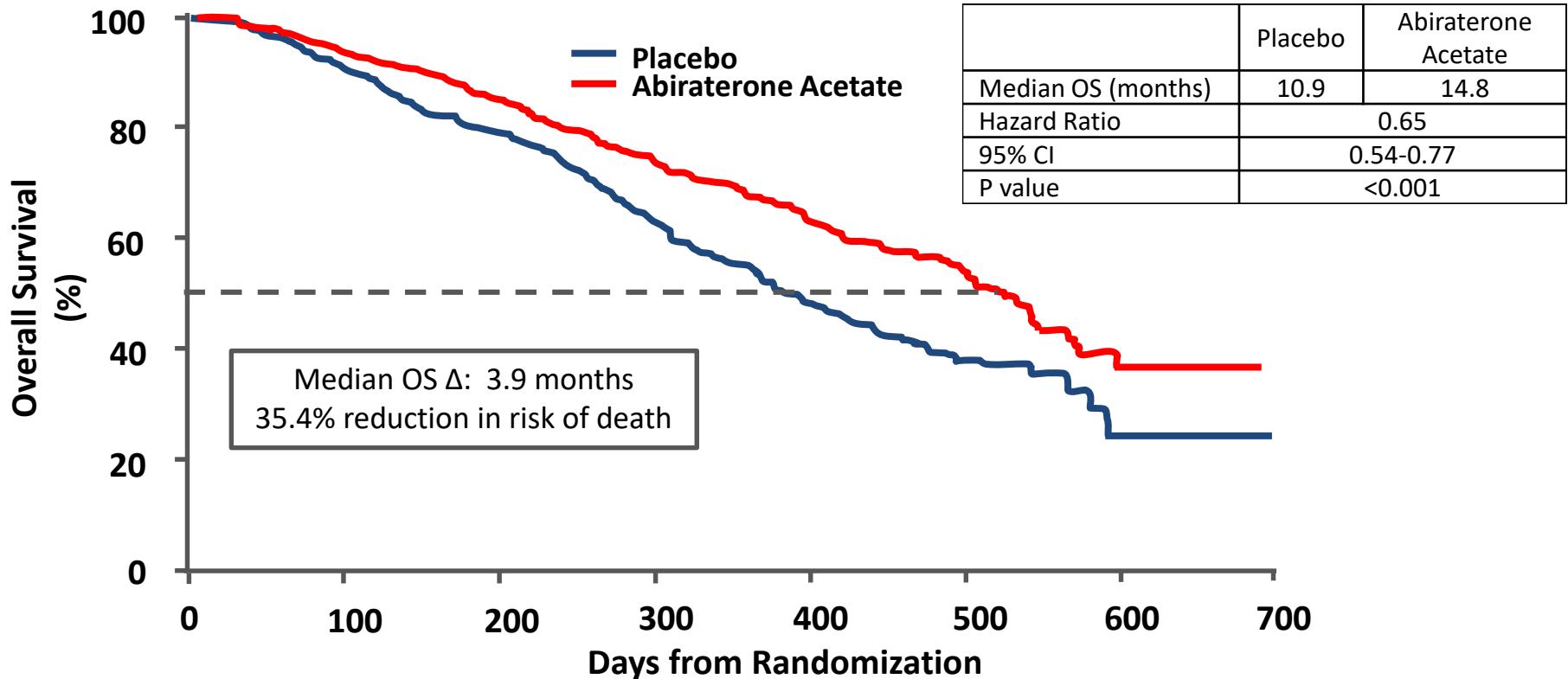
Response Outcome, n (%)	<i>BRCA1/2</i> or <i>ATM</i> (n = 19)	Other DDR Genes* (n = 10)	Negative (n = 124)
ORR	2 (11)	0	4 (3)
▪ CR	0	0	2 (2)
▪ PR	2 (11)	0	2 (2)
▪ SD (any duration)	2 (11)	2 (20)	18 (15)
▪ PD	12 (63)	5 (50)	80 (65)
DCR (any duration)	4 (22)	0	22 (18)
PSA responders	2 (11)	1 (10)	4 (3)

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

Abiraterone Acetate: Androgen Biosynthesis Inhibitor



COU 301: Overall Survival

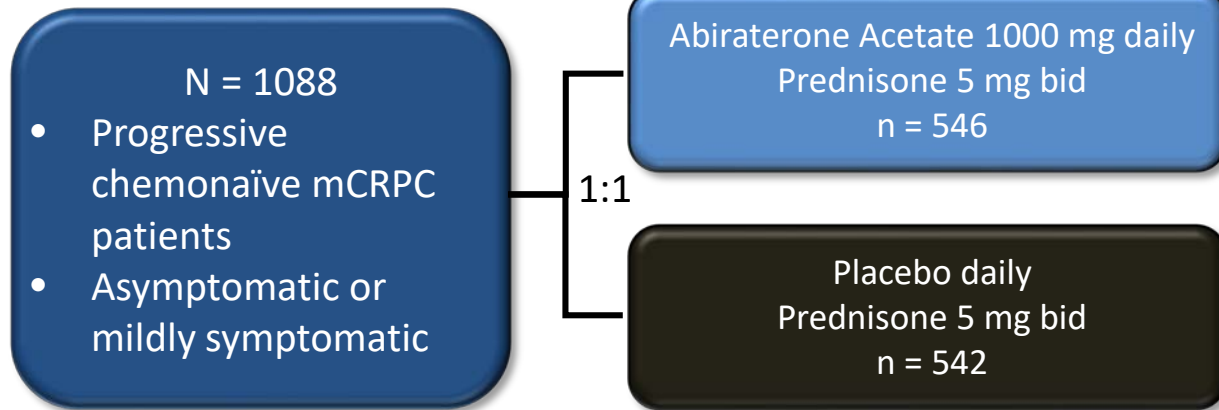


2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo¹

1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo¹

Updated results: 4.6-month difference in median survival with abiraterone acetate²

COU 302: Abiraterone Acetate Phase III Trial in Chemo-naïve mCRPC



Primary Endpoints:

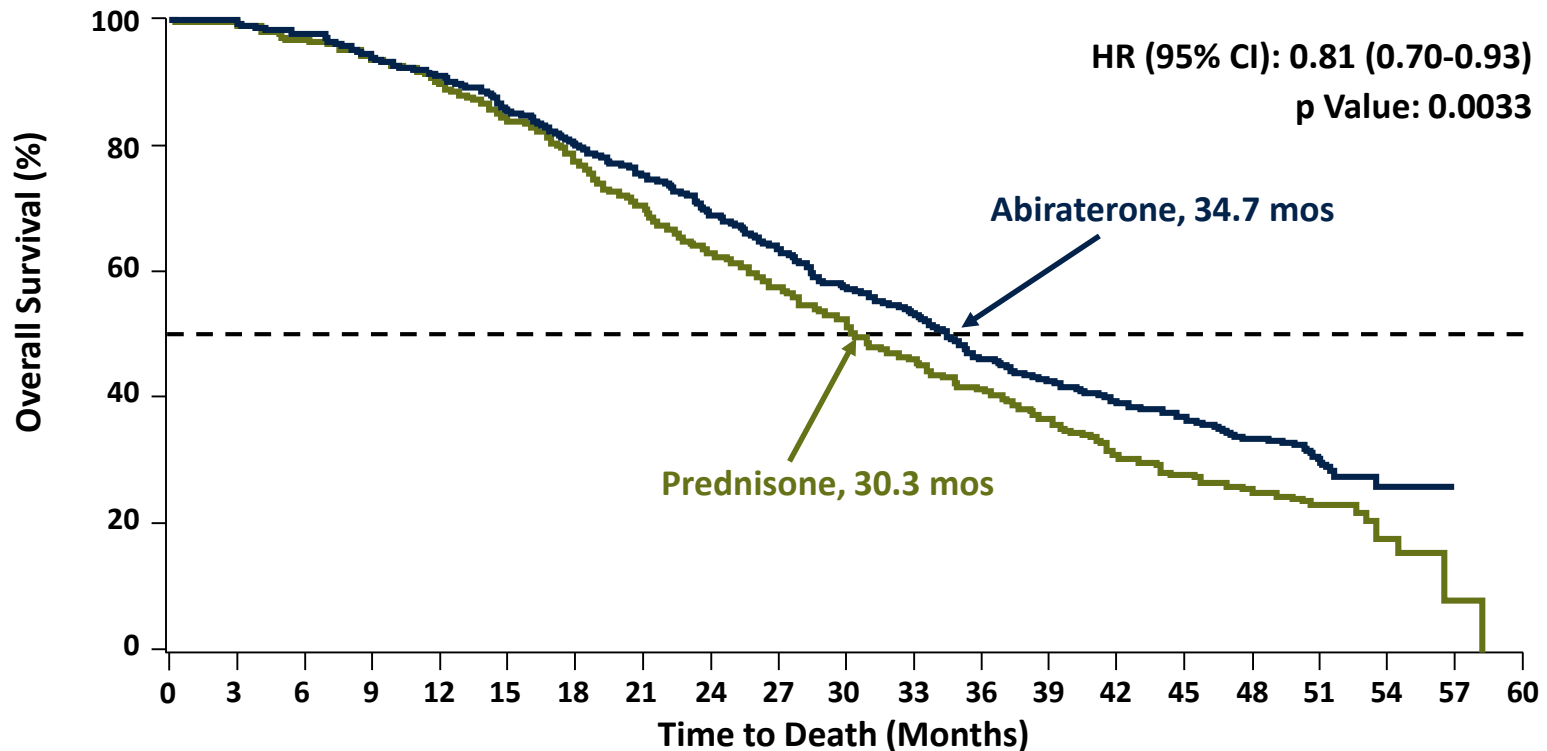
- Radiographic progression-free survival (rPFS) by central review
- OS

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

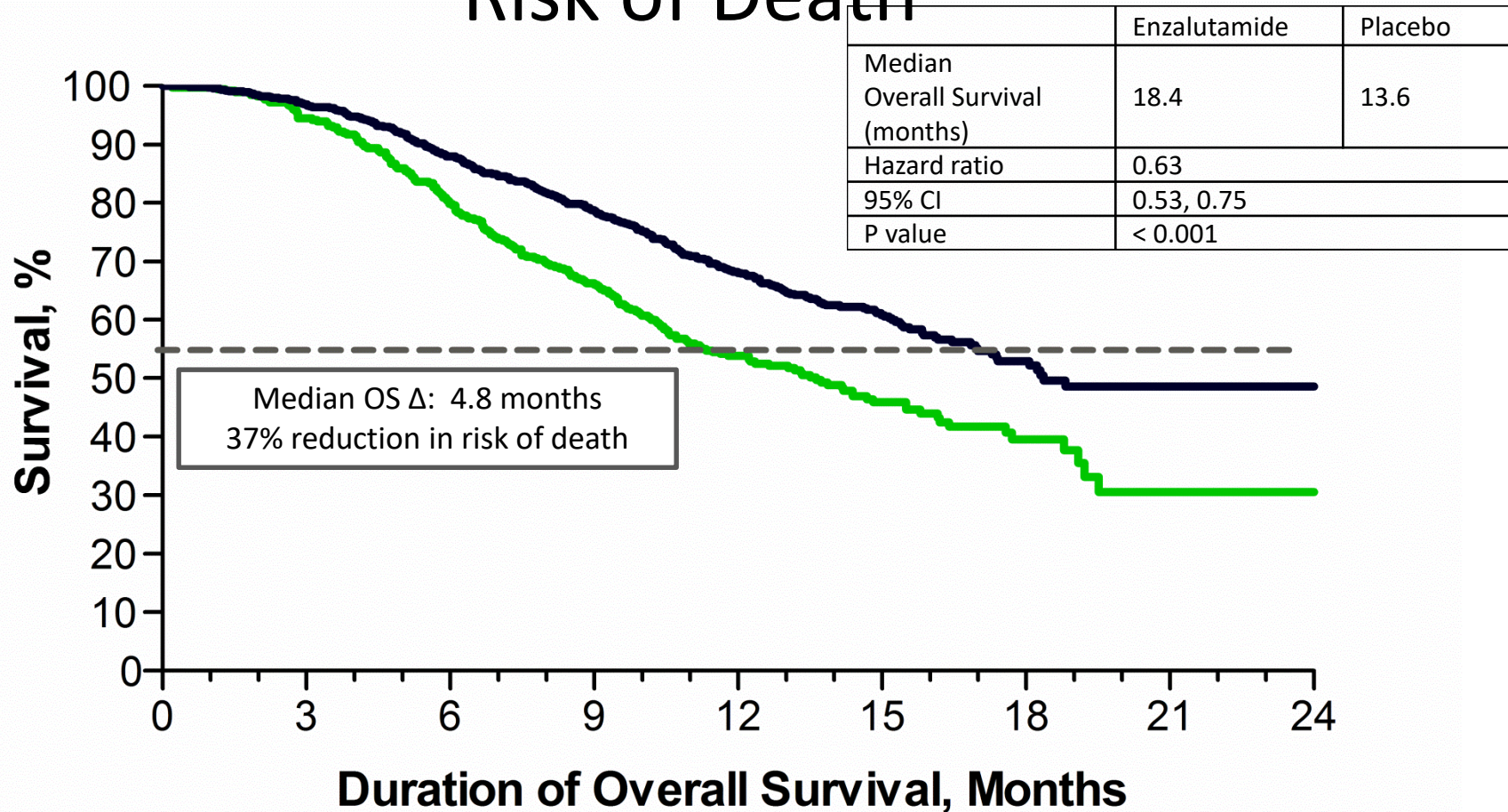
Ryan et al. Final Overall Survival Analysis of COU-AA-302, a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy



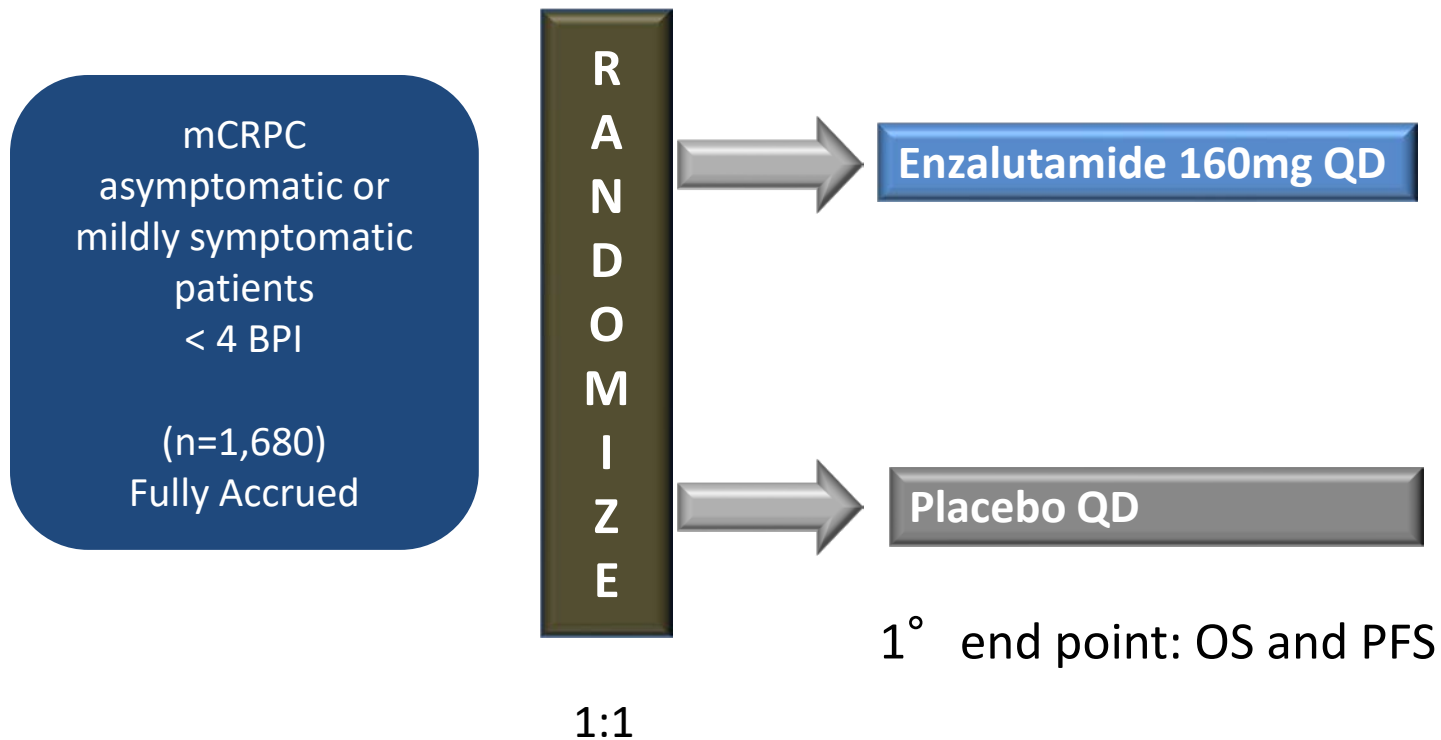
Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- 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)

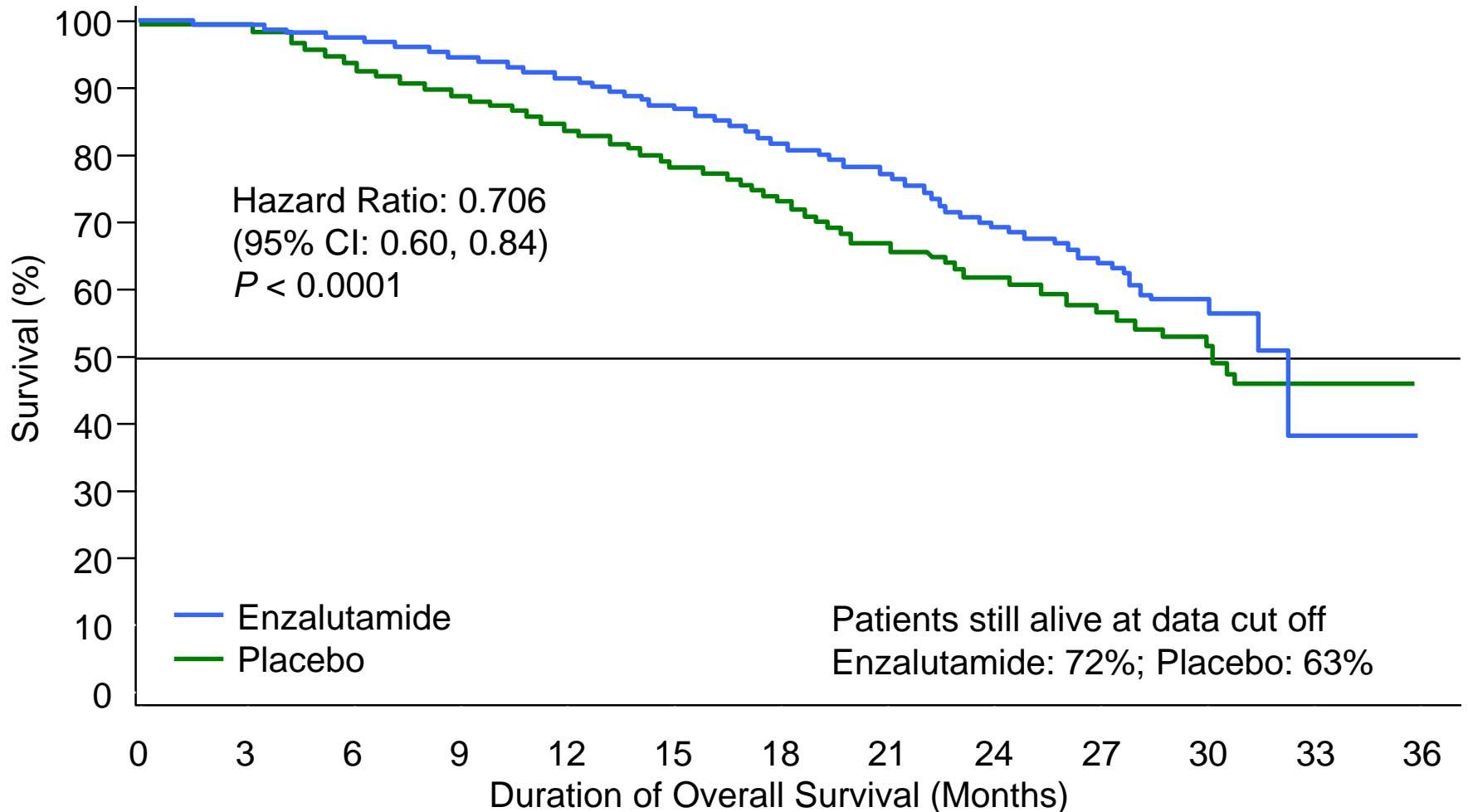
Enzalutamide Prolonged Survival, Reducing Risk of Death



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



PREVAIL: Overall Survival



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

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)

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

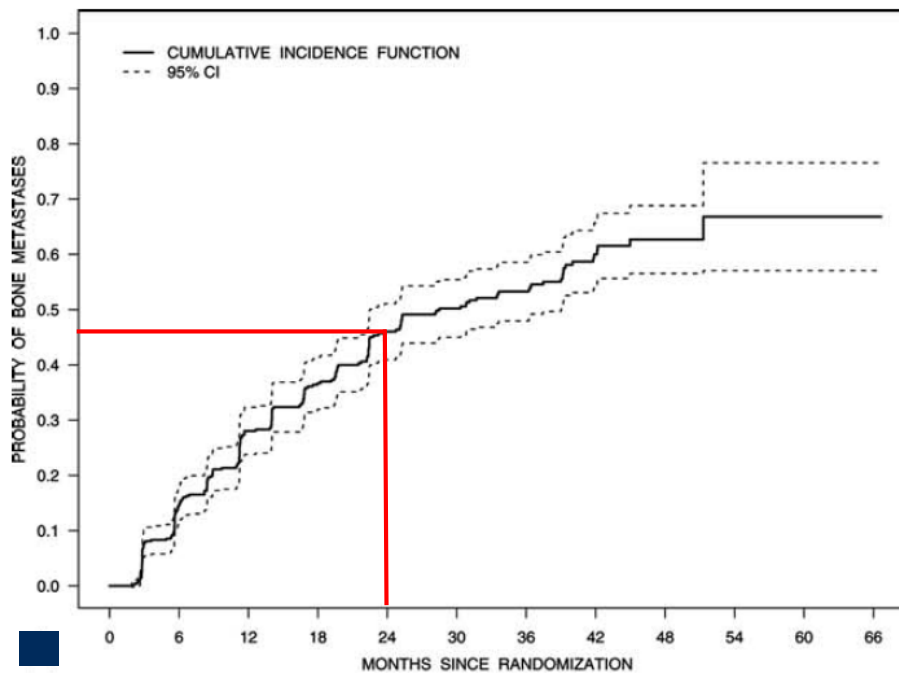
Data from retrospective and prospective observational studies involving a total of 71,179 patients observed for up to 12 years

Prevalence	<ul style="list-style-type: none">• 10–20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up
Metastases	<ul style="list-style-type: none">• $\geq 84\%$ 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	<ul style="list-style-type: none">• 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

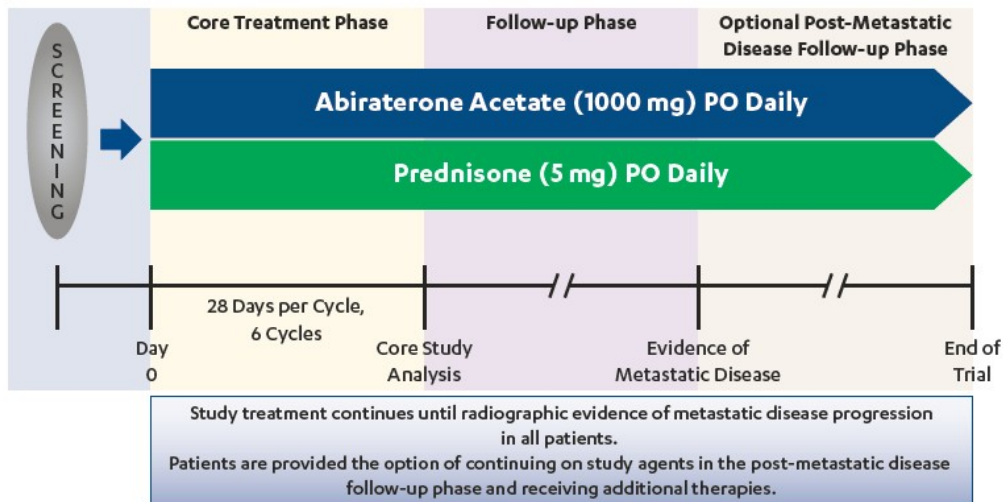


Smith MR et al. Cancer. 2011;117(10):2077-2085

RR= relative risk.

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

Figure 1: IMAAGEN Study Design



-mCRP 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 time of the data base lock, 31Dec2013

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)

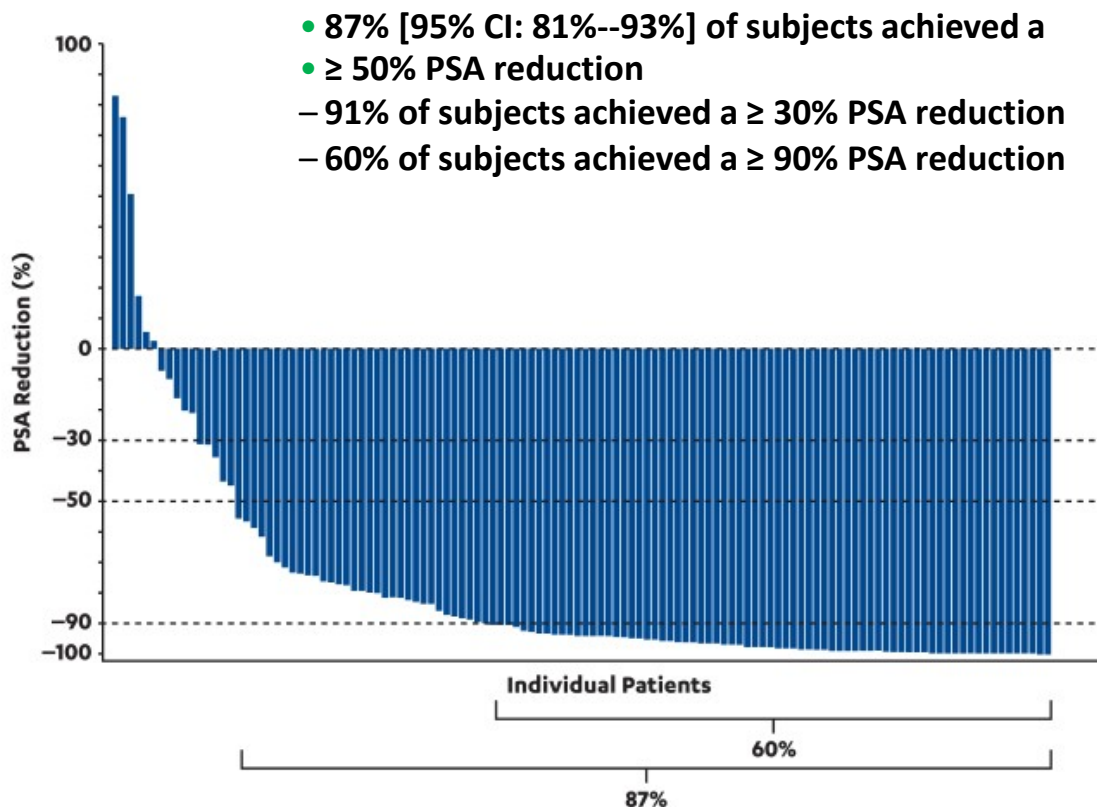
IMAAGEN Trial Update: Effect of Abiraterone Acetate and Low Dose Prednisone on PSA in Patients With Non-

Primary Endpoint

-mCRPC

Secondary Endpoints

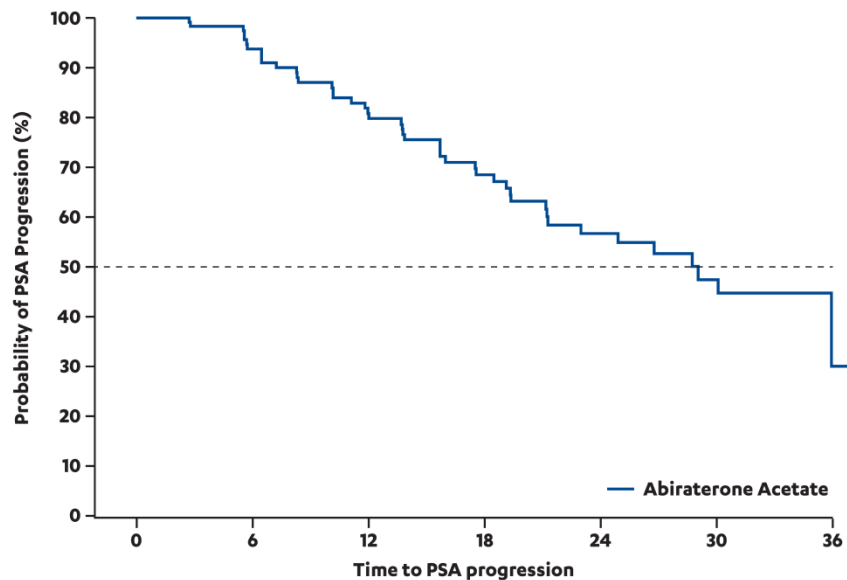
Figure 3: Maximum PSA Reduction During Cycles 1-6



- 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

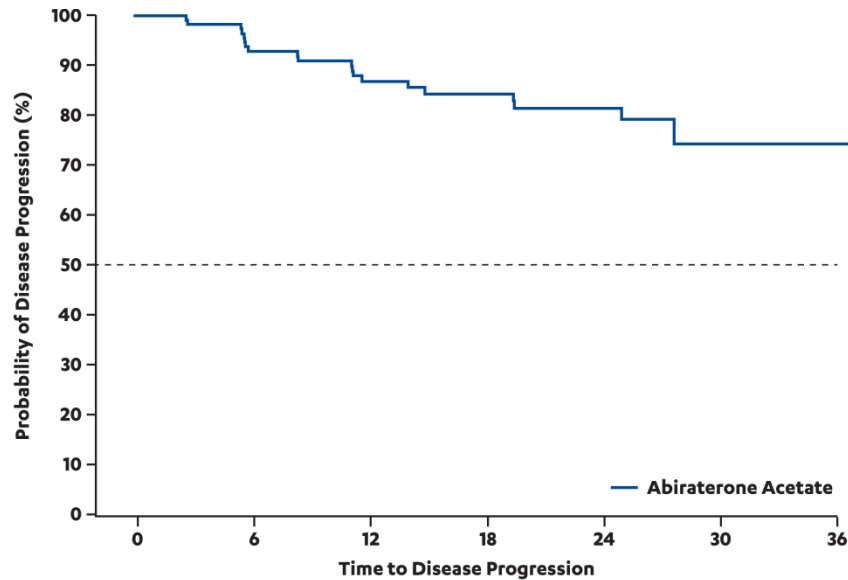
IMAAGEN Trial Update: Effect of Abiraterone Acetate and Low Dose Prednisone on PSA in Patients With Non--mCRPC

Figure 5: PSA Progression



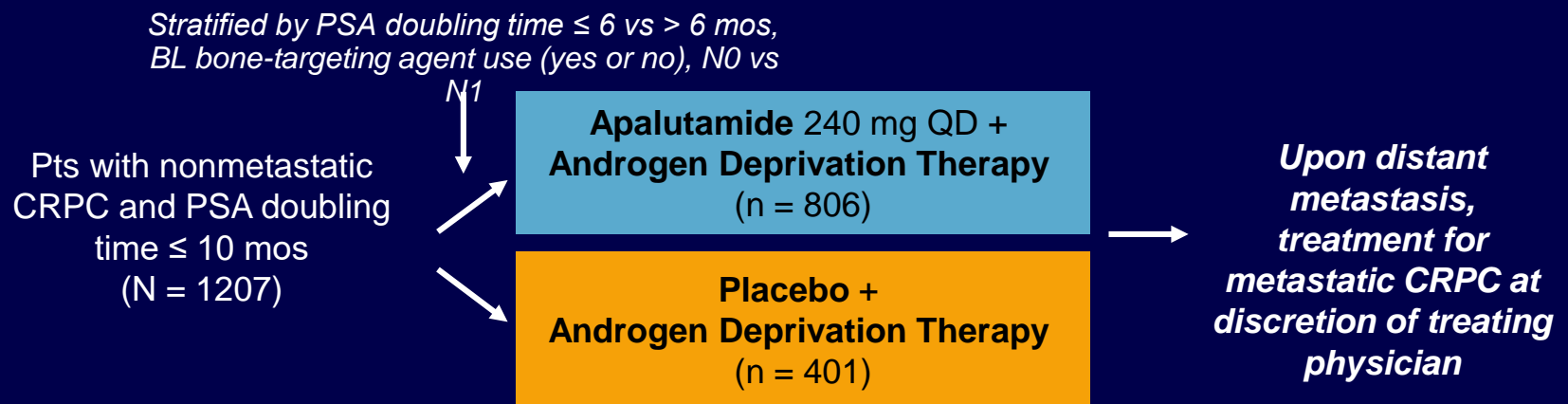
Subjects at risk: 131 101 75 52 32 18 1

Figure 4: Radiographic Evidence of Disease Progression



Subjects at risk: 131 98 82 60 43 22 2

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

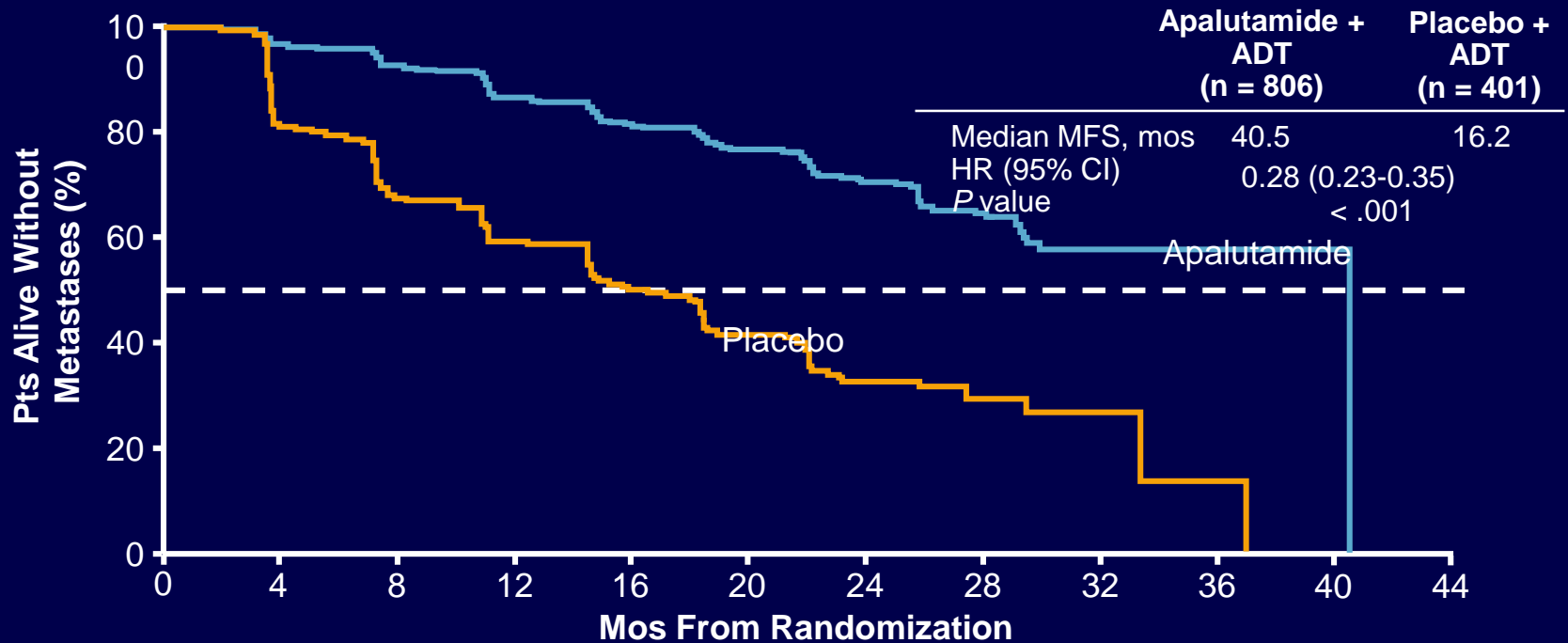
Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

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

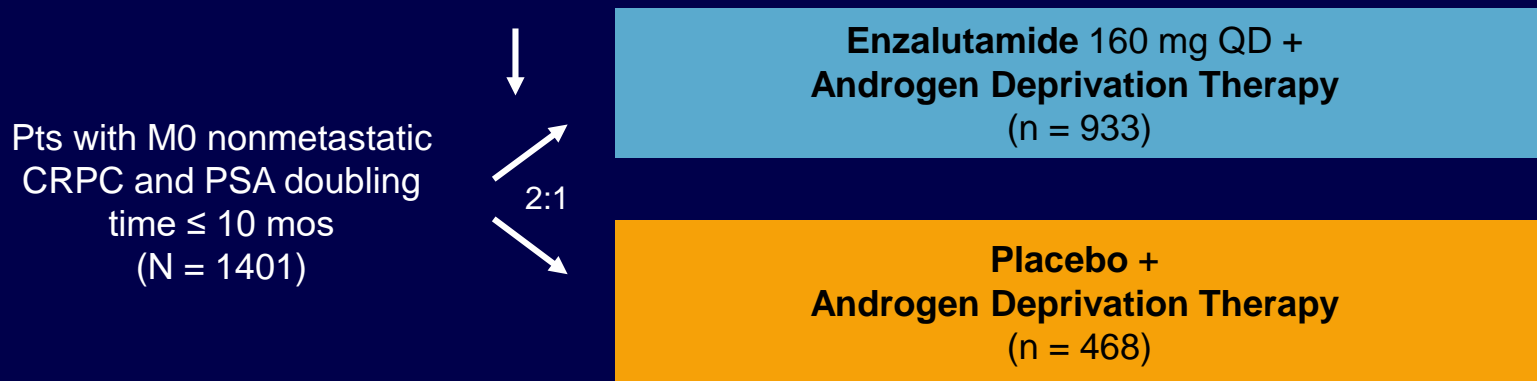
Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

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

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

Stratified by PSA doubling time < 6 mos vs 6-10 mos, BL bone-targeting agent use



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

PROSPER: Baseline Characteristics

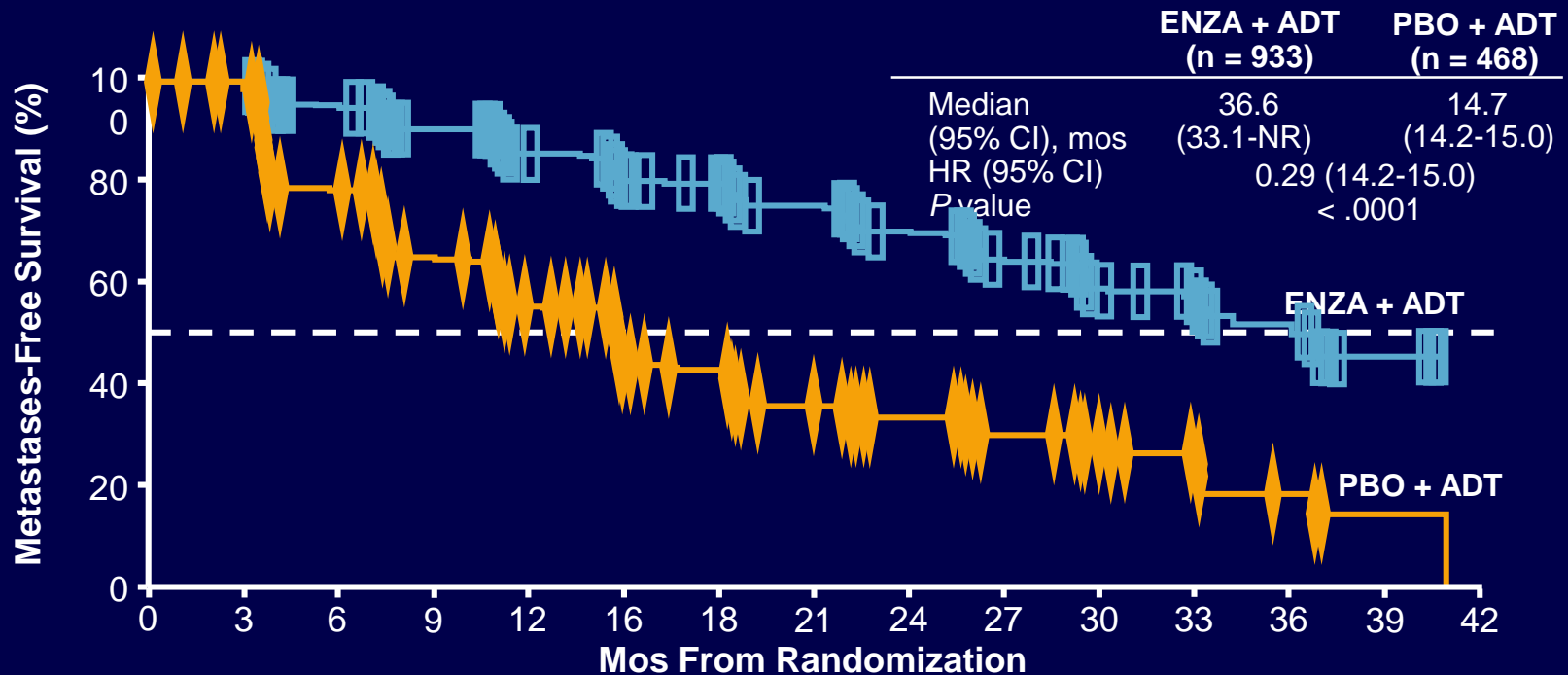
Characteristic	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)
Median age, yrs (range)	74 (50-95)	73 (53-92)
ECOG PS, %		
▪ 0	80	82
▪ 1	20	18
Median serum PSA, ng/mL (range)	11.1 (0.8-1071.1)	10.2 (0.2-467.5)
Median PSA doubling time, mos (range)	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time,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

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)

PROSPER: Metastasis-Free Survival



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

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

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)



Smarter studies
Global impact
Better health



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

Nicholas James

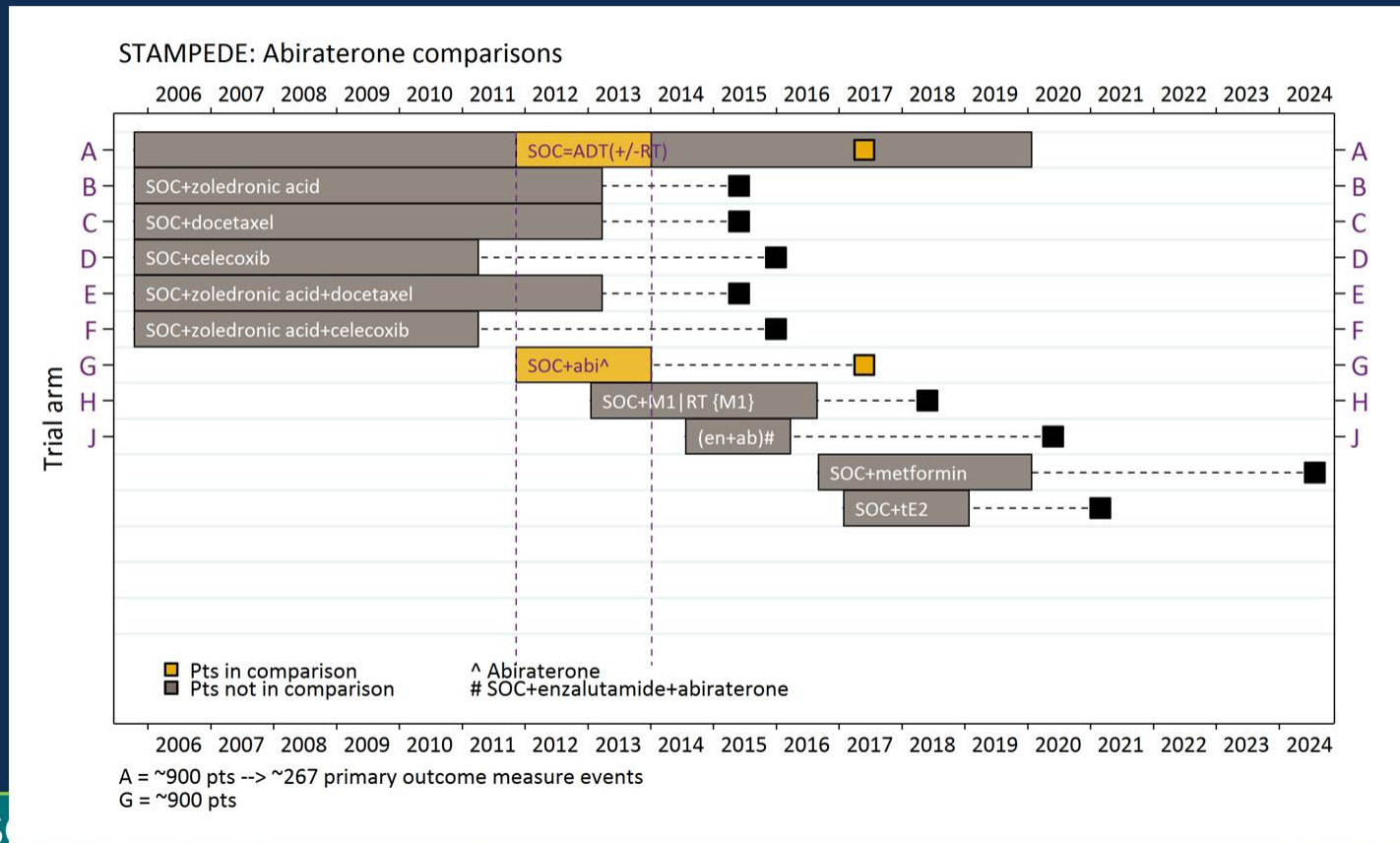
University of Birmingham and Queen Elizabeth Hospital Birmingham
on behalf of

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**

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Abiraterone comparison: patients

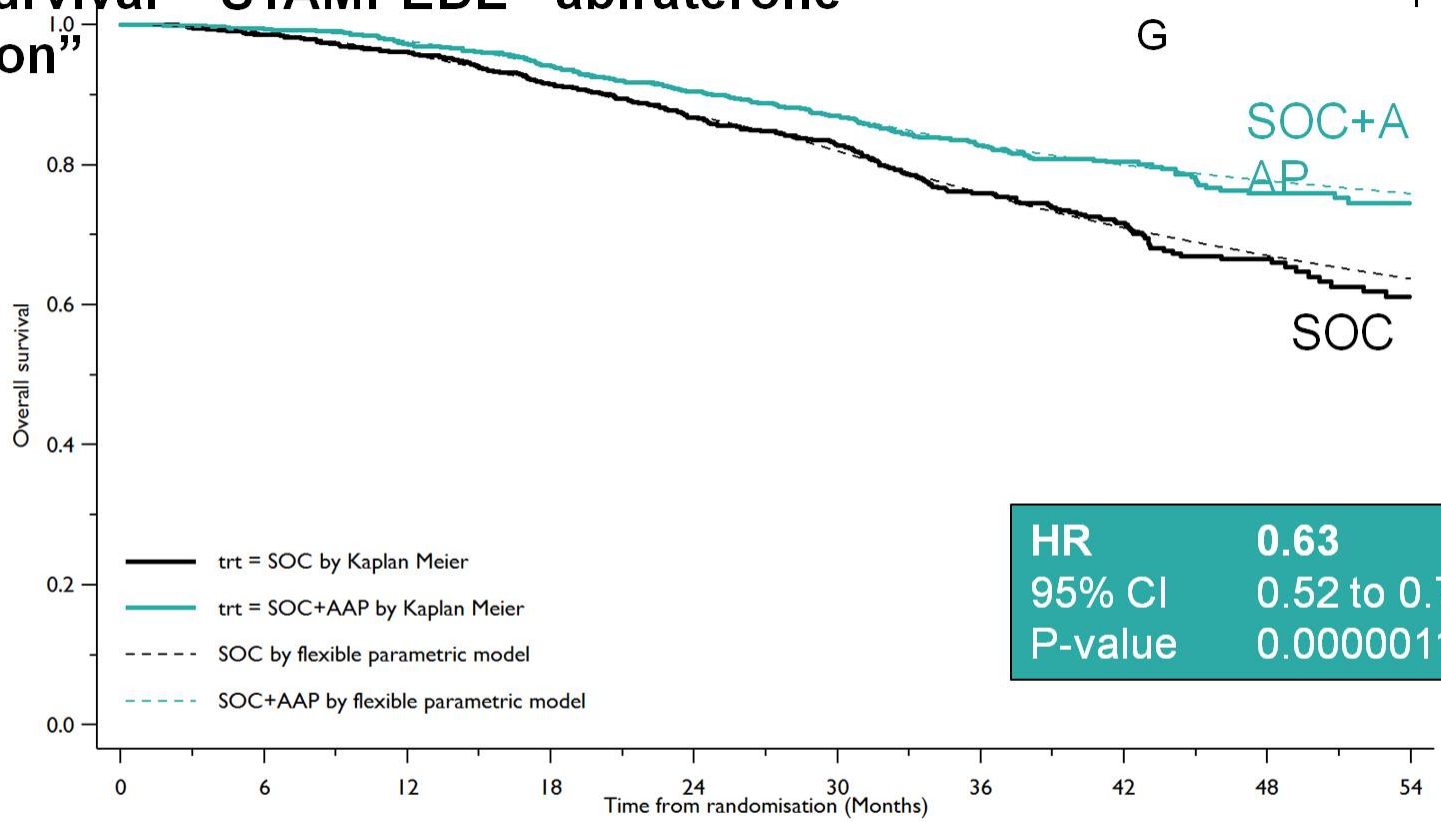


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Overall Survival – STAMPEDE “abiraterone comparison”

Events 262 A | 184 G

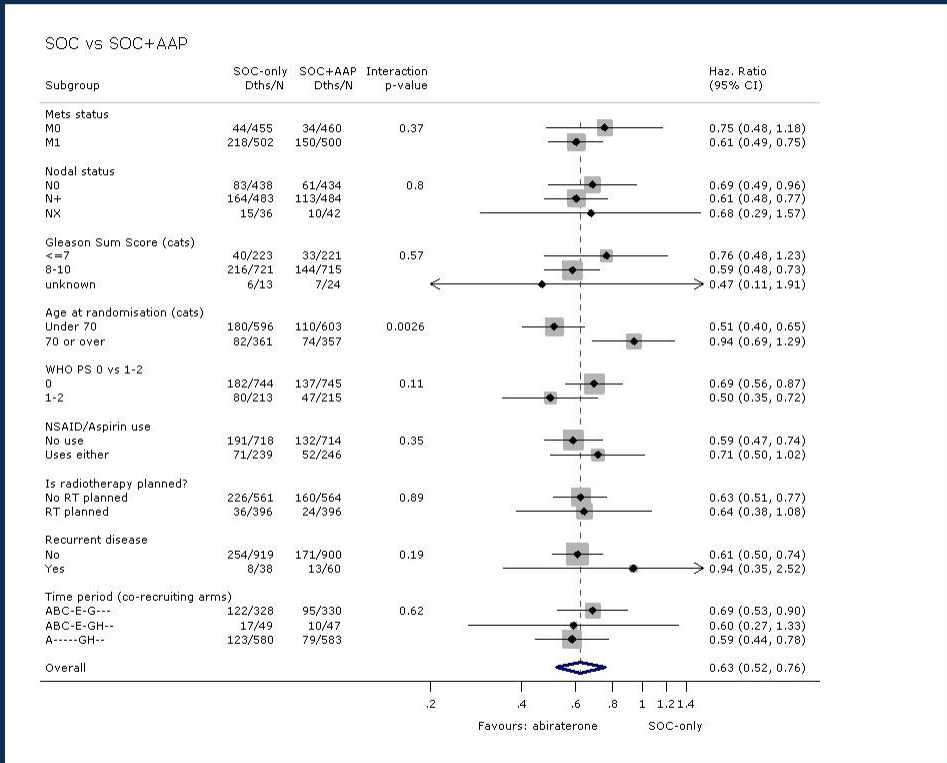


HR 0.63
95% CI 0.52 to 0.76
P-value 0.00000115

	0	6	12	18	24	30	36	42	48	54
SOC	957	(37)	909	(88)	806	(92)	491	(36)	123	
SOC+AAP	960	(26)	917	(63)	840	(67)	541	(25)	161	

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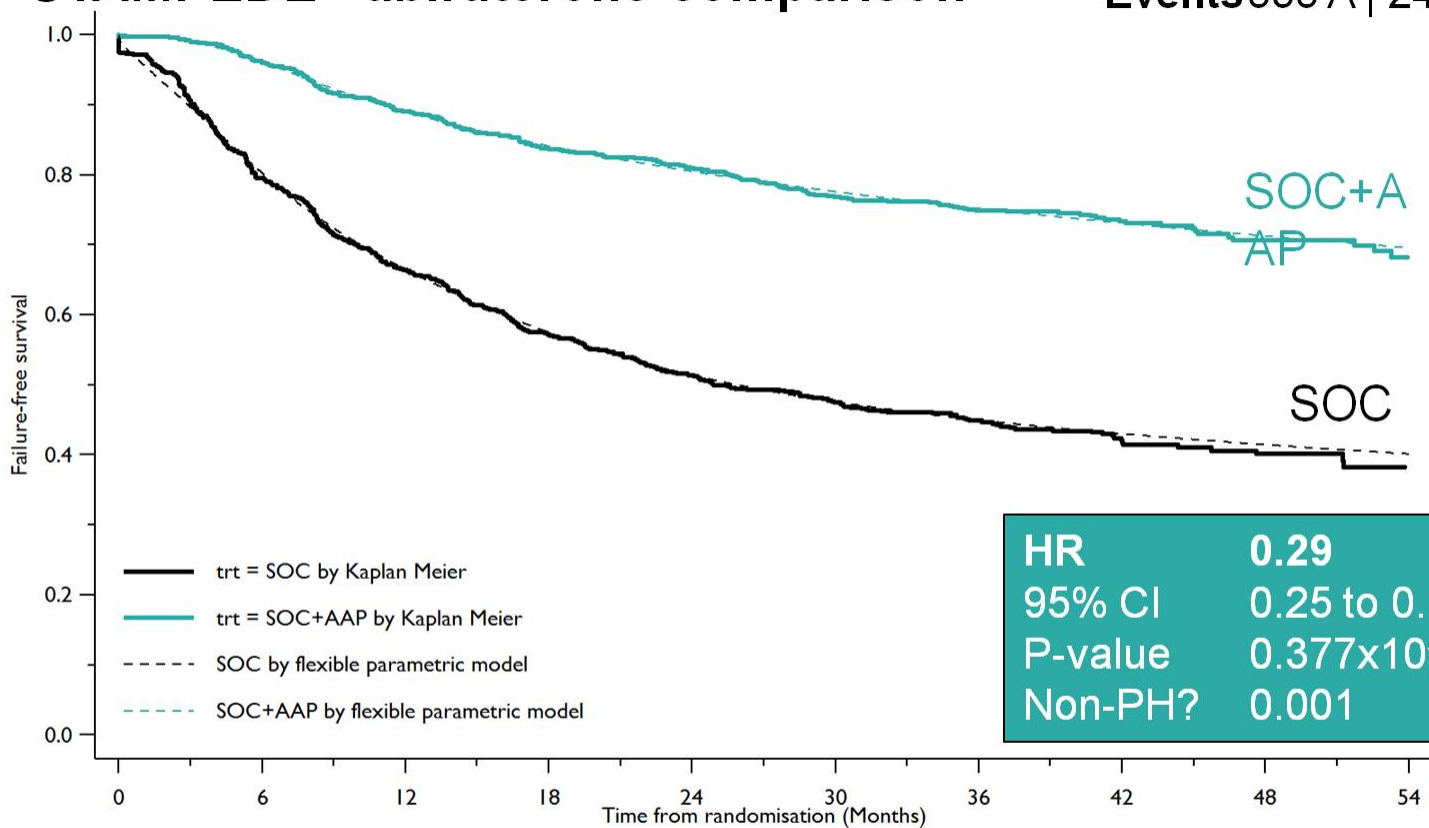
Overall Survival – STAMPEDE “abiraterone comparison”



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 (<i>incl. hot flashes, impotence</i>)	133 (14%)	129 (14%)
Cardiovascular disorder (<i>incl. hypertension, MI, dysrhythmia</i>):	41 (4%)	92 (10%)
Musculoskeletal disorder:	46 (5%)	68 (7%)
Gastrointestinal disorder:	40 (4%)	49 (5%)
Hepatic disorder (<i>incl. increased AST, increased ALT</i>):	12 (1%)	70 (7%)
General disorder (<i>incl. fatigue, oedema</i>):	29 (3%)	45 (5%)
Respiratory disorder (<i>incl. breathlessness</i>):	23 (2%)	44 (5%)
Lab abnormalities (<i>incl. hypokalaemia</i>):	21 (2%)	34 (4%)

Treatment compliance

Abiraterone

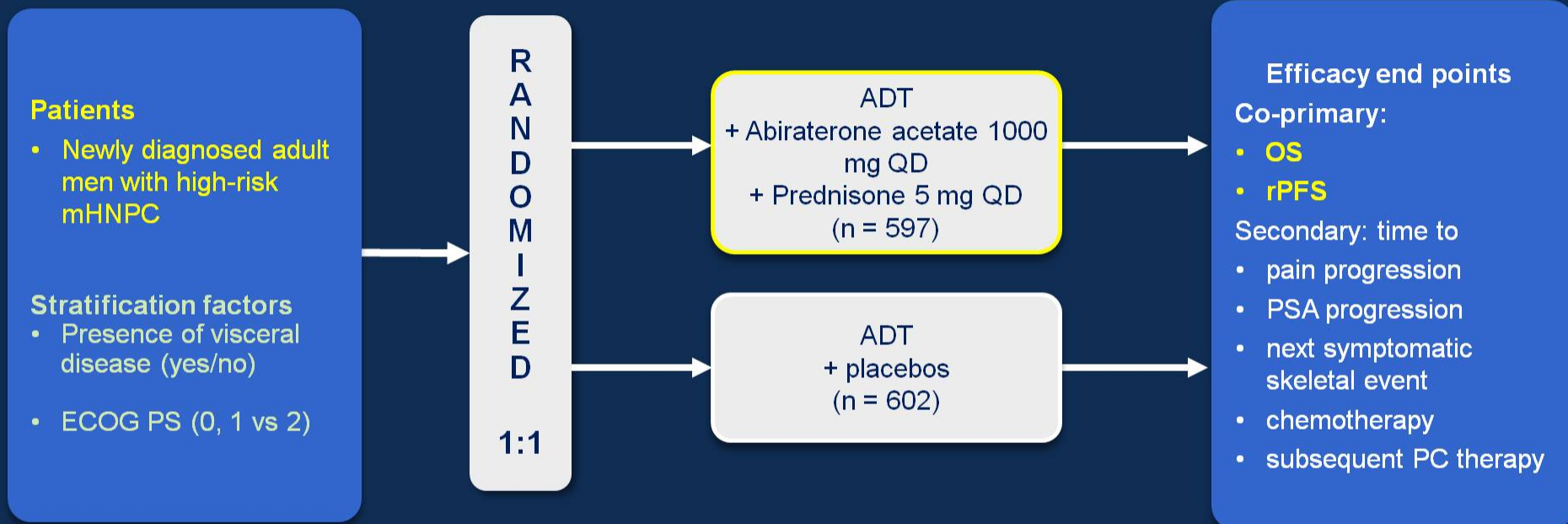
The administration of abiraterone is expected to be as follows:

- **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

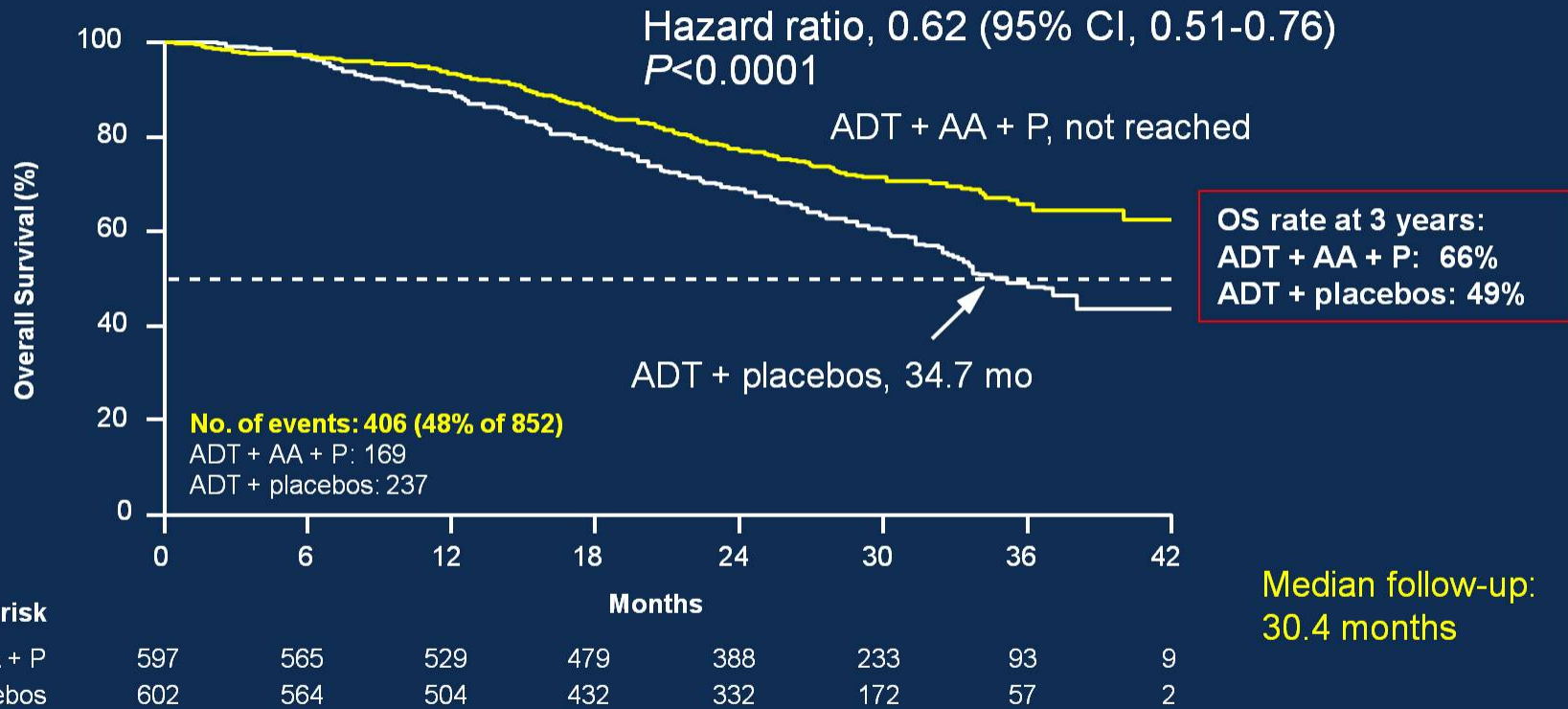


- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHARTED/STAMPEDE results

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	97%	98%
Liver	5%	5%
Lungs	12%	12%
Node	47%	48%
Baseline pain score (BPI-SF Item 3)		
0-1	50%	50%
2-3	22%	24%
≥ 4	29%	27%

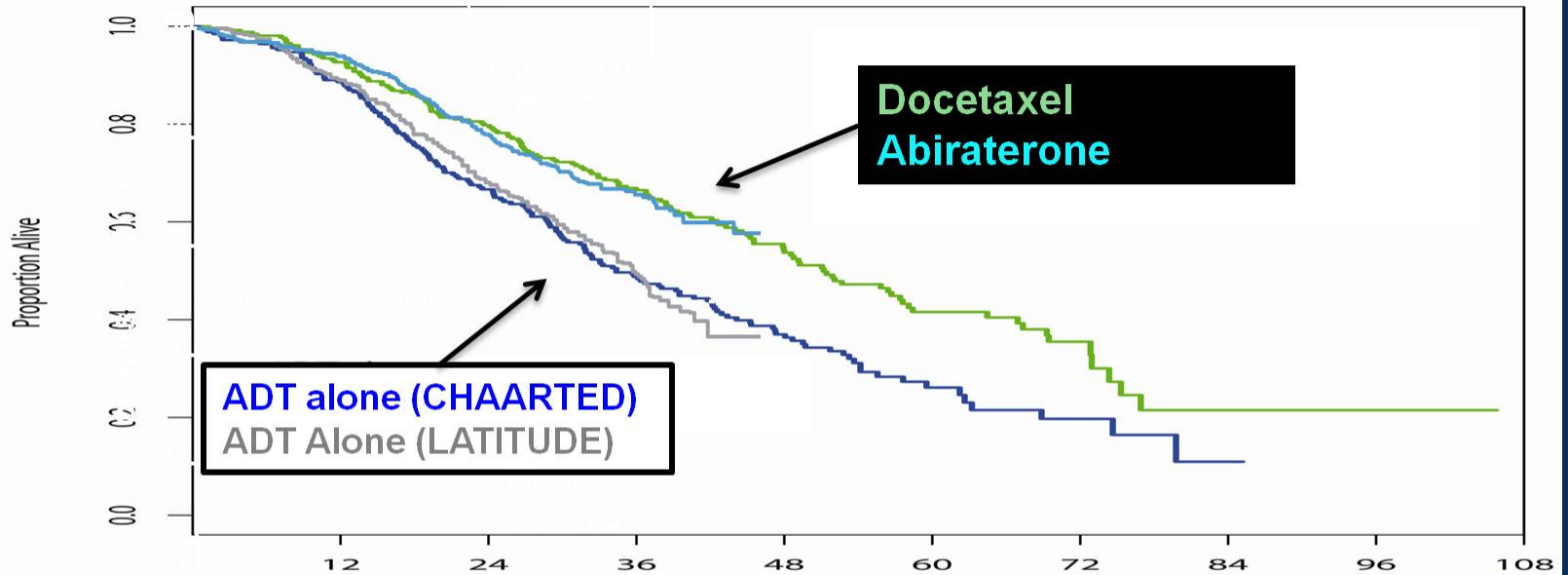
Statistically significant **38%** risk reduction of death



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%*

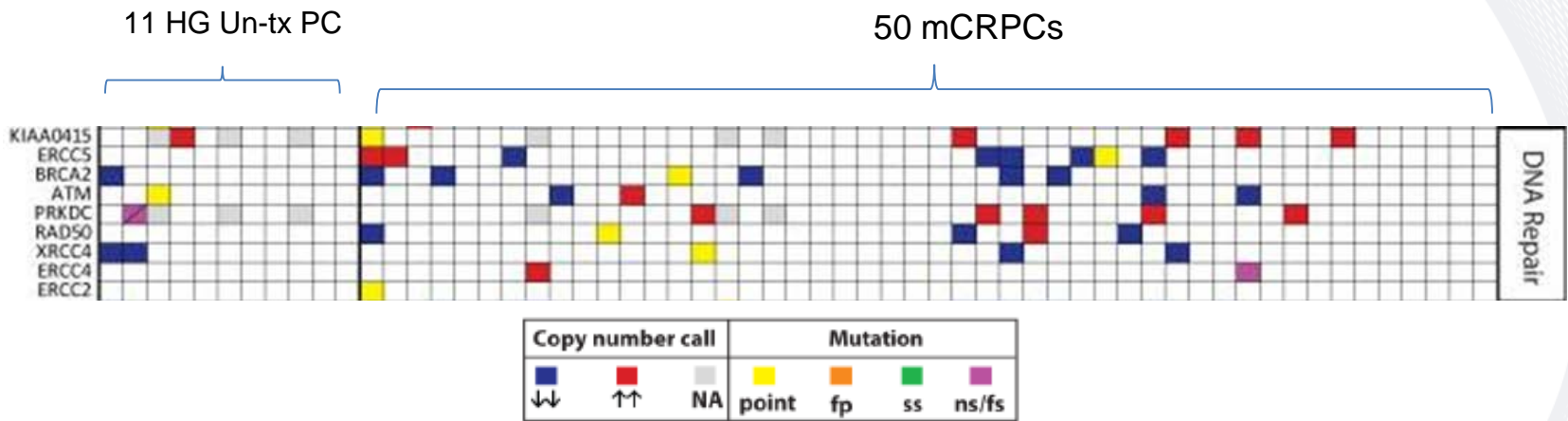
Docetaxel vs. Abiraterone



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

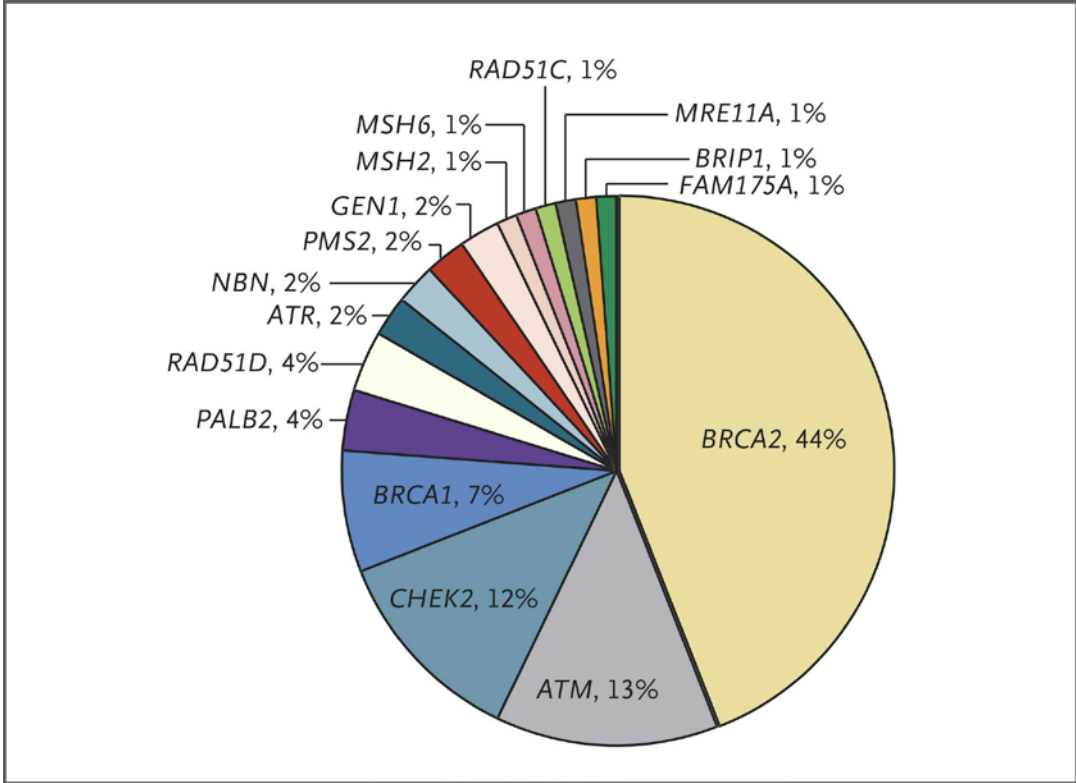


Approximately 50% (24 cases of mCRPC) with aberration in DNA repair genes

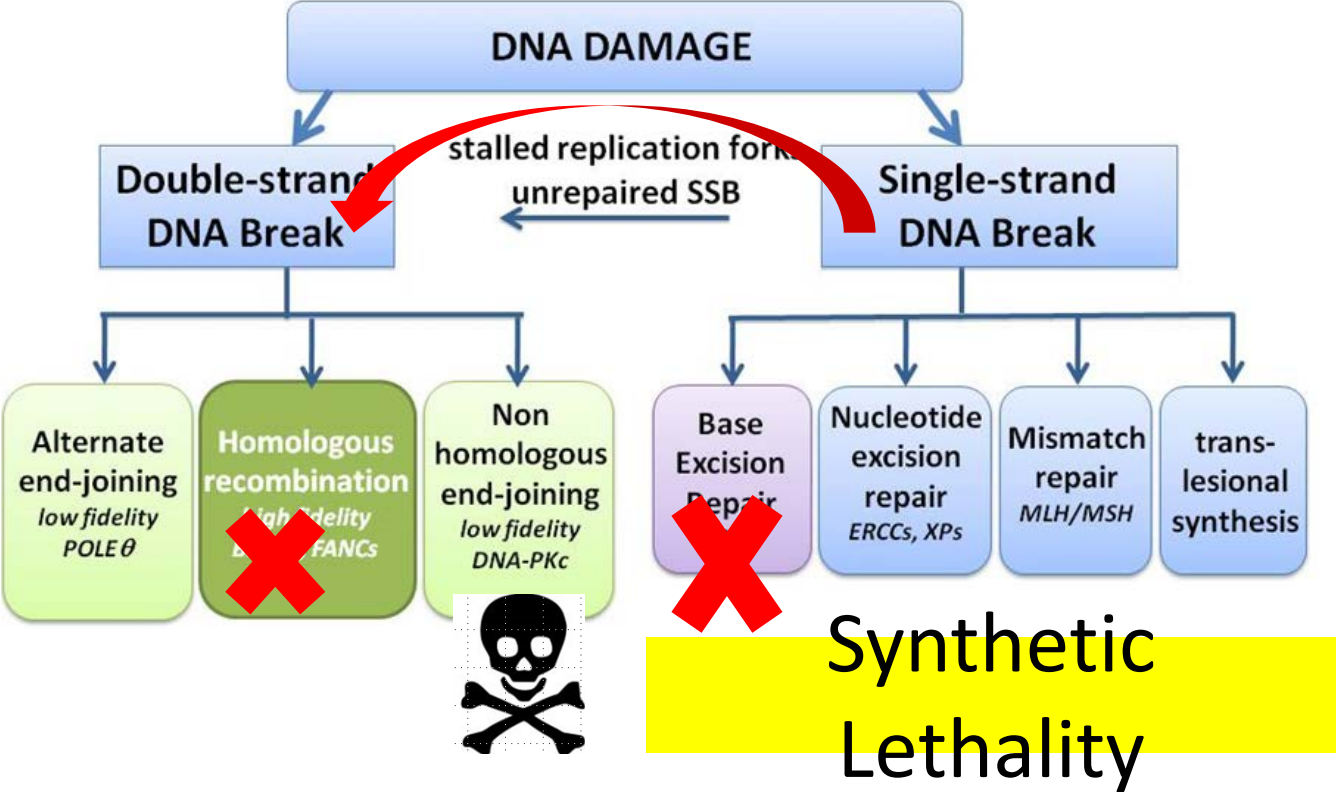
Grosso 2012. Nature

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

Case Series	Description	Patients	Patients with Mutations
		<i>no.</i>	<i>no. (%)</i>
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)



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 of these patients responded.**

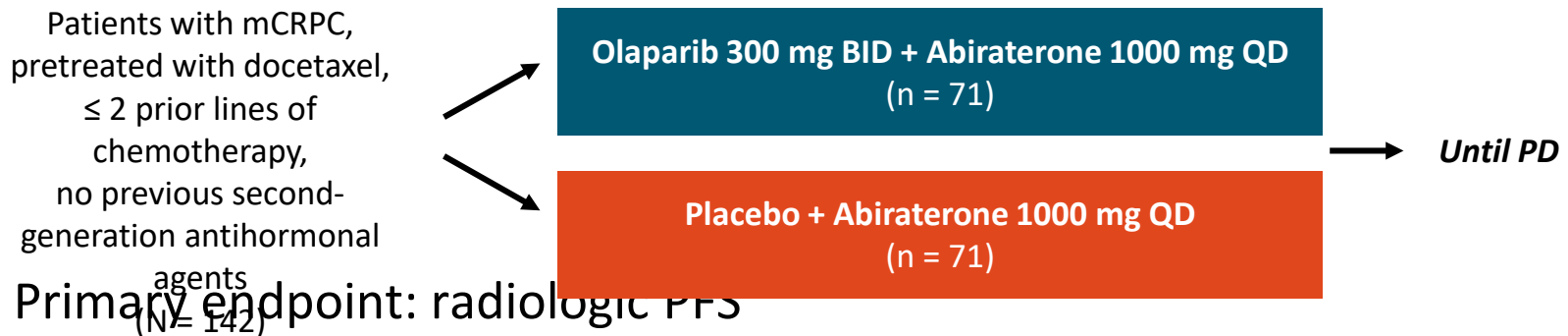
Olaparib + Abiraterone in mCRPC: Background

- 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

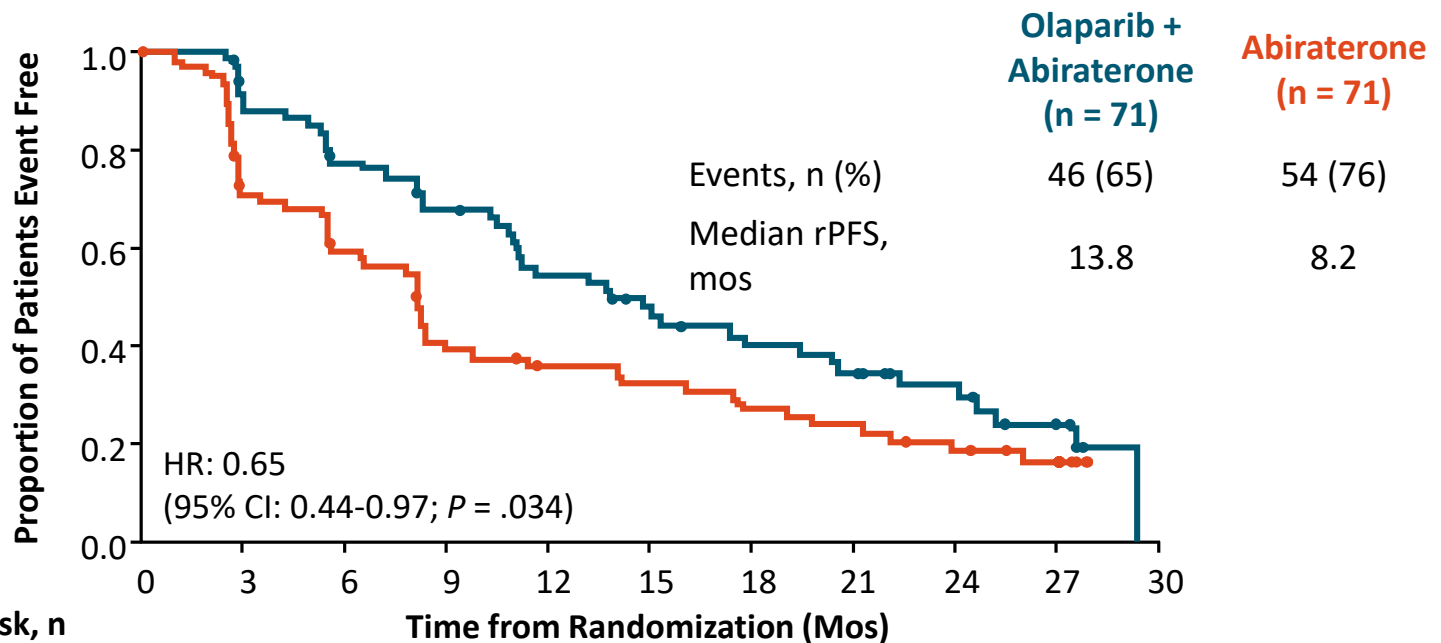
Olaparib + Abiraterone in mCRPC: Patient Population

Characteristic	Olaparib + Abirateron e (n = 71)	Abirateron e (n = 71)
Median age, yrs (IQR)	70 (65-75)	67 (62-74)
White race, n (%)	67 (94)	67 (94)
ECOG PS, n (%)		
▪ 0	34 (48)	38 (54)
▪ 1	36 (51)	30 (42)
▪ 2	1 (1)	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)

Clarke H, et al. ASCO 2016. Abstract 5005.

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

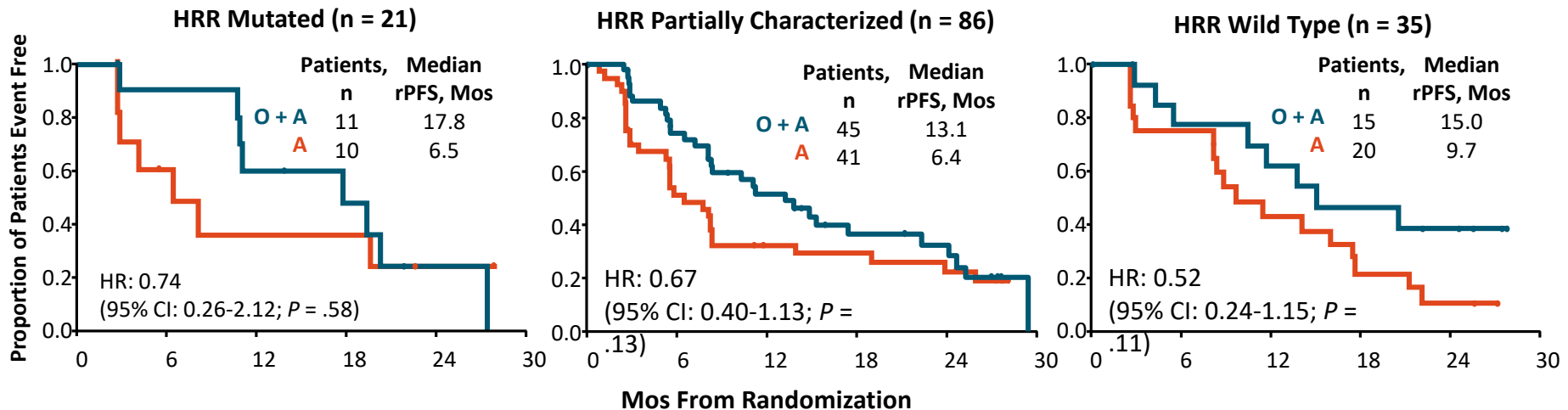
Olaparib + Abiraterone in mCRPC: Investigator-Assessed Radiologic PFS (Primary Endpoint)



	Patients at Risk, n										
	0	3	6	9	12	15	18	21	24	27	30
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*

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

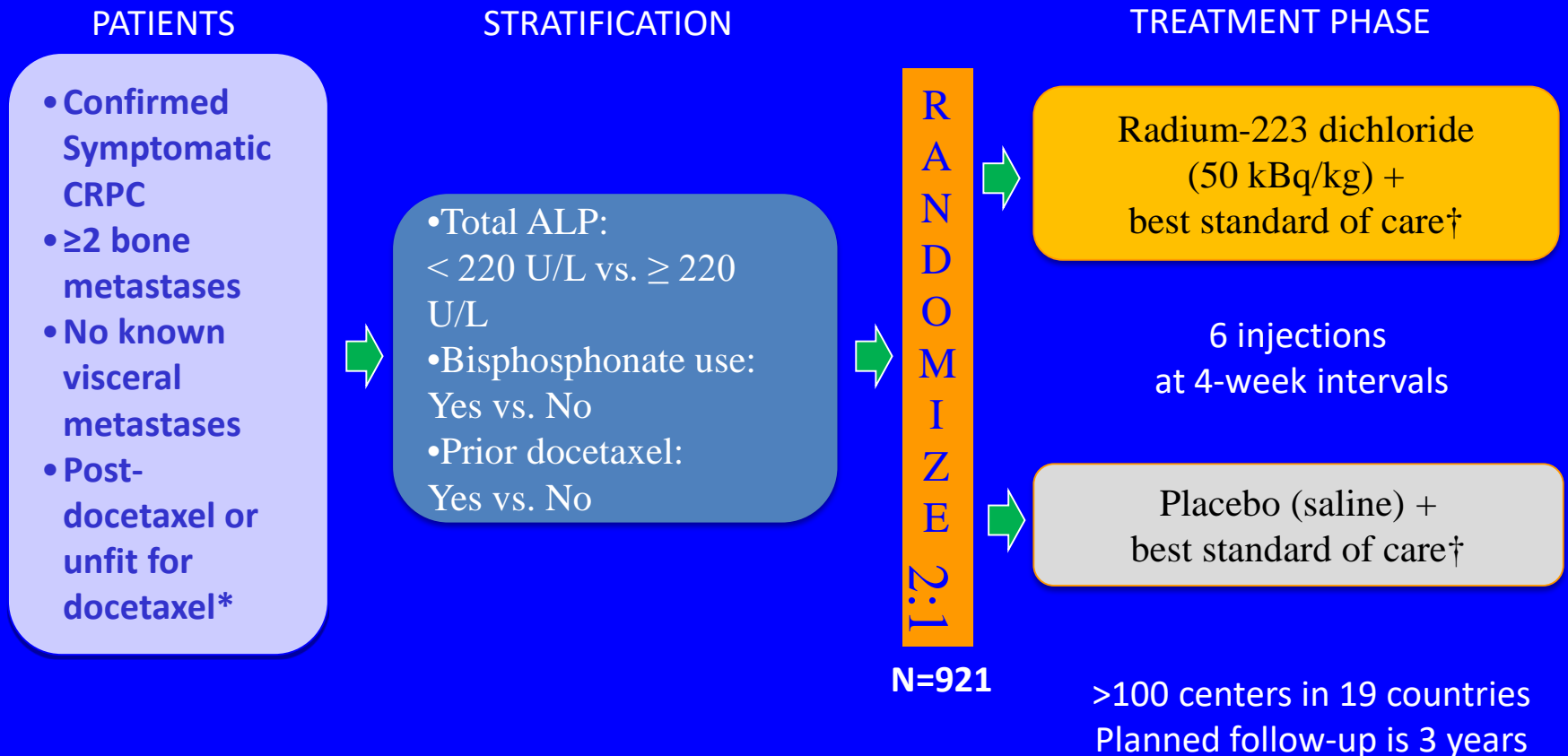
Ongoing Trials of PARP inhibitor

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 toxicity	KEYNOTE-365
R-II	Olaparib	mCRPC (≥ 2 prior lines)	Cediranib plus Olaparib vs Olaparib	rPFS	NCT02893917
I / II	Olaparib	mCRPC, (lung , breast, Ov, CRC)	Durva+Ced Durva+Ola Durva+CO	Safety and dose finding	NCT02484404

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design¹

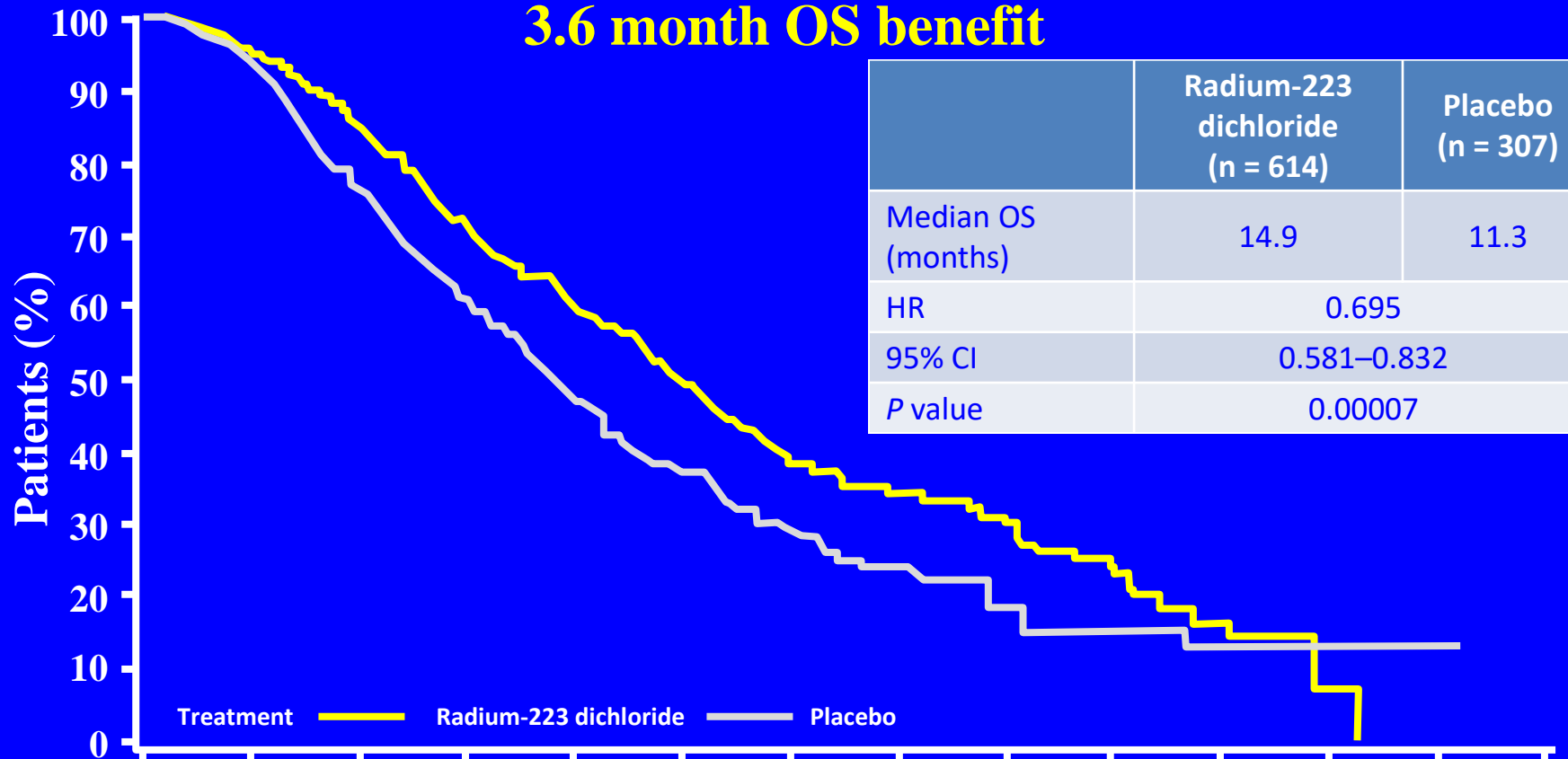


*Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable

†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

ALSYMPCA Updated Analysis: Overall Survival

3.6 month OS benefit



	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	

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

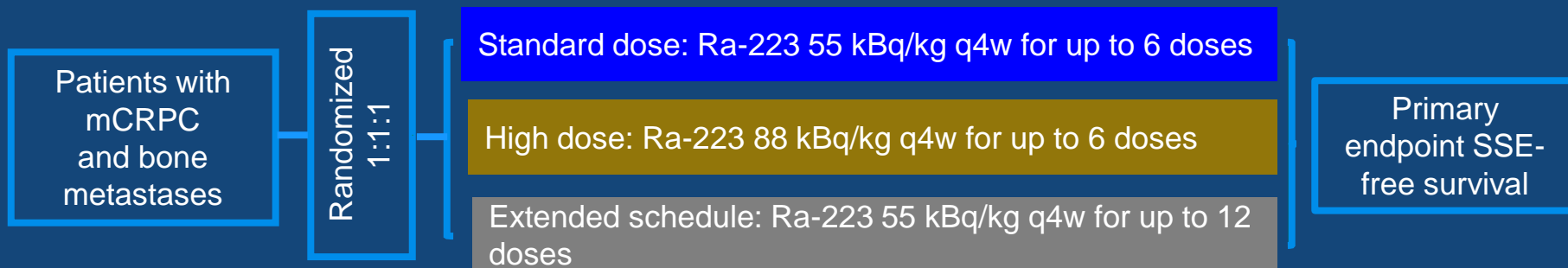
Reference: Parker et al. *J Clin Oncol*. 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

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)

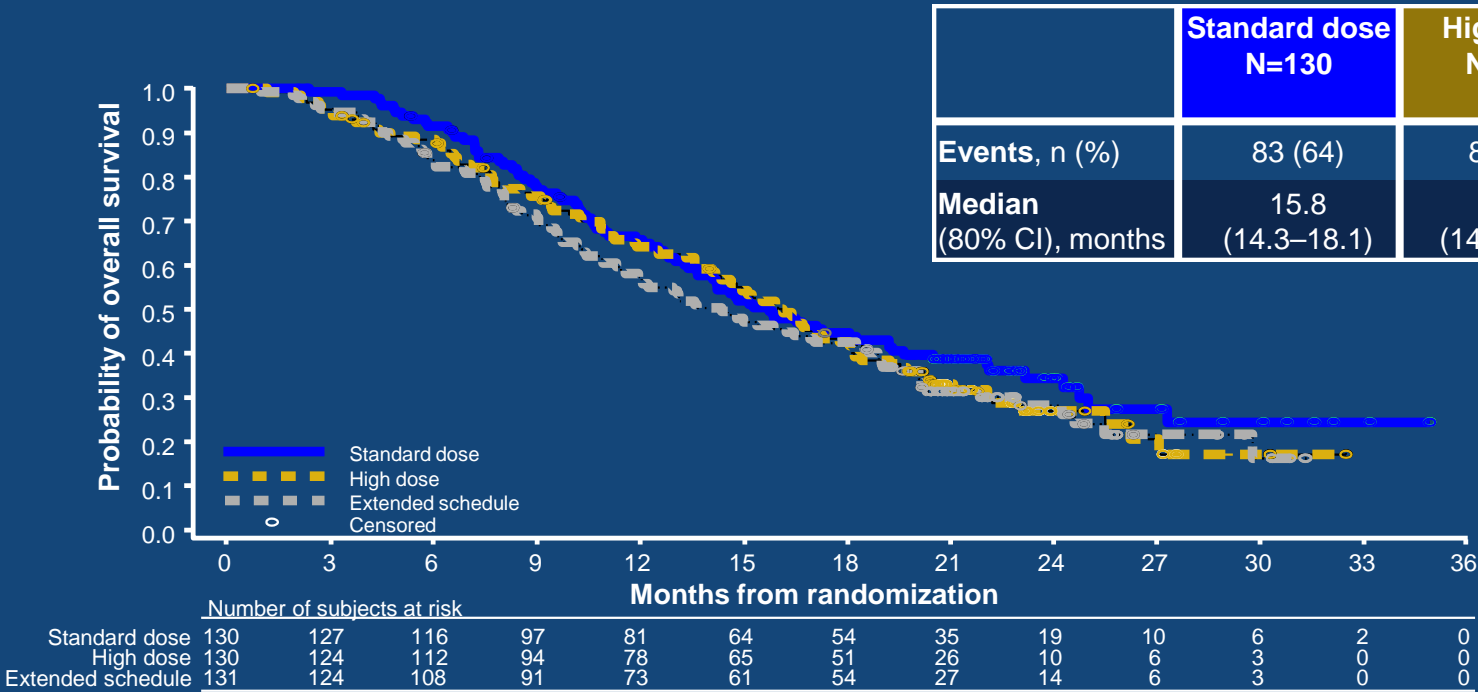


- Stratification:
 - Prior chemotherapy: ≤ 1 prior regimen vs > 1 prior regimen
 - Total ALP: < 220 U/L vs ≥ 220 U/L
 - Worst pain score by BPI: ≤ 4 vs > 4
- Concomitant therapy allowed: hormonal, bisphosphonates, RANK ligand inhibitors

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

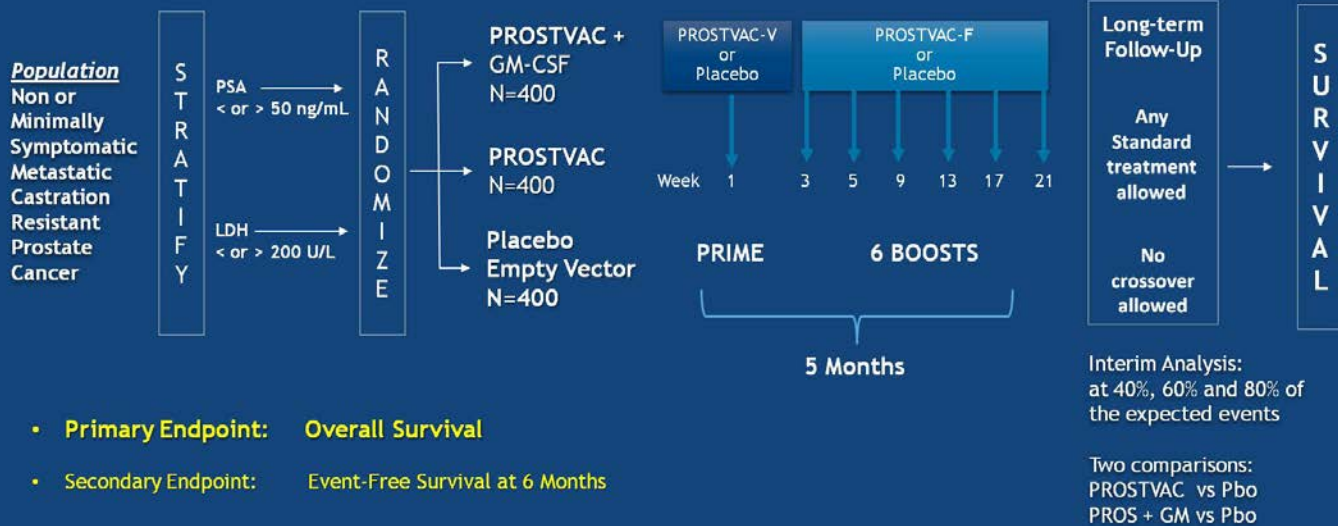
Cora N. Sternberg

Overall survival



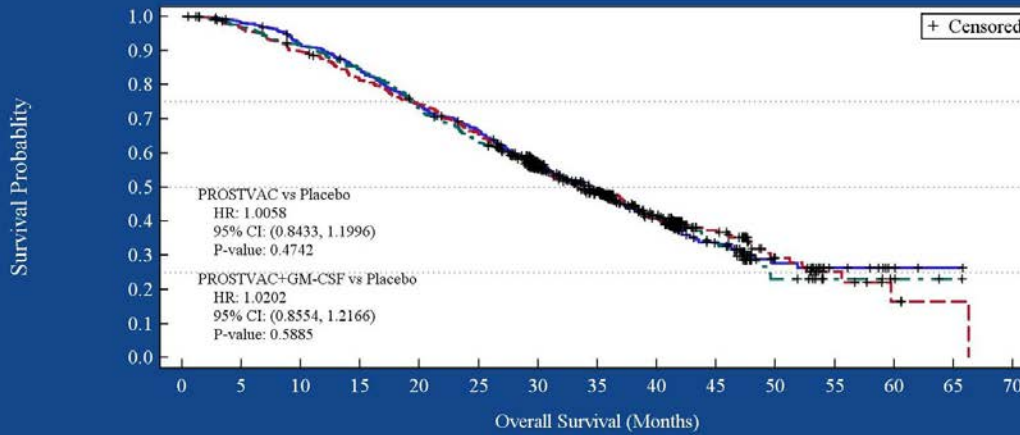
Cora N. Sternberg

PROSPECT Phase 3 Design



Overall Survival ITT

Product-Limit Survival Estimates



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

— PROSTVAC — PROSTVAC+GM-CSF - - - Placebo

PROSTVAC	432	420	391	359	315	282	212	165	97	48	22	9	3	1	0
PROSTVAC+GM-CSF	432	416	385	347	317	278	203	154	97	51	21	8	3	1	0
Placebo	433	418	392	362	312	268	202	161	89	36	12	5	3	1	0

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