Advanced prostate cancer

New treatment options

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CLINICAL CARE OPTIONS® ONCOLOGY

Genitourinary Cancers

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San Francisco, California

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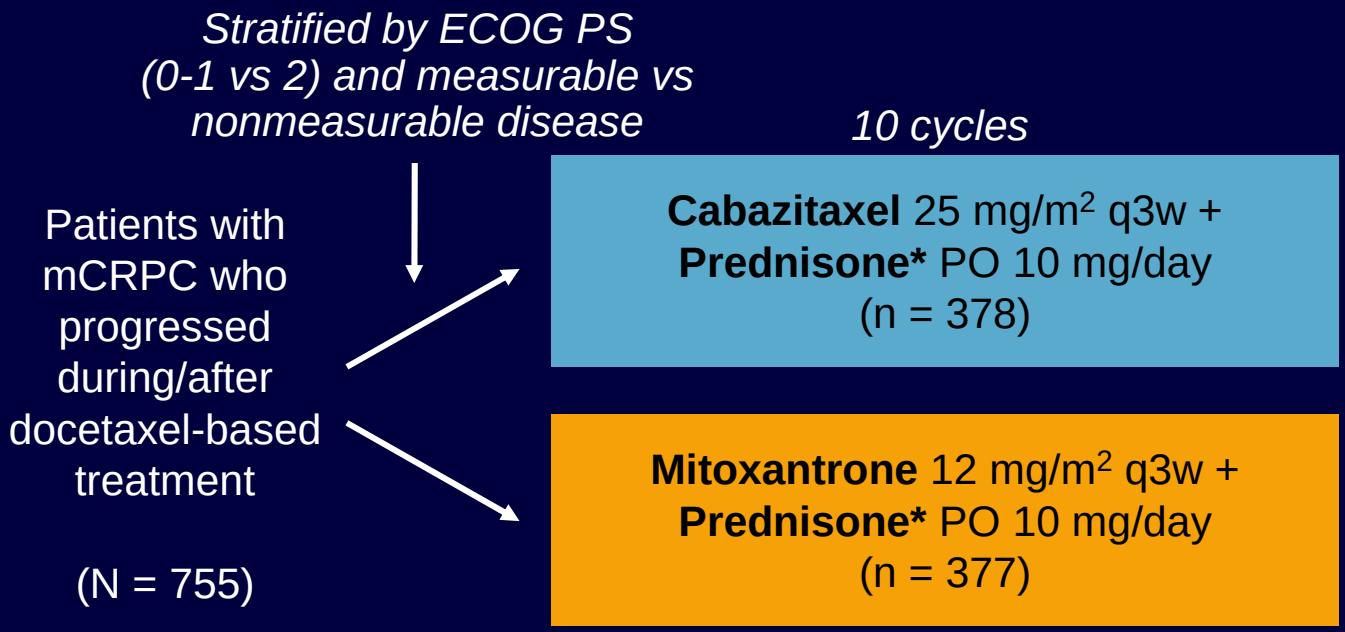
This program is supported by educational grants from Amgen, Bristol-Myers Squibb, Celgene, Genentech BioOncology, Millennium Pharmaceuticals, Inc., Novartis Oncology, and Pfizer, Inc.

TROPIC: Cabazitaxel vs Mitoxantrone in Docetaxel-Treated mCRPC. Randomized, Prospective, Open-Label, Multinational Phase III Trial

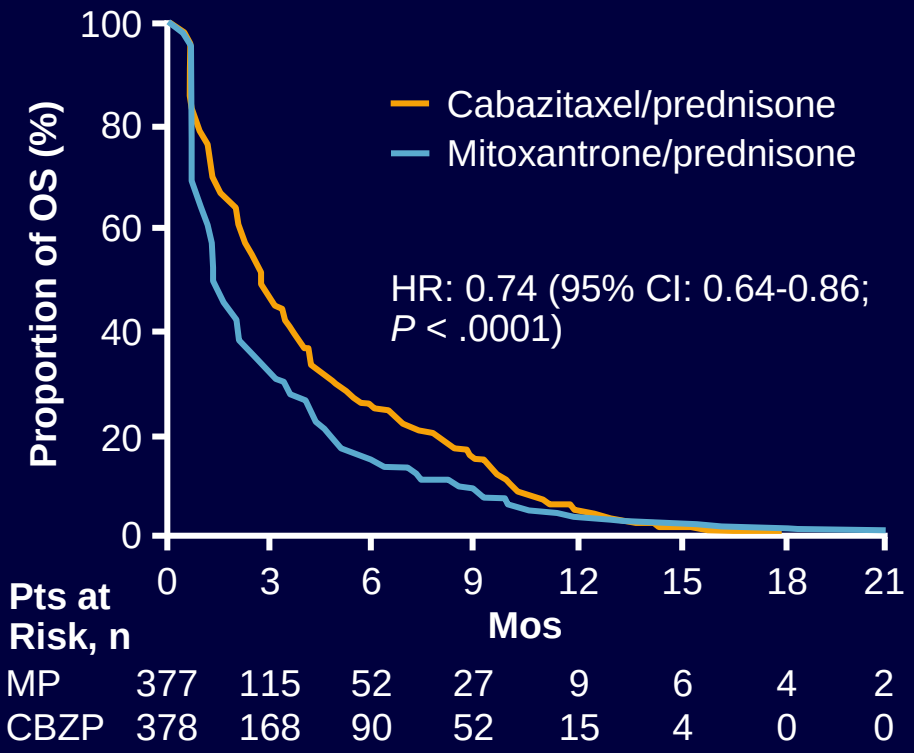
- Cabazitaxel: novel semisynthetic taxane developed to overcome taxane resistance



- Primary endpoint: OS; secondary endpoints: PFS, response, safety

Sartor AO, et al. ASCO GU 2010. Abstract 9. *Lancet.* 2010;376: 1147-1154

TROPIC: Progression-Free Survival



Outcome, Mos	Cabazitaxel/ Prednisone (n = 378)	Mitoxantrone/ Prednisone (n = 377)
Median PFS	2.8	1.4
Median TTP		
▪ Tumor assessment	8.8	5.4
▪ PSA assessment	6.4	3.1
▪ Pain assessment	11.1	Not reached

TROPIC: Response Rates and Toxicity

- Significantly higher response rates with cabazitaxel plus prednisone vs mitoxantrone plus prednisone
  - Tumor assessment: 14.4% response with cabazitaxel plus prednisone vs 4.4% with mitoxantrone plus prednisone (*P* = .0005)
  - PSA assessment: 39.2% response with cabazitaxel plus prednisone vs 17.8% with mitoxantrone plus prednisone (*P* = .0002)
- Toxicity profile generally manageable and similar between treatment arms
  - Higher incidence of grade 3 neutropenia: 82% vs 58%; febrile neutropenia: 7.5% vs 1.3%; all grade diarrhea 46.6% vs 10.5% with cabazitaxel plus prednisone vs mitoxantrone plus prednisone, respectively

De Bono JS, et al. ASCO 2010. Abstract 4508.

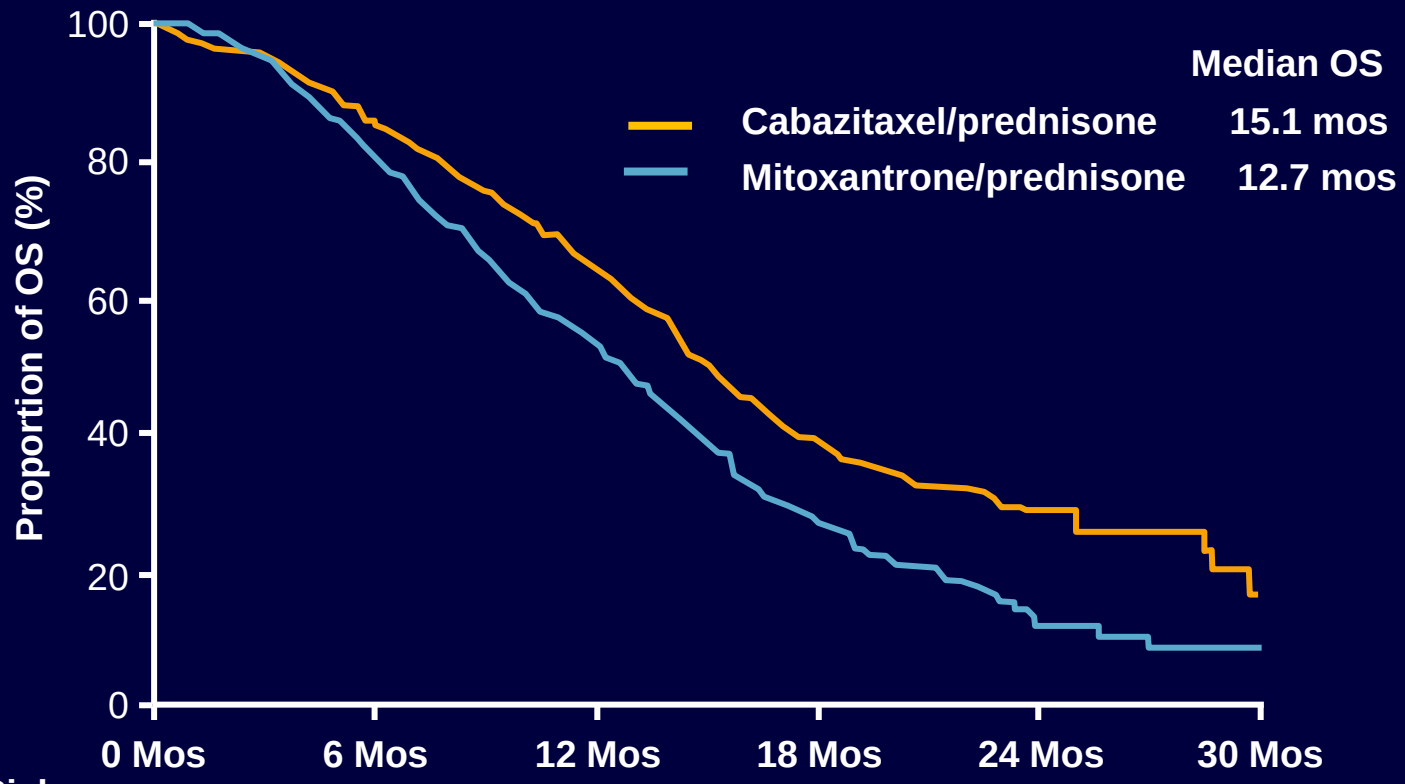
TROPIC: Safety

- Deaths from AEs more common with cabazitaxel vs mitoxantrone (4.9% vs 1.9%)

AE, %	Cabazitaxel/Prednisone (n = 371)		Mitoxantrone/Prednisone (n = 371)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Anemia	97.3	10.5	81.4	4.9
Leukopenia	95.7	68.2	92.5	42.3
Neutropenia	93.5	81.7	87.6	58.0
Thrombocytopenia	47.4	4.0	43.1	1.6
Diarrhea	46.6	6.2	10.5	0.3
Fatigue	36.7	4.9	27.5	3
Nausea	34.2	1.9	22.9	0.3
Vomiting	22.6	1.9	10.2	0
Asthenia	20.5	4.6	12.4	2.4
Hematuria	16.7	1.9	3.8	0.5
Back pain	16.2	3.8	12.1	3
Abdominal pain	11.6	1.9	3.5	0
Febrile neutropenia	7.5	7.5	1.3	1.3

Sartor AO, et al. ASCO GU 2010. Abstract 9.

TROPIC: Overall Survival



Pts at Risk, n						
MP	377	300	188	67	11	1
CBZP	378	321	231	90	28	4

Sartor AO, et al. ASCO GU 2010. Abstract 9.

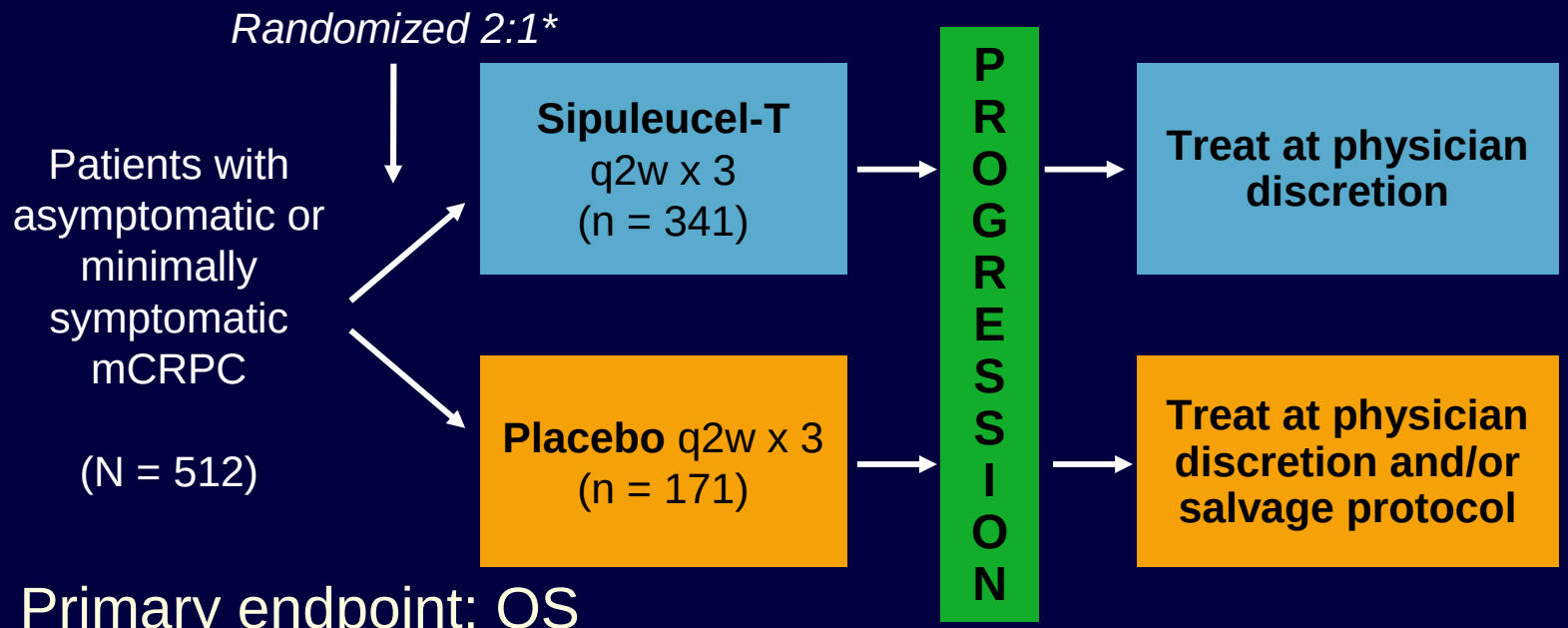
TROPIC: Conclusions

- Cabazitaxel/prednisone significantly improved OS vs mitoxantrone/prednisone in metastatic CRPC
  - Reduced risk of death: 28% (HR: 0.72; *P* < .0001)
- Cabazitaxel/prednisone also significantly improved PFS, response rates, and TTP vs mitoxantrone/prednisone
- Associated with acceptable safety profile
  - Febrile neutropenia and diarrhea more common with cabazitaxel/prednisone vs mitoxantrone/prednisone
- Cabazitaxel/prednisone first treatment to demonstrate survival benefit in patients with metastatic CRPC who failed docetaxel-based therapy

De Bono JS, et al. ASCO 2010. Abstract 4508.

IMPACT: Phase III Sipuleucel-T in mCRPC

- Sipuleucel-T: cellular immunotherapy produced by exposing a patient's leukapheresed cells to recombinant fusion protein consisting of prostatic acid phosphatase antigen and GM-CSF



- Primary endpoint: OS

*Stratified by primary Gleason score, number of bone metastases, and bisphosphonate use

Kantoff P, et al. ASCO GU 2010. Abstract 8.

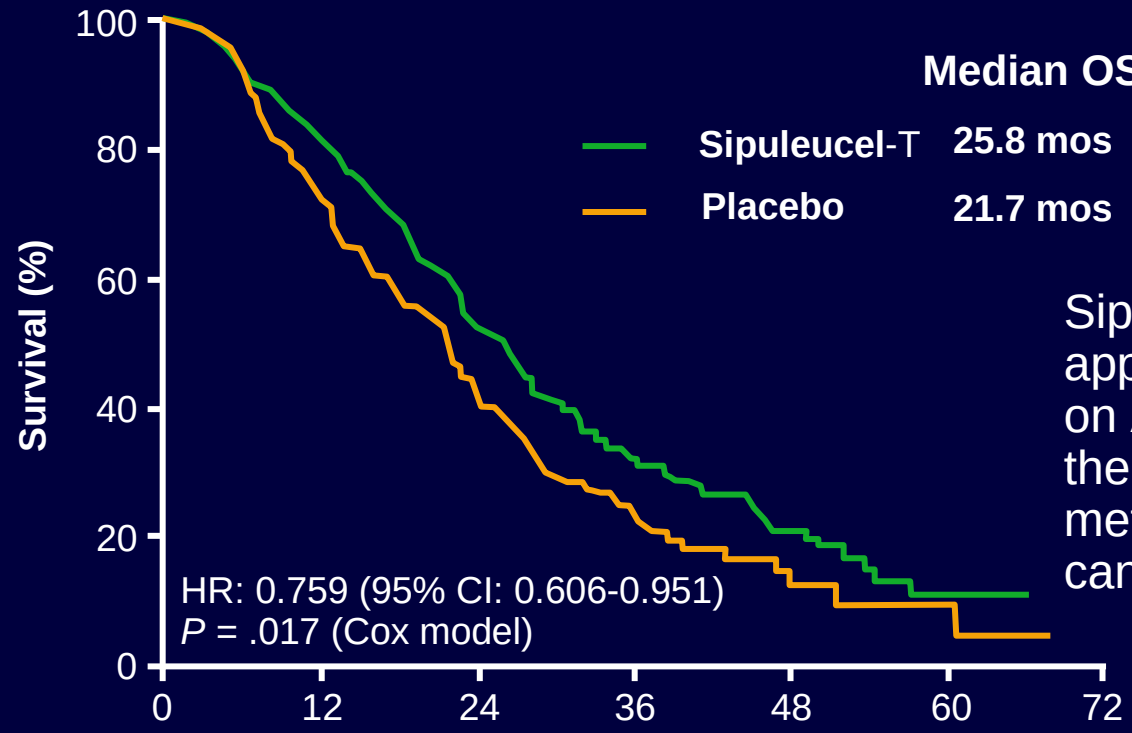
IMPACT: Baseline Characteristics

Characteristic	Sipuleucel-T (n = 341)	Placebo (n = 171)
ECOG PS 0, %	82.1	81.3
Gleason score ≤ 7, %	75.4	75.4
> 10 bone metastases, %	42.8	42.7
Bisphosphonate use, %	48.1	48.0
Prior docetaxel, %	15.5	12.3
Serum PSA, ng/mL	51.7	47.2
Alkaline phosphatase, g/dL	99.0	109.0
LDH, u/L	194.0	193.0

Kantoff P, et al. ASCO GU 2010. Abstract 8.

IMPACT: Overall Survival

- Median follow-up: 36.5 mos (349 events)



	Median OS	36-Month OS
Sipuleucel-T	25.8 mos	32.1%
Placebo	21.7 mos	23.0%

Sipuleucel-T was approved by the FDA on April 30, 2010, for the treatment of metastatic prostate cancer

Pts at Risk, n						
Sipuleucel-T	341	274	142	56	18	3
Placebo	171	123	59	22	5	2

Kantoff P, et al. ASCO GU 2010. Abstract 8.

IMPACT: Safety

- Overall AEs more frequent with sipuleucel-T vs placebo
  - Incidence of any serious AE similar between arms: 24.3% vs 23.8%, respectively

AE,* %	Sipuleucel-T	Placebo
Chills	54.1	12.5
Pyrexia	29.3	13.7
Headache	16.0	4.8
Influenzalike illness	9.8	3.6
Myalgia	9.8	4.8
Hypertension	7.4	3.0
Hyperhidrosis	5.3	0.6
Groin pain	5.0	2.4

*Occurring in ≥ 5% of patients receiving sipuleucel-T with ≥ 2-fold increase in incidence relative to placebo.

Kantoff P, et al. ASCO GU 2010. Abstract 8.

Alpharadin (Radium-223): Phase I/II Study

- Alpharadin (radium-223)
  - First-in-class bone-seeking radioactive alpha-pharmaceutical
  - Targets osteoblastic/sclerotic metastatic sites
- Current analysis included 292 pts with CRPC and bone metastases who were treated with alpharadin in phase I/II studies
  - 2 open-label phase I trials: n = 37
  - 3 double-blind phase II trials: n = 255
  - Doses: 5-250 kBq/kg

Nilsson S, et al. ASCO GU 2010. Abstract 106.

Alpharadin (Radium-223): Phase I/II Results

- Overall grade 3/4 hematologic toxicities each occurred in < 5% of pts
- Randomized, placebo-controlled phase II study (n = 64)
  - More AEs in placebo group (n = 31) vs alpharadin group (n = 33)
    - 174 vs 155, respectively
  - Median survival 4.5 mos longer with alpharadin vs placebo (*P* = .017)

Nilsson S, et al. ASCO GU 2010. Abstract 106.

CALGB 90401: Phase III Trial of Chemotherapy ± Bevacizumab in CRPC

Stratified by 24-mo survival probability (< 10%, 10% to 29.9%, ≥ 30%), age (< 65 yrs ≥ 65 yrs), previous history of arterial events

Patients with CRPC previously untreated withchemotherapy or biologic agents

(N = 1050)

Dexamethasone 8 mg PO x 3 doses +
Docetaxel 75 mg/m^2 on Day 1 of 21-day cycle +
Prednisone 10 mg/day PO +
Bevacizumab 15 mg/kg IV on Day 1 of 21-day cycle
(n = 524)

Dexamethasone 8 mg PO x 3 doses +
Docetaxel 75 mg/m^2 on Day 1 of 21-day cycle +
Prednisone 10 mg/day PO +
Placebo IV on Day 1 of 21-day cycle
(n = 526)

Kelly WK, et al. ASCO 2010. Abstract LBA4511.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CALGB 90401: Overall and Progression-Free Survival

Outcome, Mos (Range)	*Bevacizumab (n = 524)*	*Placebo (n = 526)*	*HR (95% CI)*	*P Value*
Median OS	22.6 (21.1-24.5)	21.5 (20.0-23.0)	0.91 (0.78-1.05)	.181
Median PFS	9.9 (9.1-10.6)	7.5 (6.7-8.0)	0.77 (0.68-0.88)	< .0001

Kelly WK, et al. ASCO 2010. Abstract LBA4511.

Addition of Bevacizumab Significantly Improved Other Clinical Endpoints

Outcome, % (95% CI)	Bevacizumab (n = 524)	Placebo (n = 526)	*P* Value
≥ 50% decline in PSA	69.5 (65.2-73.5)	57.9 (53.3-62.3)	.0002
Objective response	53.2 (46.8-59.6)	42.1 (36.2-48.2)	.0113

Kelly WK, et al. ASCO 2010. Abstract LBA4511.

Addition of Bevacizumab Associated With More Severe Toxicities

Adverse Event, %	Bevacizumab + CT (n = 524)	Placebo + CT (n = 526)
Hematologic		
▪ Grade 3	11	12
▪ Grade 4	24	17
▪ Death	0	0
Nonhematologic		
▪ Grade 3	53	35
▪ Grade 4	11	10
▪ Death*	3.8	1.1

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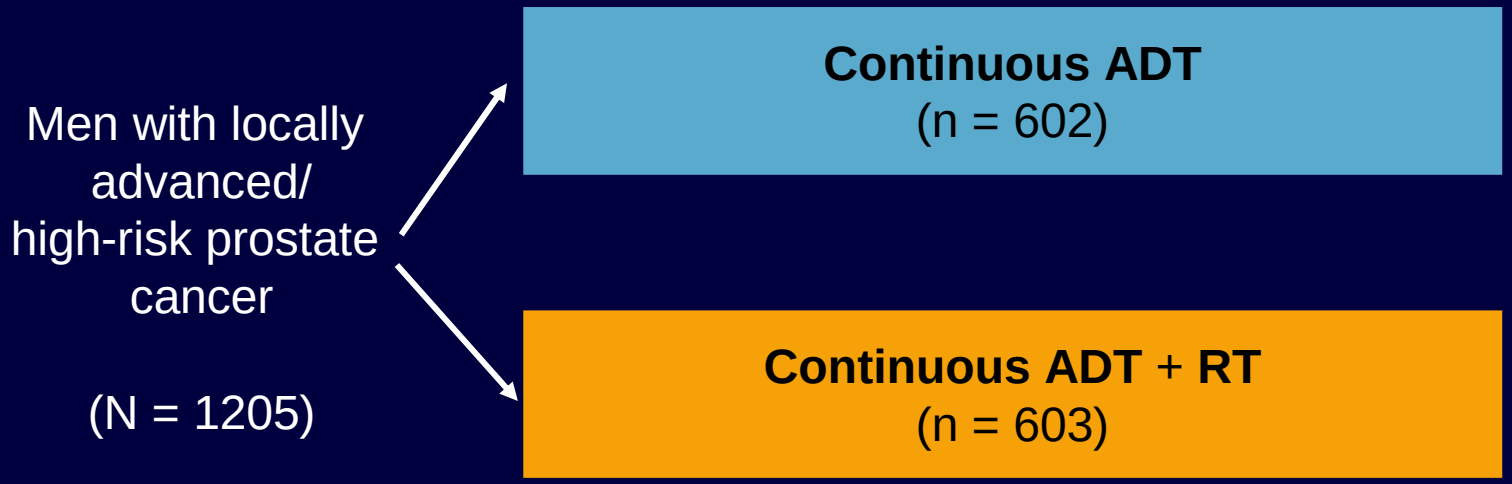
Kelly WK, et al. ASCO 2010. Abstract LBA4511.

CALGB 90401: Conclusions

- Addition of bevacizumab to docetaxel/prednisone/dexamethasone did not significantly increase OS of patients with CRPC
- Bevacizumab did significantly improve other clinical outcomes
  - PFS, PSA decline, incidence of measurable disease
- Bevacizumab treatment associated with more severe toxicities, including death from infections

Kelly WK, et al. ASCO 2010. Abstract LBA4511.

ADT ± EBRT in Locally Advanced/High-Risk Prostate Cancer: Phase III Trial



Stratified by baseline PSA (< 20 vs 20-50 vs > 50 µg/L), hormonal therapy (orchiectomy vs LHRH analogue + antiandrogen therapy), lymph node staging (clinical vs radiological vs surgical), Gleason score (< 8 vs 8-10), previous hormonal therapy, and treatment center.

Warde PR, et al. ASCO 2010. Abstract CRA4504.

Eligibility and Patient Characteristics at Baseline

- Main inclusion criteria
  - T3/T4, N0/Nx prostate cancer or
  - T2 prostate cancer with PSA > 40 µg/L or
  - T2 prostate cancer with PSA > 20 µg/L and Gleason stage 8-10

Characteristic	ADT + RT (n = 603)	ADT (n = 5)
Median age, yrs	69.7	69.7
T3/T4 prostate cancer, %	88	89
Gleason score ≤ 7, %	81	81
PSA, %		
▪ < 20 ng/mL	36	37
▪ 20-50 ng/mL	38	38
▪ > 50 ng/mL	26	25

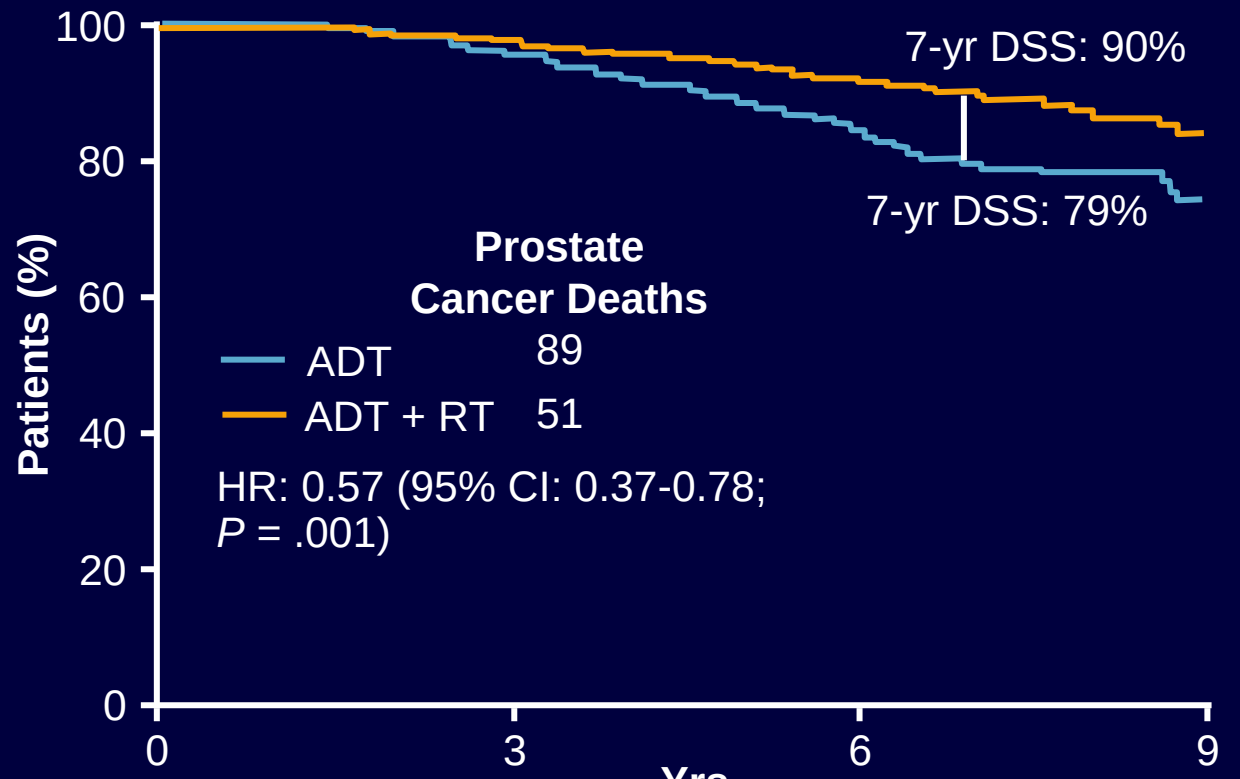
Warde PR, et al. ASCO 2010. Abstract CRA4504.

ADT ± EBRT: Safety

Late Adverse Event, %	ADT + RT (n = 595)	ADT (n = 596)
Diarrhea		
▪ Grade 1/2	14	8
▪ Grade ≥ 3	1.3	0.7
Rectal bleeding		
▪ Grade 1/2	12	5
▪ Grade ≥ 3	0.3	0.5
Genitourinary effects		
▪ Grade 1/2	44	42
▪ Grade ≥ 3	2.3	2.3

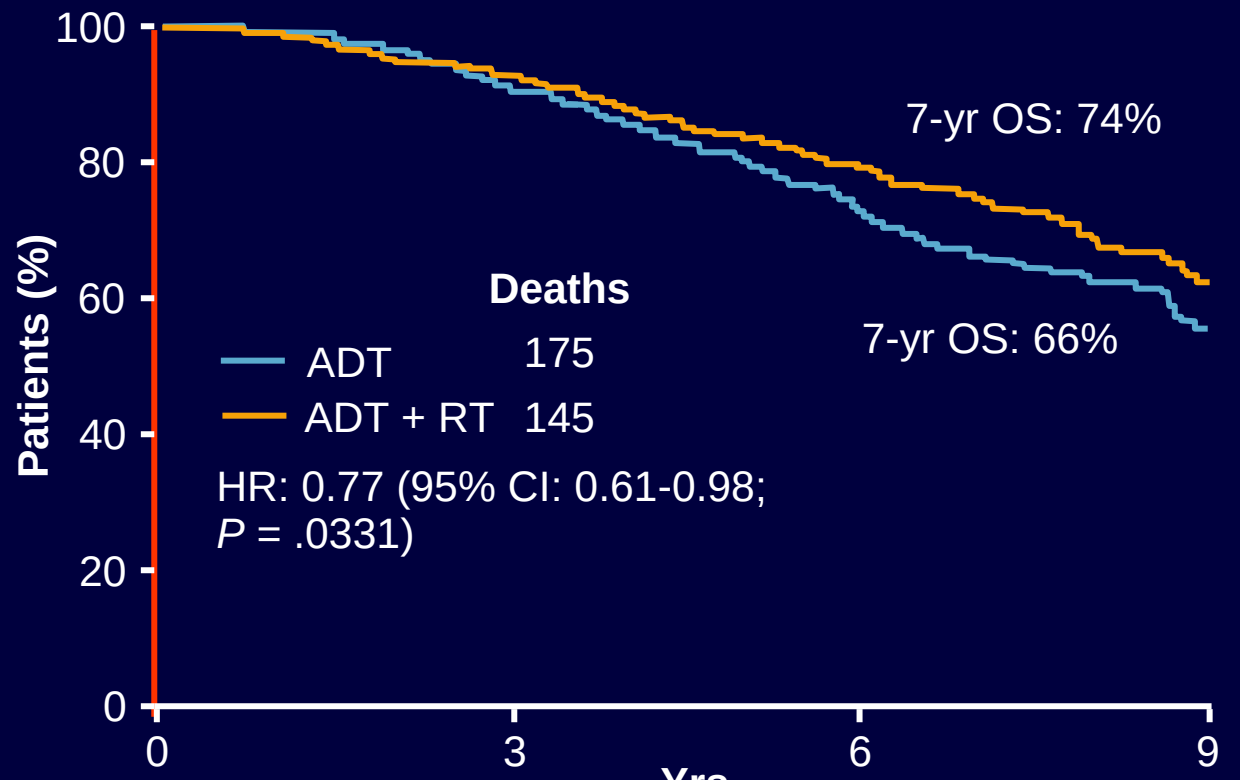
Warde PR, et al. ASCO 2010. Abstract CRA4504.

ADT ± EBRT: Disease-Specific Survival



Warde PR, et al. ASCO 2010. Abstract CRA4504. Reprinted with permission.

ADT ± EBRT: Overall Survival



Warde PR, et al. ASCO 2010. Abstract CRA4504. Reprinted with permission.

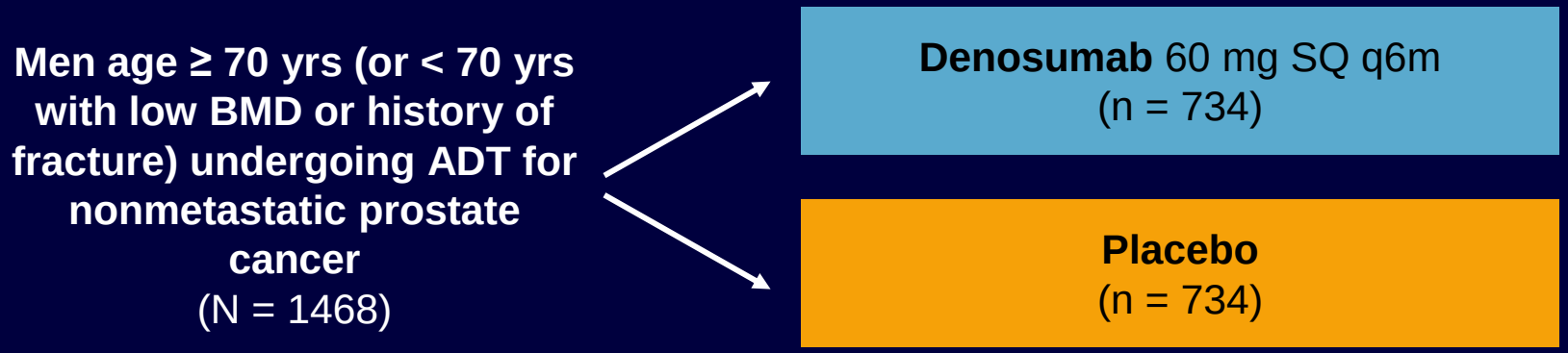
ADT ± EBRT: Conclusions

- In men with locally advanced or high-risk prostate cancer, addition of EBRT to ADT associated with significant efficacy improvements vs ADT alone
  - 23% improvement in OS
  - 43% improvement in disease-specific survival
- Late toxicity similarly low with ADT vs ADT plus EBRT
- According to the investigators, these data suggest combined modality therapy should be standard of care for patients with locally advanced/high-risk prostate cancer

Warde PR, et al. ASCO 2010. Abstract CRA4504.

Vertebral Fracture and OS During ADT for Nonmetastatic Prostate Cancer

- Phase III randomized denosumab trial[1]
  - Denosumab: monoclonal antibody against RANKL



- Lumbar spine BMD increased by 5.6% with denosumab vs decrease of 1.0% with placebo ($P < .001$) at 24 mos[1]
- Current analysis assessed association between prevalent vertebral fracture and OS in men receiving ADT for nonmetastatic prostate cancer in denosumab trial[2]

1. Smith MR, et al N Engl J Med. 2009;361:745-755. 2. Smith MR, et al. ASCO GU 2010. Abstract 25.

Denosumab: Properties and Pivotal Clinical Investigation

- High affinity human monoclonal antibody that binds RANKL
- Administered via SC injection
- Specific: does not bind to TNF-α, TNF-β, TRAIL, or CD40L
- Inhibits formation and activation of osteoclasts
- Superior to zoledronic acid for preventing/delaying SREs in metastatic breast cancer[1]
- Noninferior to zoledronic acid for preventing/delaying SREs in solid tumors and multiple myeloma[2]

1. Stopeck A, et al. SABCS 2009. Abstract 22.
2. Henry D, et al. ECCO/ESMO 2009. Abstract 20LBA.

Vertebral Fracture and OS During ADT for Nonmetastatic Prostate Cancer

- 329/1468 men had ≥ 1 prevalent vertebral fracture (PVF) at baseline
- On-study mortality higher with vs without PVF
  - Higher mortality with PVF persisted after adjusting for age and ADT duration

On-Study Mortality, %	PVF	No PVF	Unadjusted HR	*P* Value	Adjusted* HR	*P* Value
All patients	7.6	5.1	1.57	.062	1.55	.070
Placebo arm	9.2	4.6	2.14	.019	2.13	.021
Denosumab arm	5.8	5.6	1.09	.81	1.08	.84

*Adjusted for age and ADT duration.

Smith MR, et al. ASCO GU 2010. Abstract 25.

Denosumab vs Zoledronic Acid in Patients With CRPC and Bone Metastases

- Prospective, double-blind, placebo-controlled phase III trial

Patients with CRPC and bone metastases, no current or previous IV treatment with bisphosphonate

(N = 1901)

Denosumab 120 mg SC + **Placebo** IV q4w (n = 950)

Zoledronic Acid 4 mg IV + **Placebo** SC q4w (n = 951)

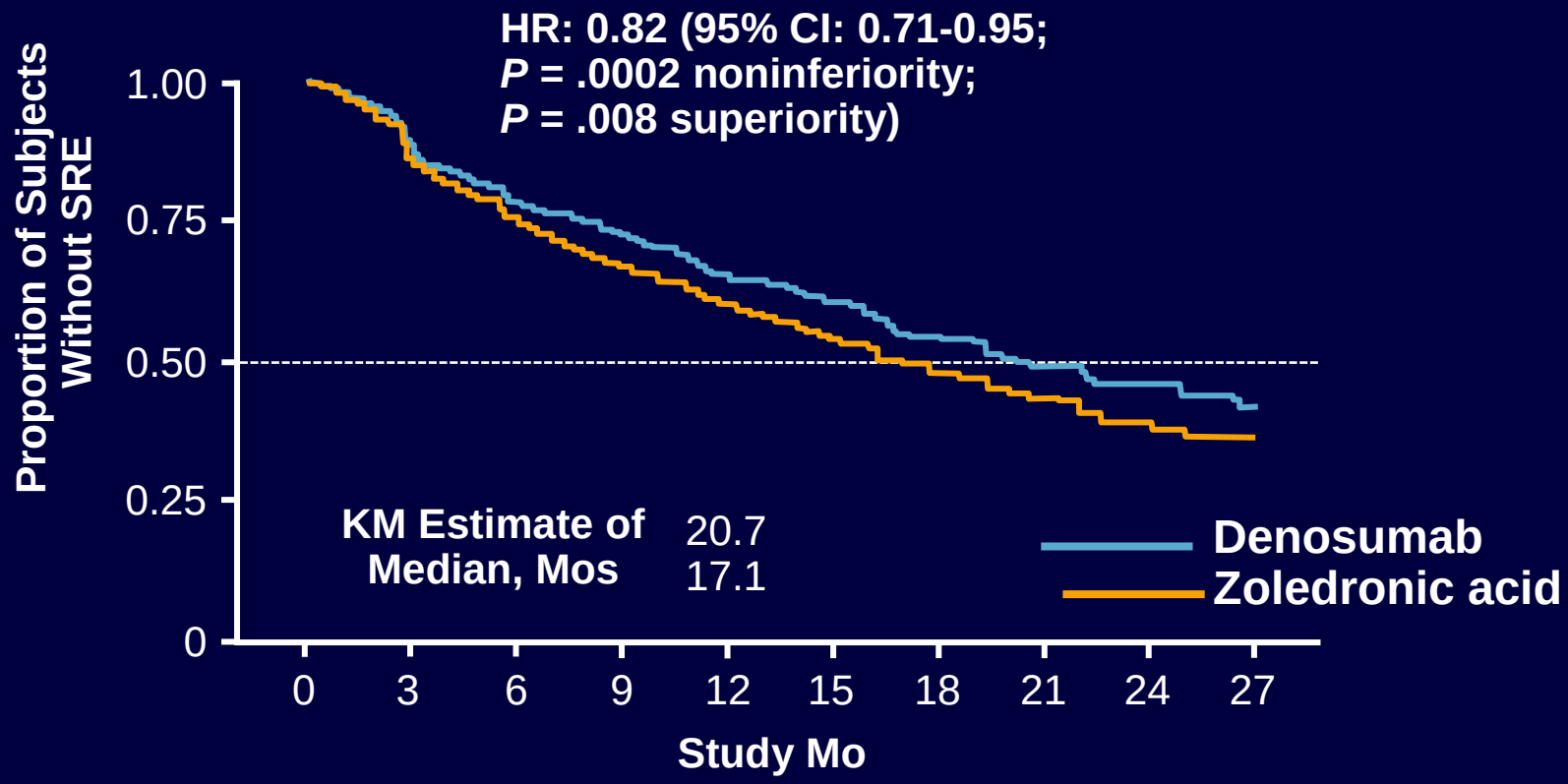
Fizazi K, et al. ASCO 2010. Abstract LBA4507.

Drug Exposure and Adjustments for Renal Function

Overall Exposure	Zoledronic Acid (n = 946)	Denosumab (n = 942)
Median number of doses (Q1, Q3)	10.5 (5.0, 17.0)	13.0 (6.0, 19.0)
Cumulative exposure, patient-yrs	913.6	991.3
Adjustments for Renal Function		
Subjects with dose adjustments for creatinine clearance at baseline, n (%)	213 (22.5)	Not applicable
Subjects with doses withheld for serum creatinine increases on study, n (%)	143 (15.1)	Not applicable
Total number of does withheld due to serum creatinine increases on study	592	Not applicable

Fizazi K, et al. ASCO 2010. Abstract LBA4507. Reprinted with permission.

Denosumab vs Zoledronic Acid: Time to First On-Study SRE



Patients at Risk, n

951	733	544	407	299	207	140	93	64	47
950	758	582	472	361	259	168	115	70	39

Fizazi K, et al. ASCO 2010. Abstract LBA4507. Reprinted with permission.

Denosumab vs Zoledronic Acid: Safety

Adverse Event, %	Zoledronic Acid (n = 945)	Denosumab (n = 943)
Serious adverse events	60	63
Adverse events causing treatment discontinuation	15	17
Most common adverse events		
▪ Anemia	36	36
▪ Back pain	30	32
▪ Decreased appetite	29	28
▪ Nausea	26	29
▪ Fatigue	24	27
Acute-phase reactions (first 3 days)	17.8	8.4
Renal adverse events	16.2	14.7
ONJ	1.3	2.3
Hypocalcemia	5.8	12.8

Fizazi K, et al. ASCO 2010. Abstract LBA4507.

Denosumab vs Zoledronic Acid: Conclusions

- Denosumab superior to zoledronic acid in delaying or preventing SREs in patients with CRPC and bone metastases
- No significant difference between treatments in survival or disease progression
- High incidence of adverse events in both arms
  - More patients who received zoledronic acid experienced acute phase reaction
  - More patients who received denosumab experienced hypocalcemia
  - ONJ rare but occurred in approximately twice as many patients with denosumab vs zoledronic acid
- Denosumab potential treatment option for patients with CRPC and bone metastases

Fizazi K, et al. ASCO 2010. Abstract LBA4507.

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Abiraterone acetate plus low dose prednisone improves overall survival in patients with metastatic castration-resistant prostate cancer (CRPC) who have progressed after docetaxel-based chemotherapy: Results of COU-AA-301, a randomized double-blind placebo-controlled phase 3 study

JS de Bono[1], C Logothetis[2], K Fizazi[3], S North[4], L Chu[5], KN Chi[6], T Kheoh[7], CM Haqq[7], A Molina[7], and HI Scher[8] on behalf of the COU-AA-301 Investigators

[1]Royal Marsden Foundation Trust/The Institute of Cancer Research, Sutton, Surrey, United Kingdom; [2]M. D. Anderson Cancer Center, Houston, TX, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, CA; [5]Oncology Hematology Consultants, Sarasota, FL, USA; [6]BC Cancer Agency, Vancouver, BC, CA; [7]Ortho Biotech ORD, Unit of Cougar Biotechnology, Los Angeles, CA, USA; [8]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

ESMO congress Milan 2010

COU-AA-301 Patient Disposition

	AA (n = 797)	Placebo (n = 398)
Subjects treated	791	394
Median number of cycles of therapy, range	8 (1-21)	4 (1-21)
Treatment ongoing	222 (28.1%)	54 (13.7%)
Treatment discontinued	569 (71.9%)	340 (86.3%)

Overall median duration of follow up was 12.8 months

ESMO congress Milan 2010

COU-AA-301 Baseline Demographics

	AA (n = 797)	Placebo (n = 398)	Total (n = 1195)
Median age, years (range)	69.0 (42-95)	69.0 (39-90)	69.0 (39-95)
Race			
White	93.3%	92.7%	93.1%
Black	3.5%	3.8%	3.6%
Asian	1.4%	2.3%	1.7%
ECOG-PS 2	10.7%	11.1%	10.8%
Significant pain present	44.3%	44.0%	44.2%
2 Prior chemotherapies	28.2%	28.4%	28.3%
Radiographic Progression	70.1%	68.6%	69.6%

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COU-AA-301 Baseline Disease Characteristics (1)

	AA (n = 797)	Placebo (n = 398)
Extent of disease		
Bone	89.2%	90.4%
Node	45.4%	41.5%
Visceral Metastasis	29.0%	24.1%
Liver	11.3%	7.6%
Lung	13.0%	11.4%
Other Visceral	5.8%	5.3%

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COU-AA-301 Baseline Disease Characteristics (2)

	AA (n = 797)	Placebo (n = 398)
PSA (median, ng/mL)	128.8	137.7
Hemoglobin (median, g/dL)	11.8	11.8
Alkaline Phosphatase (median, IU/L)	133.5	134.0
LDH (median, IU/L)	223.0	237.5

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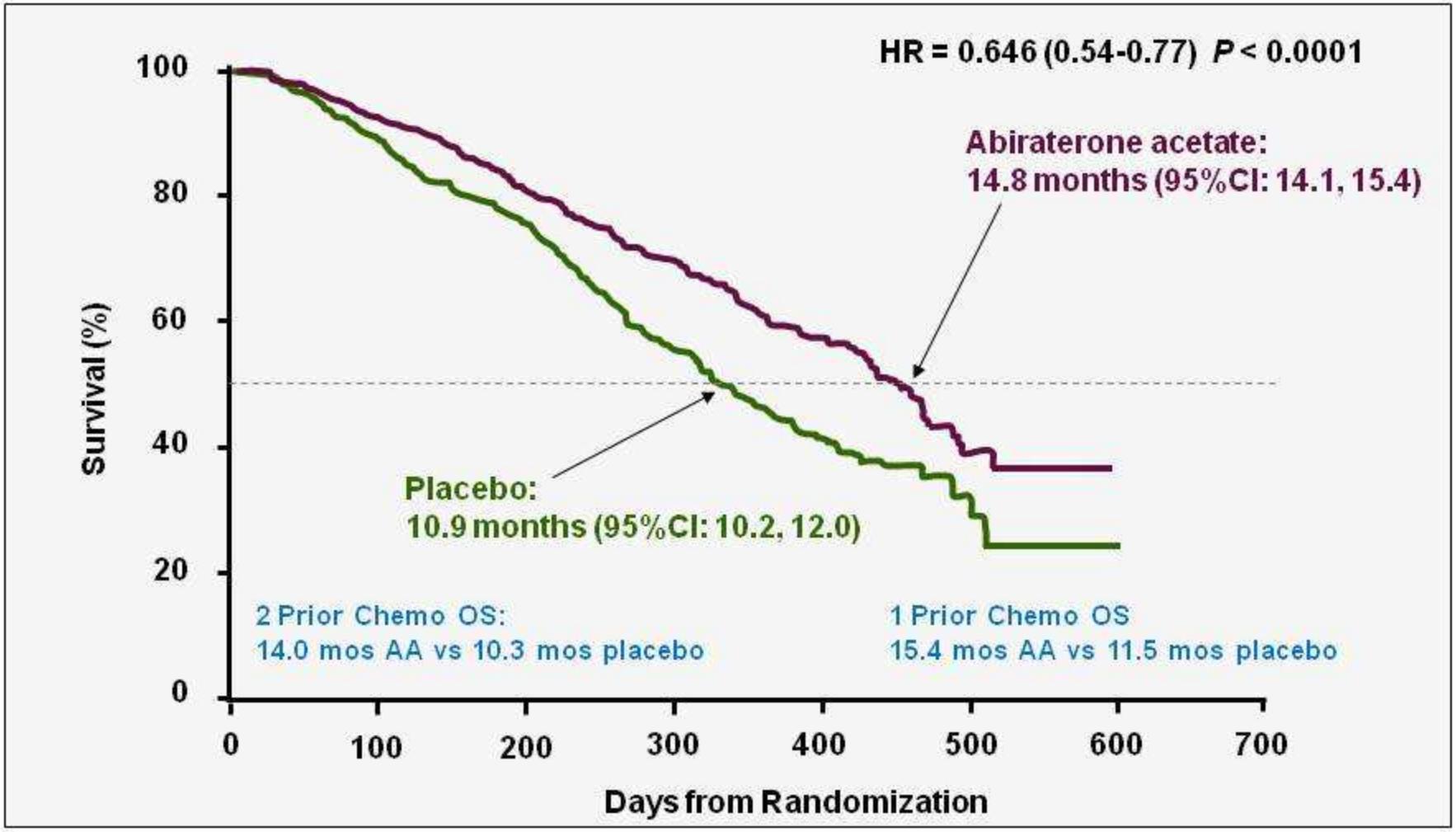
COU-AA-301: Abiraterone Acetate Improves Overall Survival in mCRPC



AA	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

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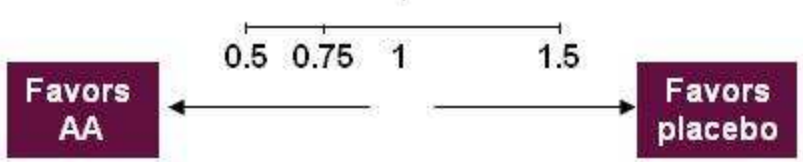
Survival Benefit Consistently Observed Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
All subjects	All	1195	0.66	0.56-0.79
Baseline ECOG	0-1	1068	0.64	0.53-0.78
	2	127	0.81	0.53-1.24
Baseline BPI	< 4	659	0.64	0.50-0.82
	≥ 4	536	0.68	0.53-0.85
No. of prior chemo regimens	1	833	0.63	0.51-0.78
	2	362	0.74	0.55-0.99
Type of progression	PSA only	363	0.59	0.42-0.82
	Radiographic	832	0.69	0.56-0.84
Baseline PSA above median	YES	591	0.65	0.52-0.81
Visceral disease at entry	YES	709	0.60	0.48-0.74
Baseline LDH above median	YES	581	0.71	0.58-0.88
Baseline ALK-P above median	YES	587	0.60	0.48-0.74
Region	North America	652	0.64	0.51-0.80
	Other	543	0.69	0.54-0.90



BPI; Brief Pain Inventory, ALK-P, alkaline phosphatase

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COU-AA-301: All Secondary End Points Achieved Statistical Significance

	AA (n = 797)	Placebo (n = 398)	HR 95% CI	*P* Value
TTPP (months)	10.2	6.6	0.58 (0.46, 0.73)	< 0.0001
rPFS (months)	5.6	3.6	0.67 (0.59, 0.78)	< 0.0001
PSA response rate				
Total	38.0%	10.1%		< 0.0001
Confirmed	29.1%	5.5%		< 0.0001

ESMO congress Milan 2010

COU-AA-301: Summary of AEs

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
All treatment-emergent AEs	98.9%	54.5%	99.0%	58.4%
Serious AEs	37.5%	32.1%	41.4%	35.3%
AEs leading to discontinuation	18.7%	10.5%	22.8%	13.5%
AEs leading to death	11.6%		14.7%	
Deaths within 30 days of last dose	10.5%		13.2%	
Underlying disease	7.5%		9.9%	
Other specified cause	2.9%		3.3%	

ESMO congress Milan 2010

COU-AA-301: AEs of Special Interest

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	30.5%	2.3%	22.3%	1.0%
Hypokalaemia	17.1%	3.8%	8.4%	0.8%
LFT abnormalities	10.4%	3.5%	8.1%	3.0%
Hypertension	9.7%	1.3%	7.9%	0.3%
Cardiac disorders	13.3%	4.1%	10.4%	2.3%

LFT, liver function test