News in Prostatic Cancer

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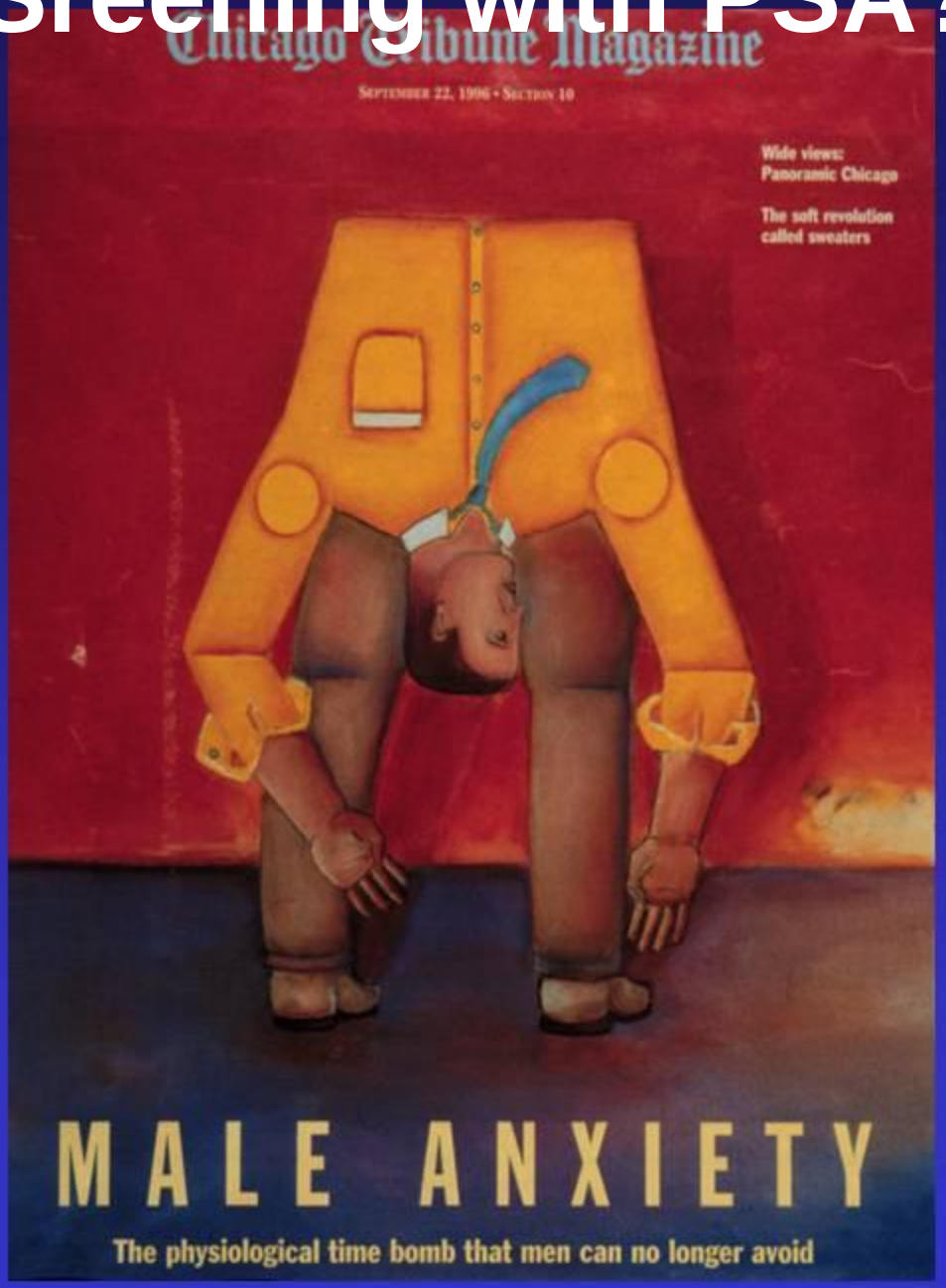
Disclosure

- Participation in advisory boards or as a speaker for:

Astrazeneca, Bayer, Merck, Sanofi-Aventis, Roche, Taiho

Sreening with PSA?



Benefits and Harms of PSA Screening

(Per 1000 men age 55-69, if screened every 1-4 years for 10 years)

Benefit of screening	
Do not die of prostate cancer	0-1 in 1000
Harms of screening	
False positive that leads to biopsy	100-120 in 1000
Prostate cancer diagnosis	110 in 1000
Complications of Treatment	
Cardiovascular Events	2 in 1000
DVT or Pulmonary Embolism	1 in 1000
Erectile dysfunction	29 in 1000
Urinary Incontinence	18 in 1000
Death from Treatment	<1 in 1000

USPSTF Statement, Annals of Internal Medicine, 2012

ASCO-recommendations for PSA-Sreening

Basch et al., JCO 30 August 2012

- Life expectancy less than 10 y: ***no screening***
- Life expectancy > 10 y: ***individual decision*** based on benefit (less mortality) and risks (complications from unnessary biopsy, surgery, radiation)

5000 patients: radical prostatectomy vs observation

PIVOT Summary

- In men with localized prostate cancer detected during the early PSA era, radical prostatectomy compared to observation did not significantly reduce all-cause and prostate cancer mortality. Absolute differences through at least 12 years were less than 3%

- Surgery did not reduce mortality more than observation in men with low PSA or low risk prostate cancer. A potential mortality benefit from surgery may exist in men with higher PSA and possibly higher risk status disease

Clinical Practice Recommendations

- Physicians can recommend observation as the preferred treatment option for most men with early stage-PSA detected prostate cancer
  - Observation helps most men live a similar length and quality of life, avoid death from prostate cancer and prevent harms from surgery & EBRT.
- Physicians can recommend addition of short term ADT for men choosing EBRT
  - Benefit may be limited to men with intermediate risk DZ

MRC Clinical Trials Unit

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Southwest Oncology Group
A National Clinical Research Group

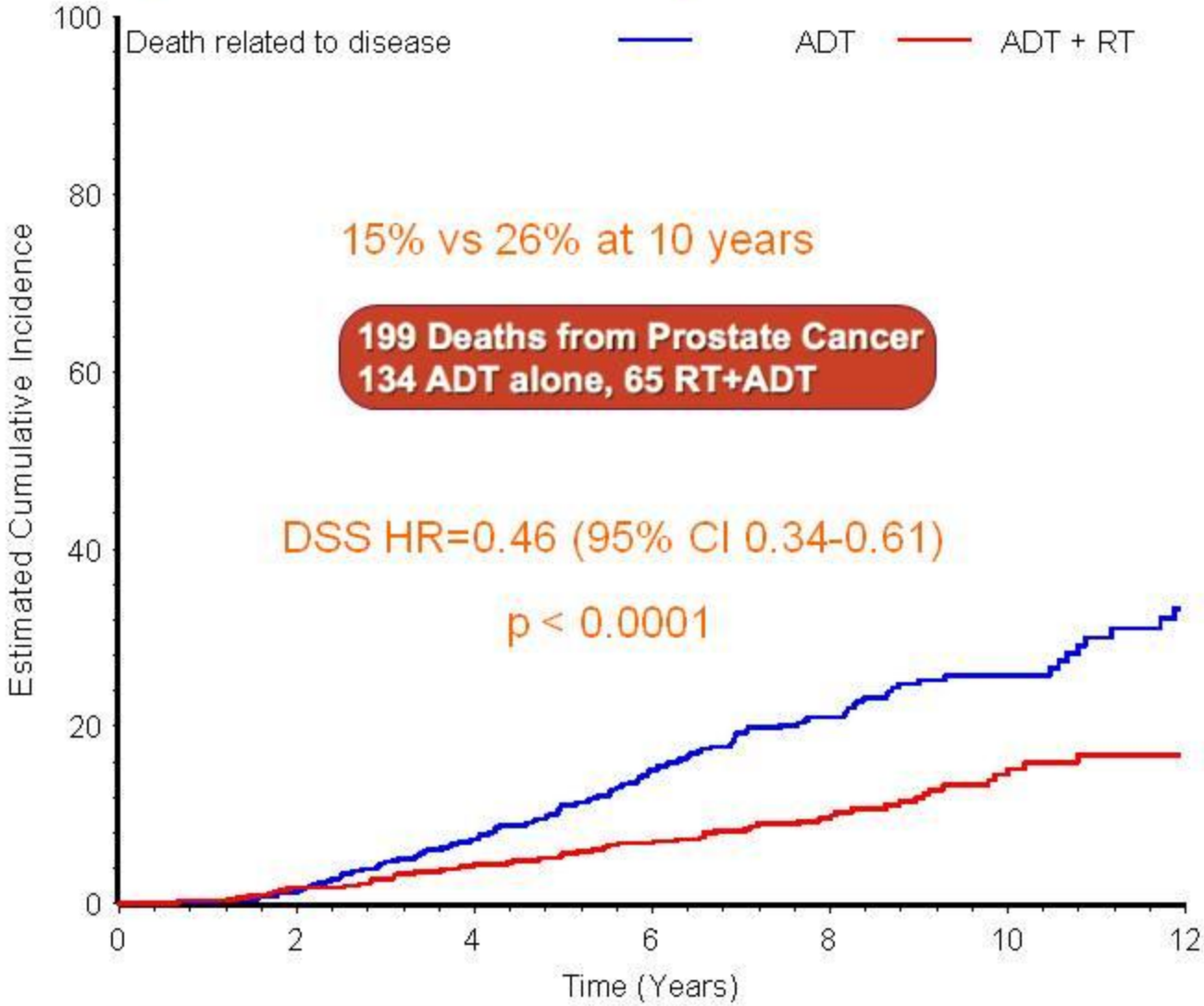
Final analysis of intergroup randomized phase III study of androgen deprivation therapy (ADT) + radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCICCTG, SWOG, MRC-UK, INT: T94-0110).

M.D. Mason, W. Parulekar, M.R. Sydes, M. Parmar,
J. Anderson, J. Barber, M.D. Brundage, R. Cowan,
M.K. Gospodarowicz, C. Hayter, J. Hetherington, A.C. Hiltz,
P. Kirkbride, E. Kostashuk, K. Sanders, J. Sathya,
G.P. Swanson, B.E. Chen, & P.R. Warde
On behalf of the NCICCTG PR3/MRC UK PR07 investigators

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '12 Meeting

Final Analysis: Cumulative Incidence Probability for Disease-Specific Survival



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NCIC Clinical Trials Group
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Southwest Oncology Group
A National Clinical Research Group
PRESENTED AT: ASCO Annual '12 Meeting

Conclusions

- Combined ADT + RT should be offered to all men with locally advanced prostate cancer who are suitable for RT

- ADT + RT is the only guideline-recommended therapeutic approach backed by level 1 evidence

Intermittent versus Continuous Androgen Deprivation in Hormone Sensitive Metastatic Prostate Cancer Patients: Results of SWOG 9346 (INT-0162) an International Phase III Trial

Hussain M, Tangen CM, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Akdas A, Small EJ, Dawson NA, Donnelly BJ, Venner P, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Vogelzang NJ, Thompson Jr, IM

Univ. of Michigan, Ann Arbor, MI; SWOG Statistical Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Colorado Health Science Center, Aurora, CO; University of Wisconsin Carbone Cancer Center, Madison, WI; St. James University Hopsital, Leeds, UK; Marmara University, Istanbul, Turkey; University of California, San Francisco, San Francisco, CA; Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC; Prostate Cancer Institute, Calgary, Alberta, Canada, Calgary, AB; Cross Cancer Institute, Edmonton, AB; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Urology of Virginia, Norfolk, VA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Levine Cancer Institute, Carolinas HealthCare System, Charlotte NC; US Oncology Research, LLC, McKesson Specialty Health, The Woodlands, TX, and Comprehensive Cancer Centers of Nevada, Las Vegas, NV; University of Texas Health Science Center at San Antonio, San Antonio, TX

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '12 Meeting

Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy

	At Risk	Death	Median in Years	7 yr Survival
Continuous therapy	765	422	5.8	42%
Intermittent therapy	770	455	5.1	38%

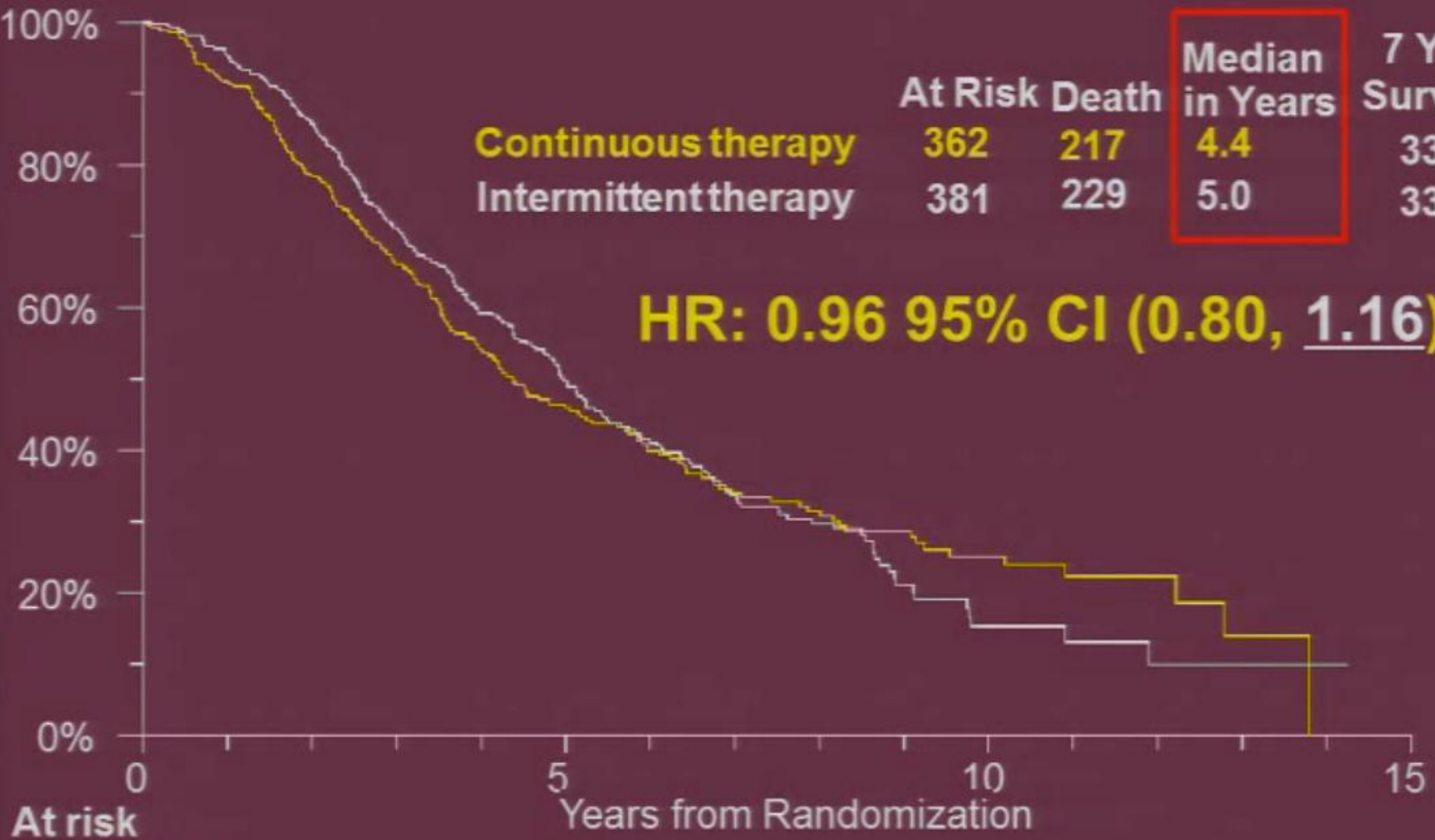
HR: 1.09 95% CI (0.95, 1.24)

At risk		
Intermittent	267	47
Continuous	301	53

PRESENTED BY: Maha Hussain, MD, FACP

PRESENTED AT: ASCO Annual '12 Meeting

Overall Survival for Patients with Extensive Disease by Treatment Arm



	At Risk	Death	Median in Years	7 Year Survival
Continuous therapy	362	217	4.4	33%
Intermittent therapy	381	229	5.0	33%

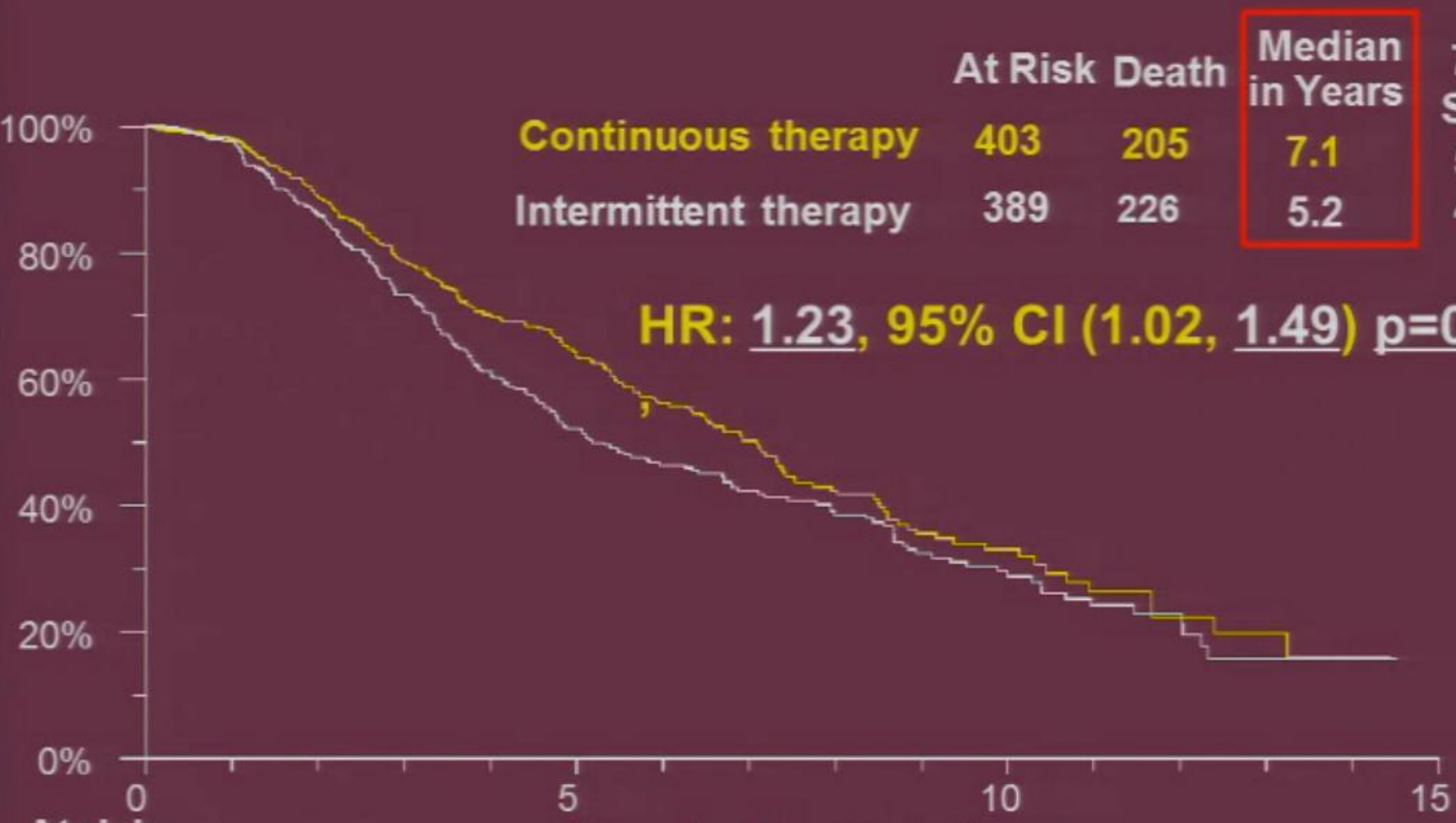
HR: 0.96 95% CI (0.80, 1.16)

At risk		
Intermittent	119	11
Continuous	106	22

PRESENTED BY: Maha Hussain, MD, FACP

PRESENTED AT: ASCO Annual '12 Meeting

Overall Survival for Patients with Minimal Disease by Treatment Arm



	At Risk	Death	Median in Years	7 yr. Survival
Continuous therapy	403	205	7.1	50%
Intermittent therapy	389	226	5.2	42%

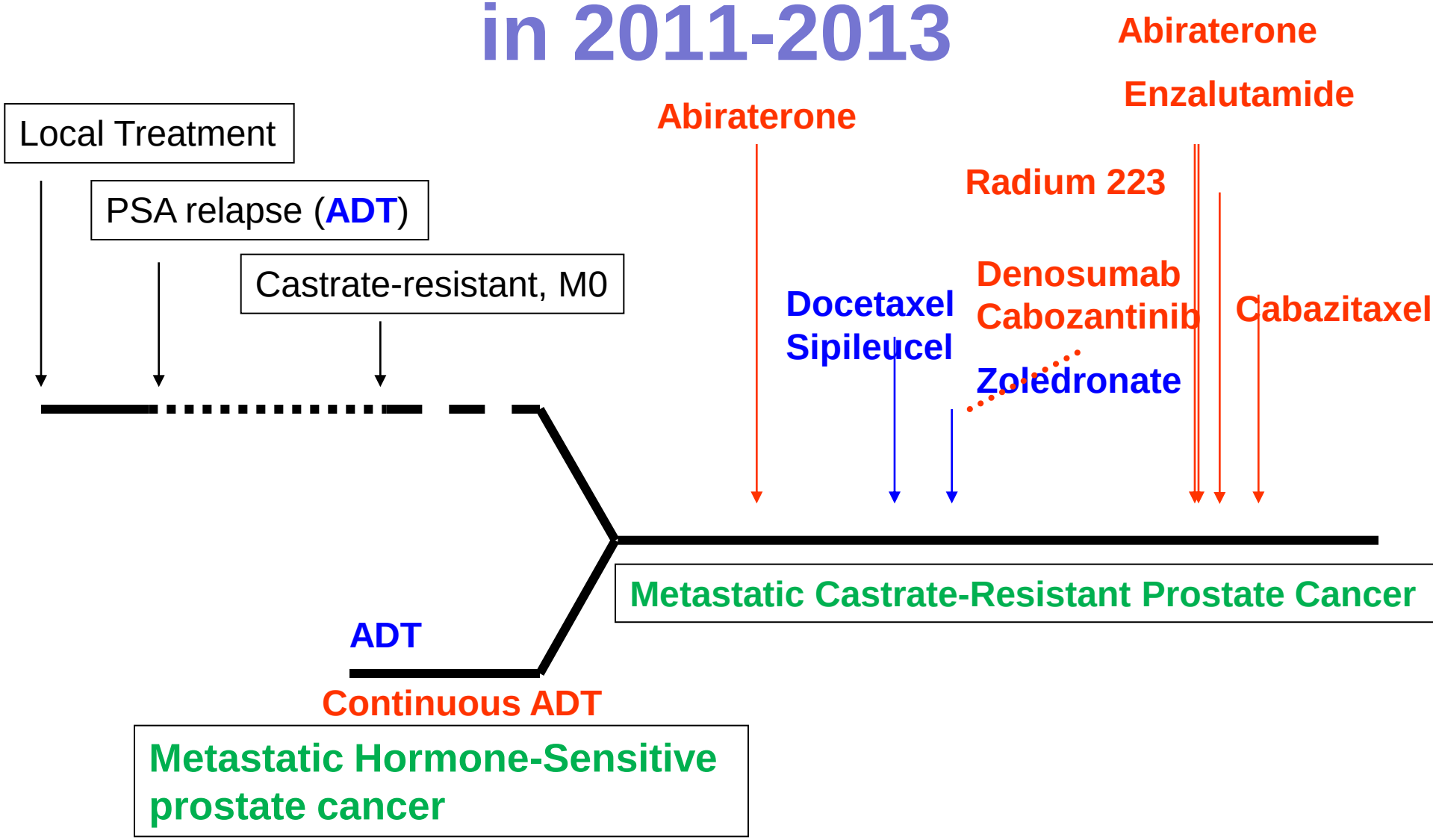
HR: 1.23, 95% CI (1.02, 1.49) p=0.034

At risk		
Intermittent	143	35
Continuous	194	30

PRESENTED BY: Maha Hussain, MD, FACP

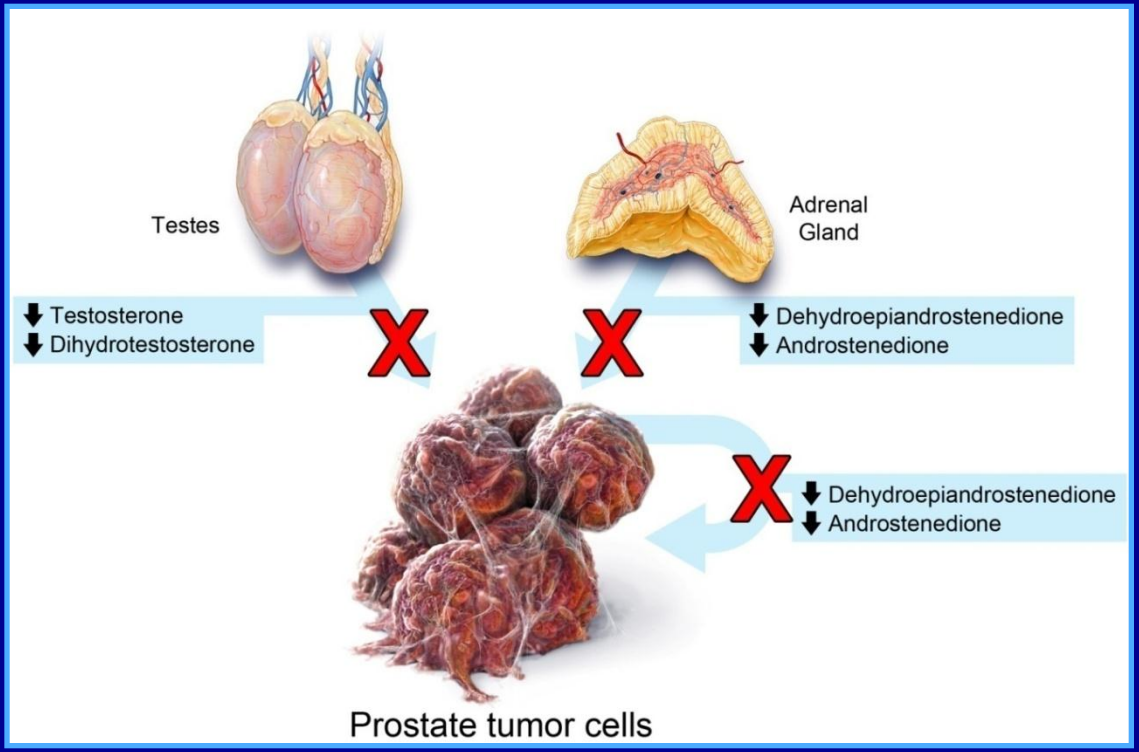
PRESENTED AT: ASCO Annual '12 Meeting

Systemic treatment for CRPC in 2011-2013



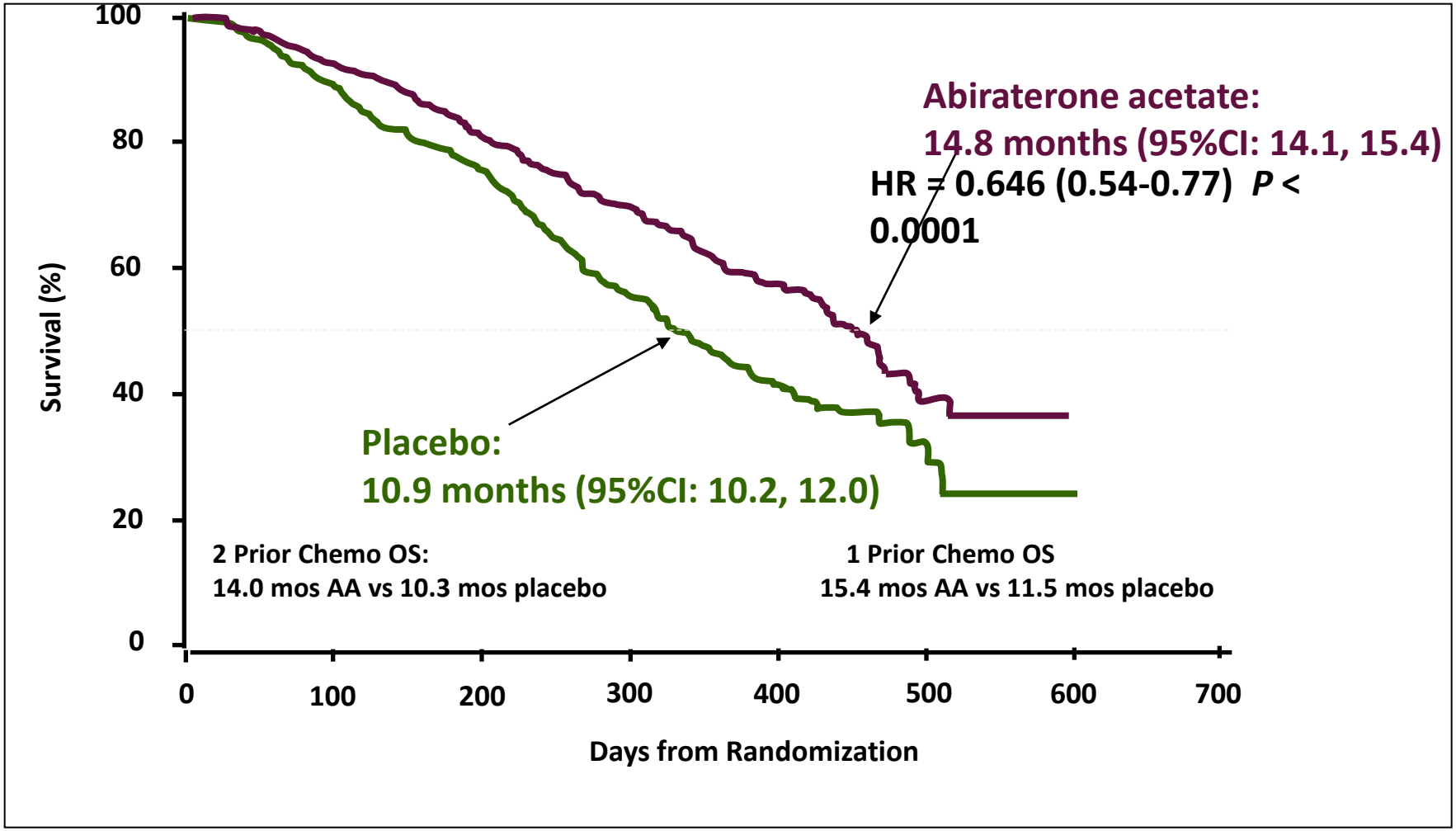
Abiraterone Inhibits Androgen Biosynthesis Through CYP17

- Androgens produced at 3 critical sites
  - Testes
  - Adrenal gland
  - Prostate tumor cells
- Abiraterone inhibits biosynthesis of androgens that stimulate tumor cell growth
- PSA and radiographic responses in Phase 2 studies of CRPC
  - Chemo-naïve and post-chemo patients[1-6]

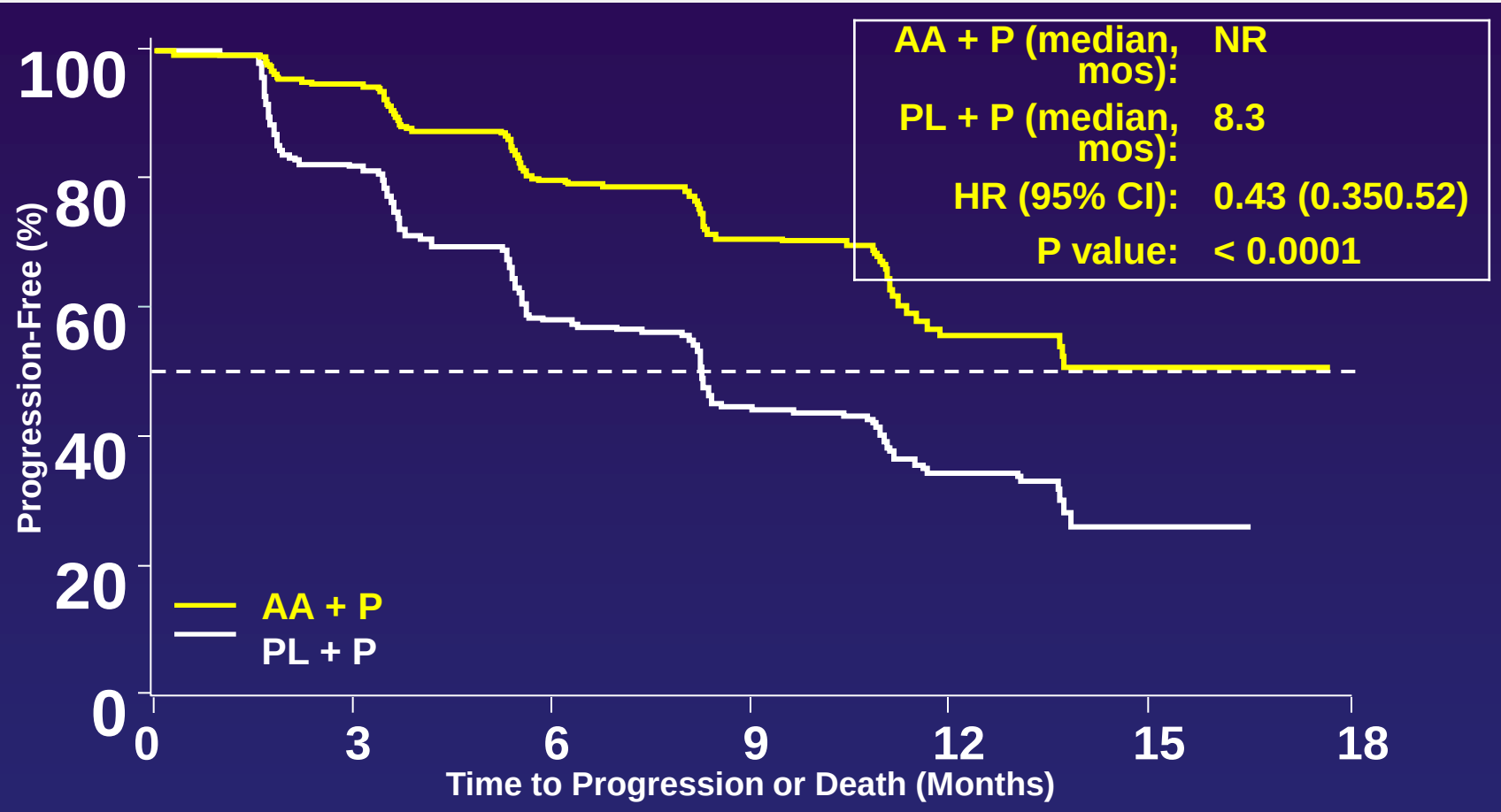


1. Attard G et al. J Clin Oncol. 2008;26:4563-4571; 2. Attard G et al. J Clin Oncol. 2009;27:3742-3748; 3. Reid AH et al. J Clin Oncol. 2010;28:1489-1495; 4. Ryan CJ et al. J Clin Oncol. 2010;28:1481-1488; 5. Danila DC et al. J Clin Oncol. 2010;28:1496-1501; 6. de Bono JS et al. Ann Oncol. 2010;21(suppl 8): Abstract LBA5.

COU-AA-301: Abiraterone post-Chemo (Docetaxel) Overall Survival



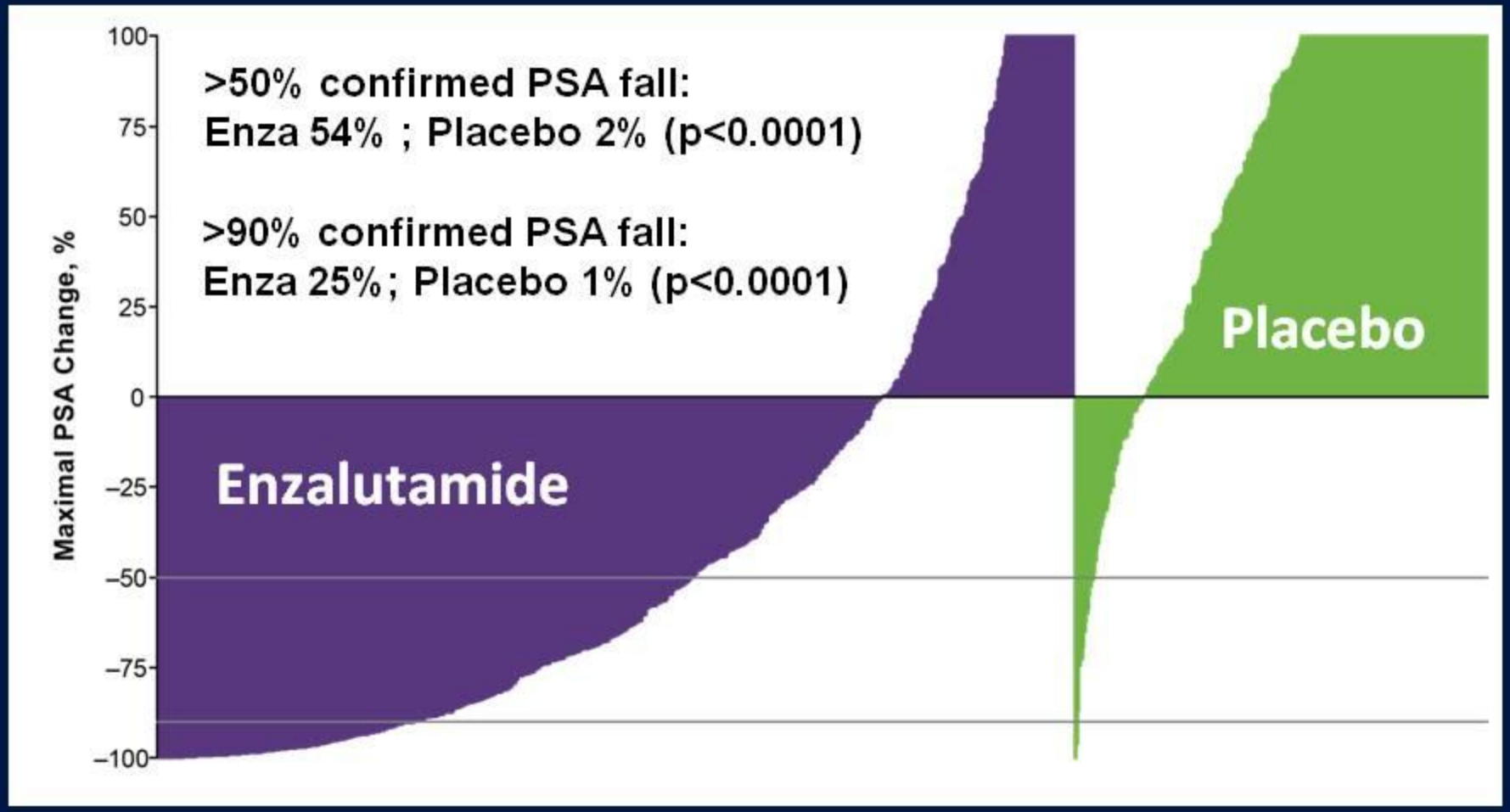
Abiraterone in hormone refractory Chemonaive pts: PFS



AA	546	489	340	164	46	12	0
PL	542	400	204	90	30	3	0

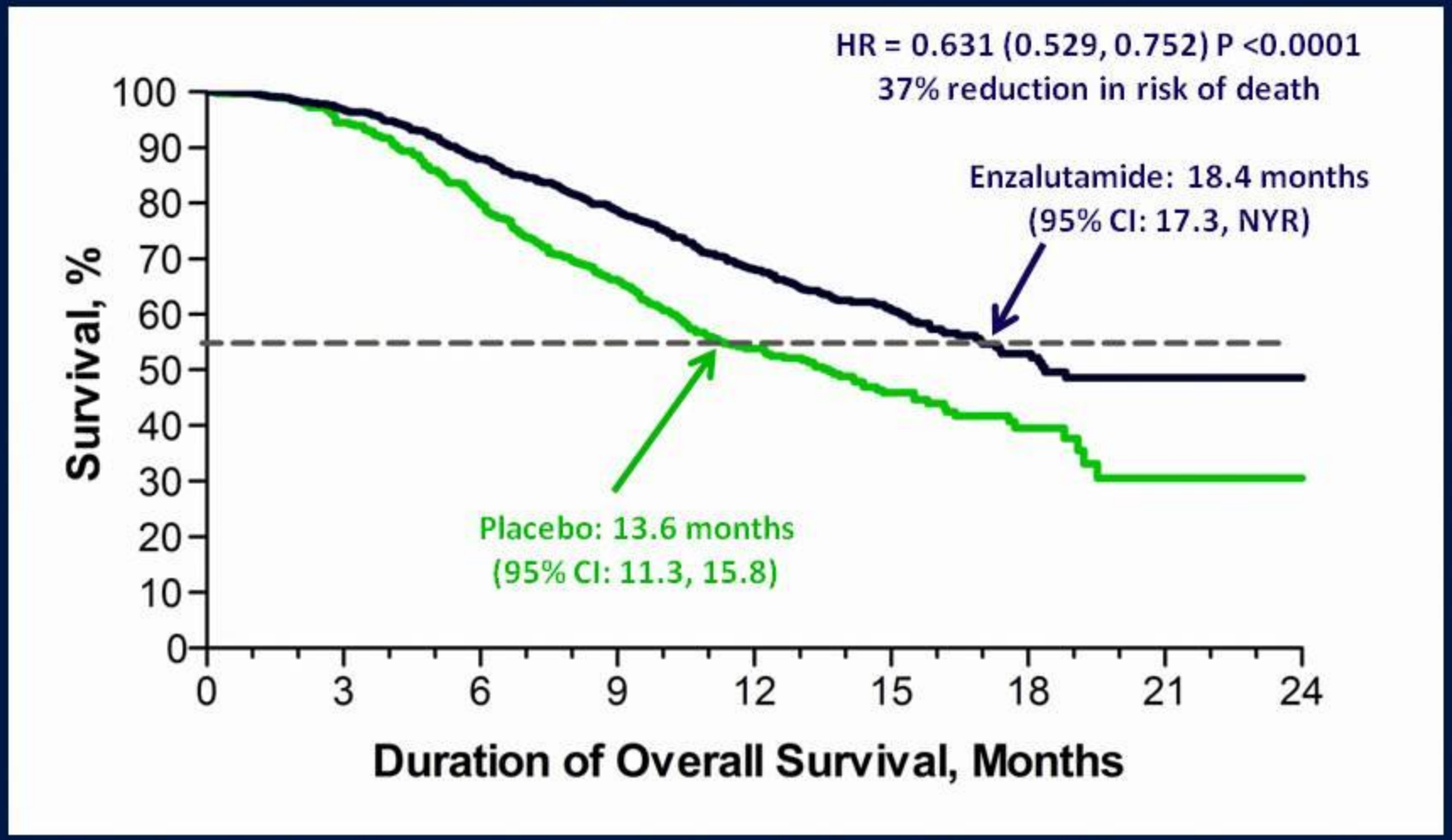
Data cutoff 20/12/2010

Enzalutamide had a high PSA Response Rate



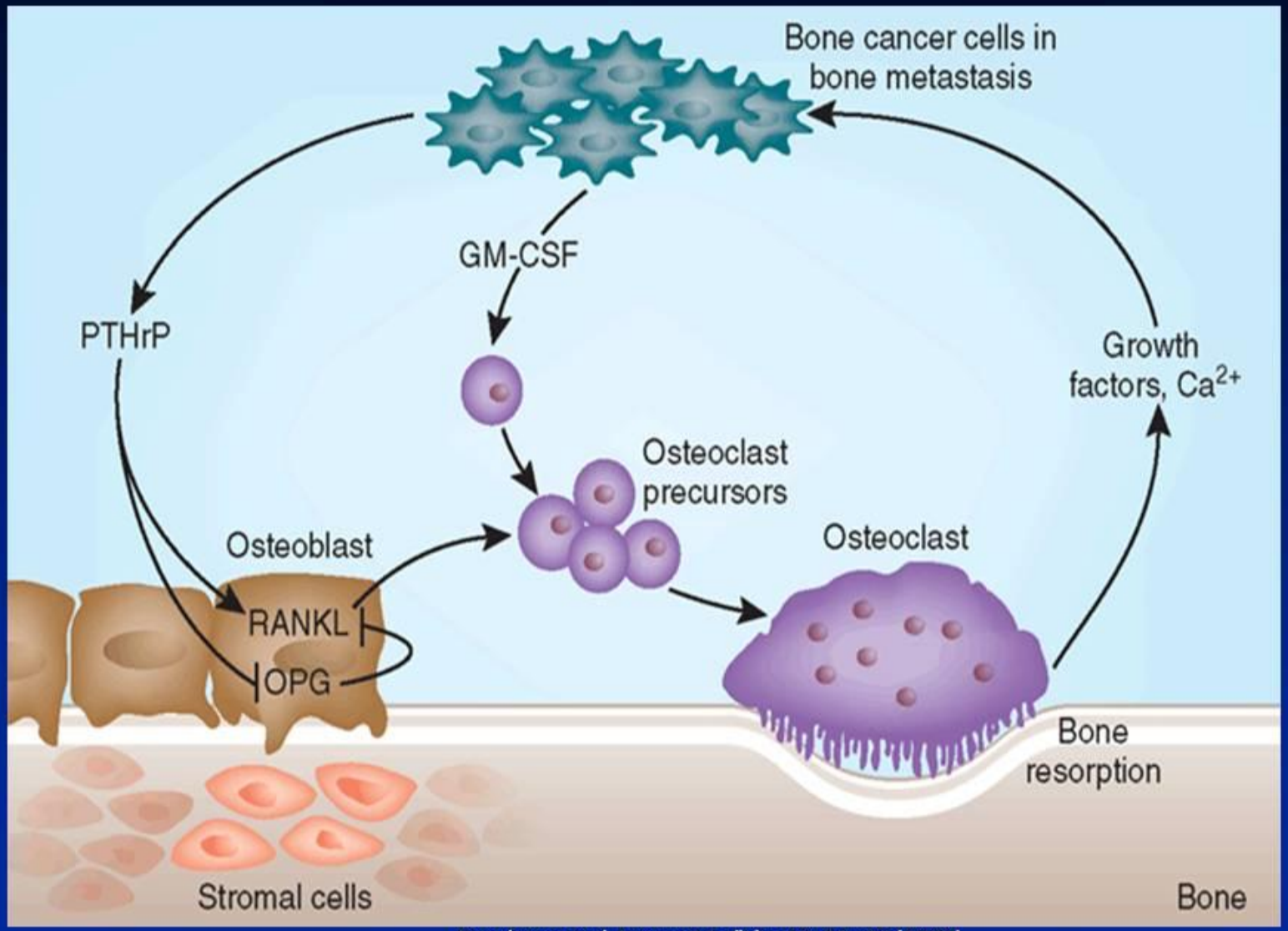
All the secondary endpoint measures favored the treatment arm

Enzalutamide Prolonged Survival, Reducing Risk of Death



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

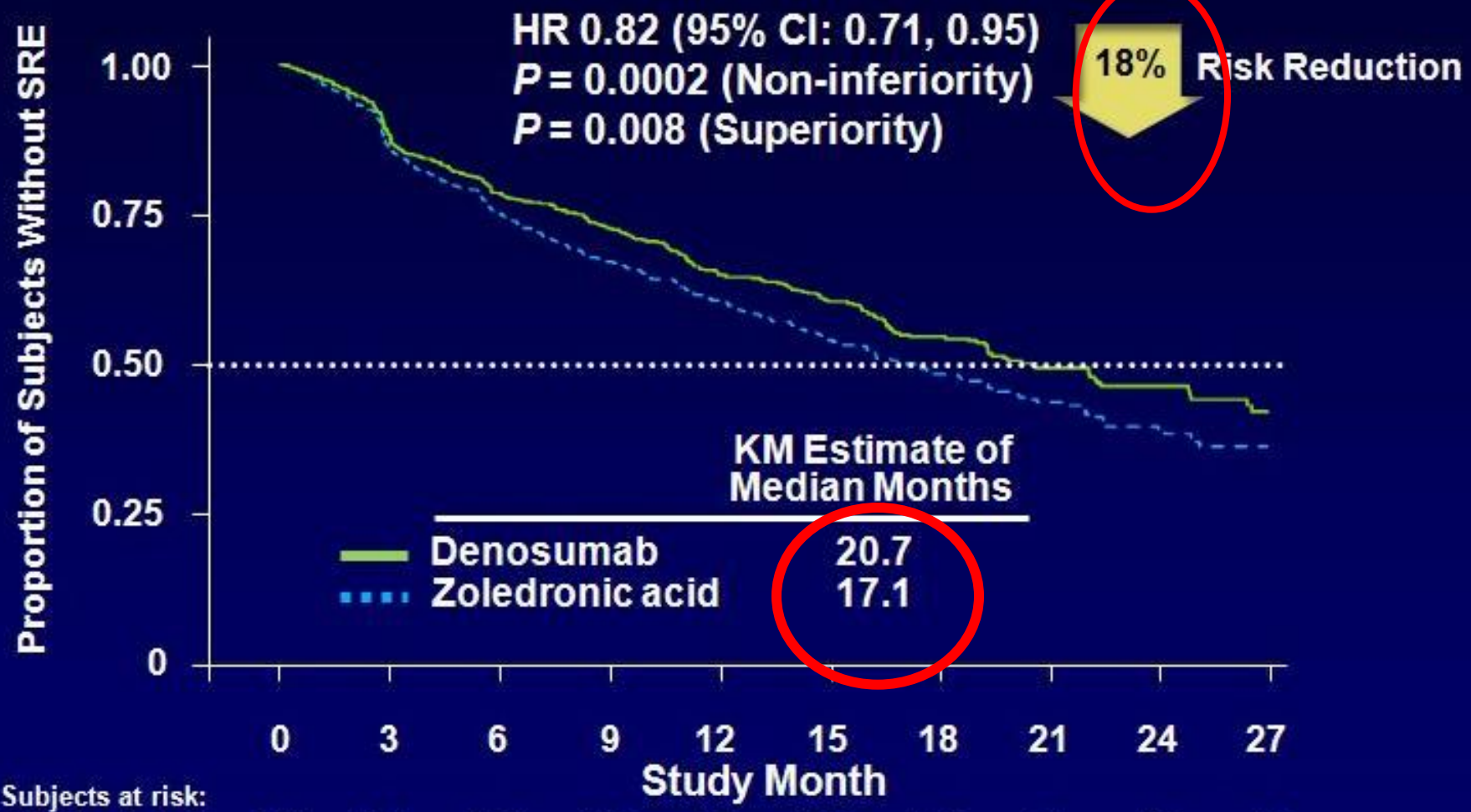
Denosumab: RANKL mAb



Roodman et al, Nature Medicine **13**, 25–26 (2007)

Amgen press release Sept 2009, ECCO 2009 abstracts LBA2, 20

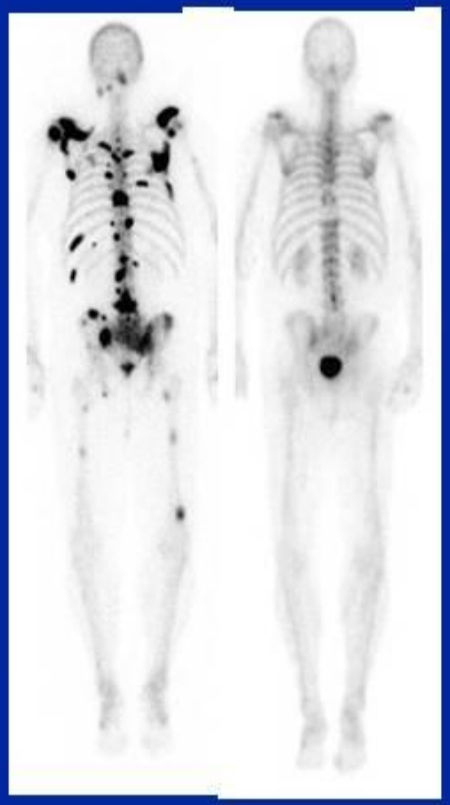
Denosumab vs Zoledronic Acid: Time to SRE (n = 1901)



Subjects at risk:	0	3	6	9	12	15	18	21	24	27
Zoledronic Acid	951	733	544	407	299	207	140	93	64	47
Denosumab	950	758	582	472	361	259	168	115	70	39

Fizazi K, et al. *Lancet.* 2011;377(9768):813-822.

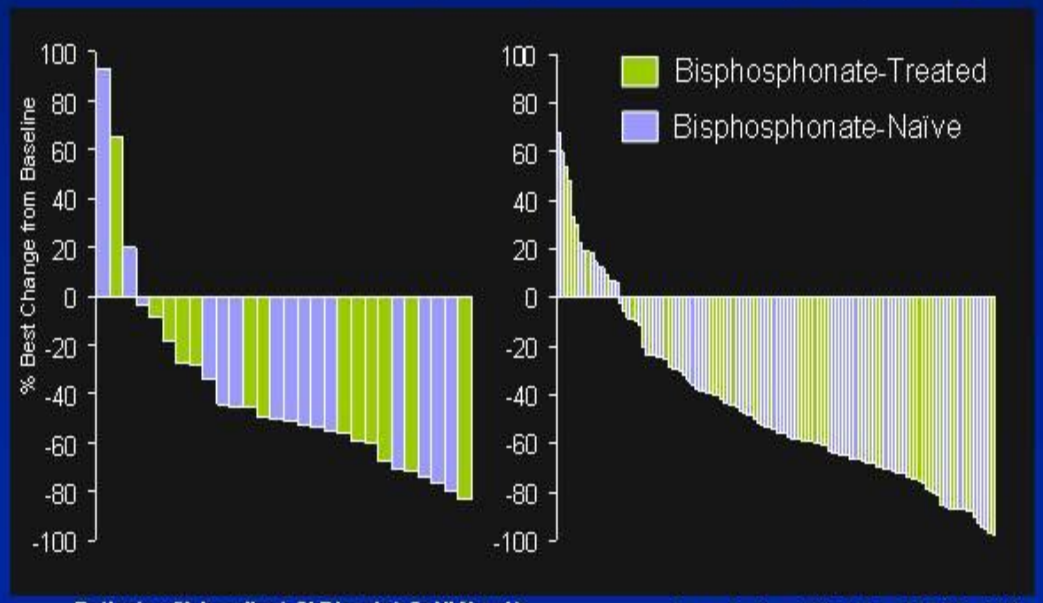
Dramatic Bone Effects of Cabozantinib in a Randomized Discontinuation Trial (RDT)



Docetaxel-pretreated

Bone scan evaluable (N = 108)	n (%)
Complete resolution	21 (19)
Partial resolution	61 (56)
Stable	23 (21)
Progressive disease	3 (3)

Effects on Osteoblast (t-ALP) and Osteoclast (CTX) Activity



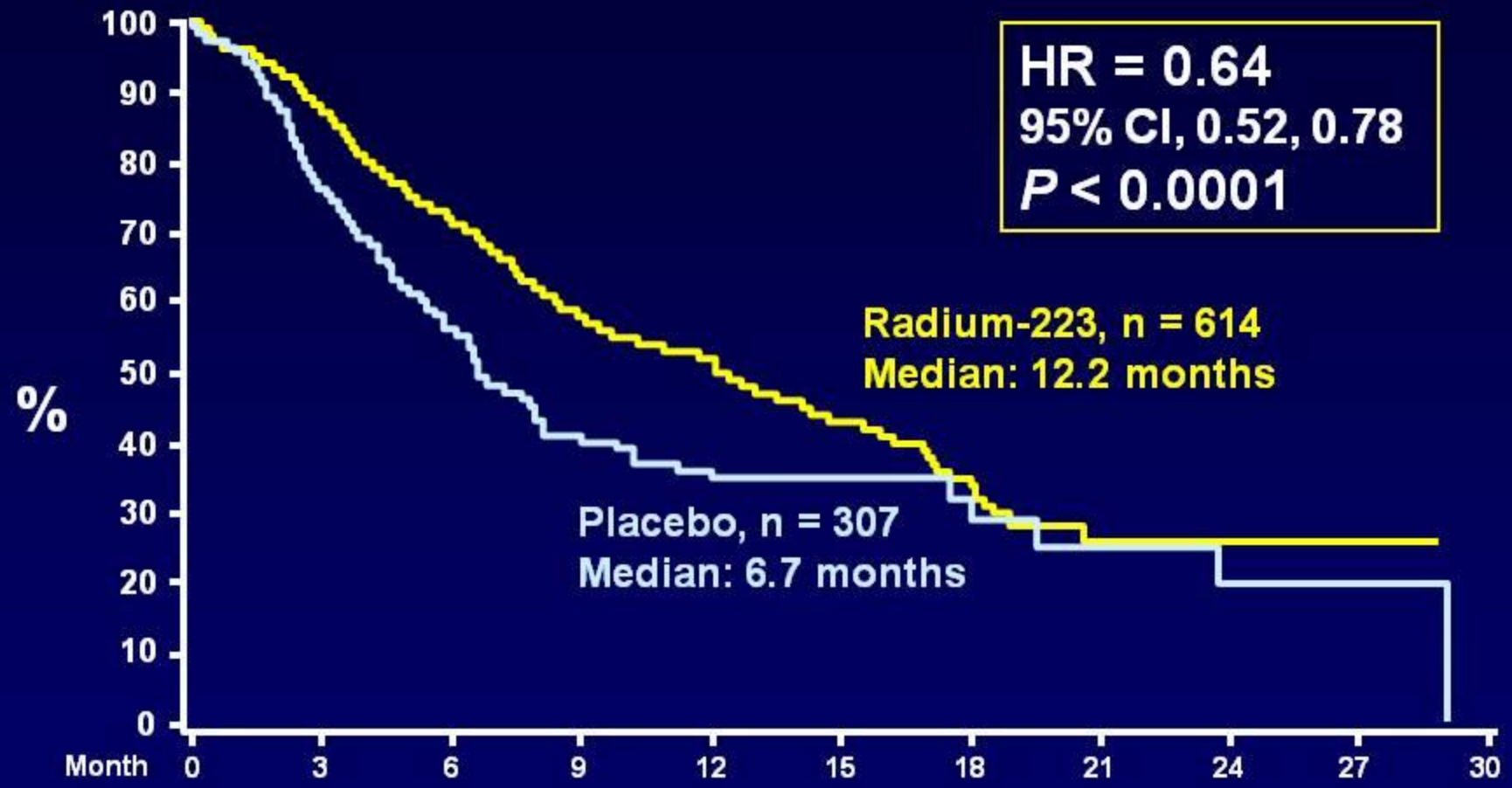
Patients with baseline t-ALP levels ≥ 2xULN and ≥ 12 weeks of followup (N = 28)

Samples from Week 6 and 12 (N = 118)

Hussain M et al. ASCO 2011. Abstract 4516.

ALSYMPCA
Time T

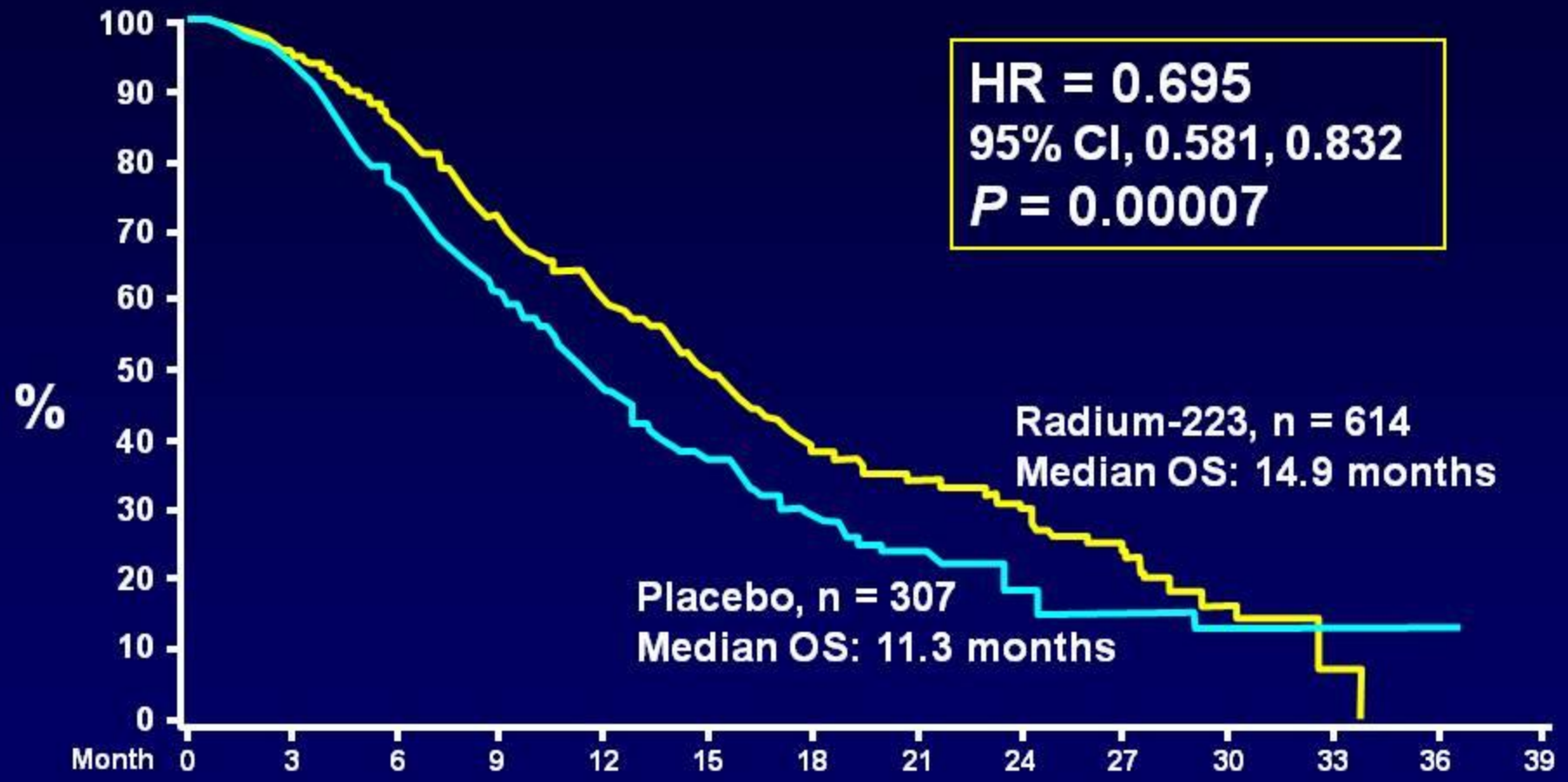
Radium 223 : cell kill + marrow penetration :PFS



Radium-223	614	487	332	193	125	62	31	8	8	1	0
Placebo	307	207	108	51	33	17	8	6	3	1	0

*Provisional data

ALSYMPCA Updated Analysis
Overall Survival



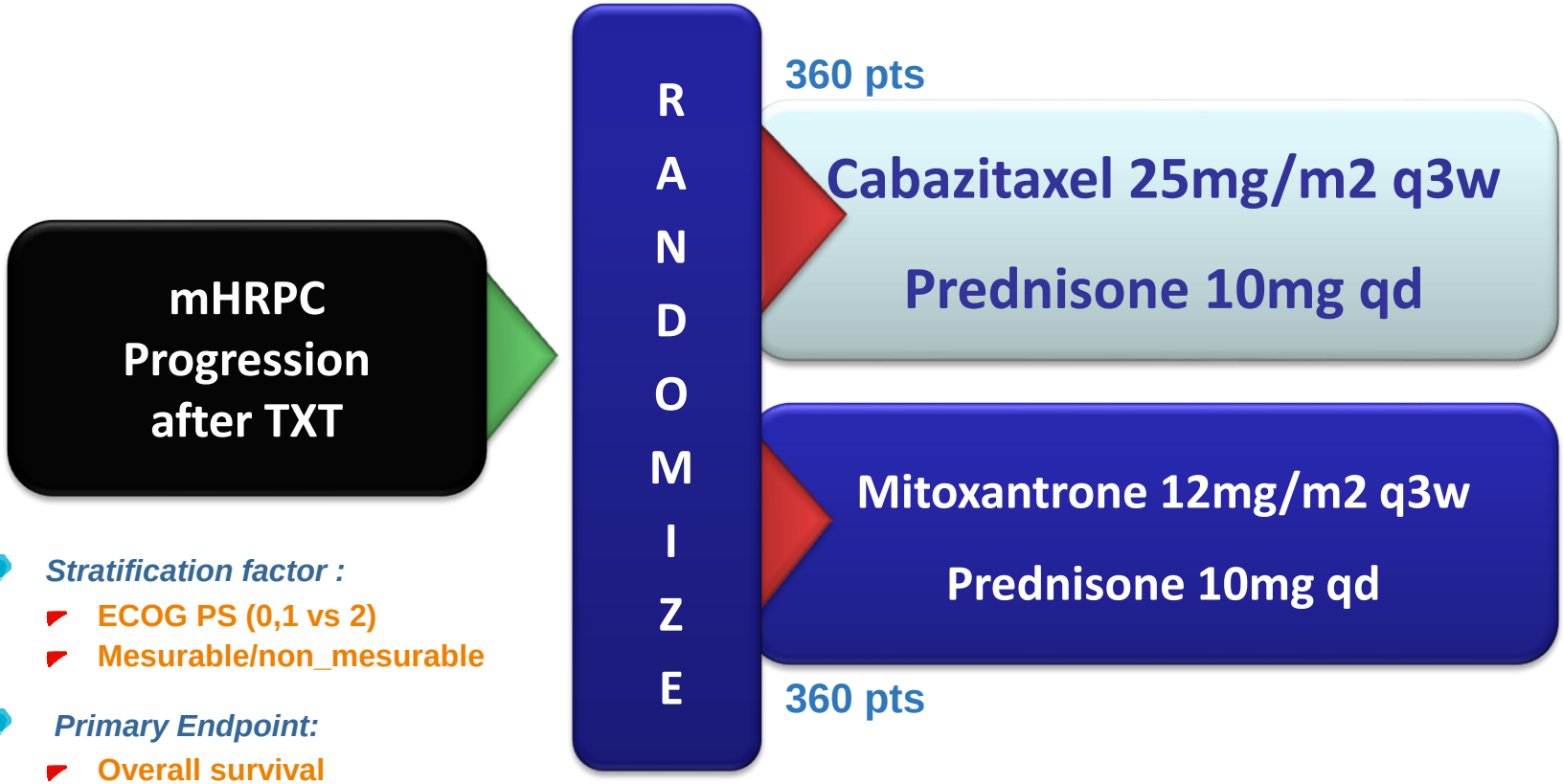
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

New drugs for CRPC

- Endocrine agents
  - Abiraterone
  - **Enzalutamide**
- Immunotherapy
  - Sipuleucel-T
- Chemotherapy
  - **Cabazitaxel**
- Bone-targeting agents
  - **Denosumab**
  - **Alpharadin**

- Endocrine agents
  - **ODM 201** (ESMO 12)
  - **ARN 509** (ASCO 12)
  - **Orteronel**
- Immunotherapy
  - **Ipilimumab** (2013?)
  - **Prostvac**
  - **Tasquinimod**
- Bone-targeting agents
  - **Cabozantinib** (ASCO 12)
  - **Dasatinib** (2013?)
- HSP-targeting drugs
  - **OGX 011**, **OGX 427**

Cabazitaxel in Second-line CRPC
TROPIC Phase III Study

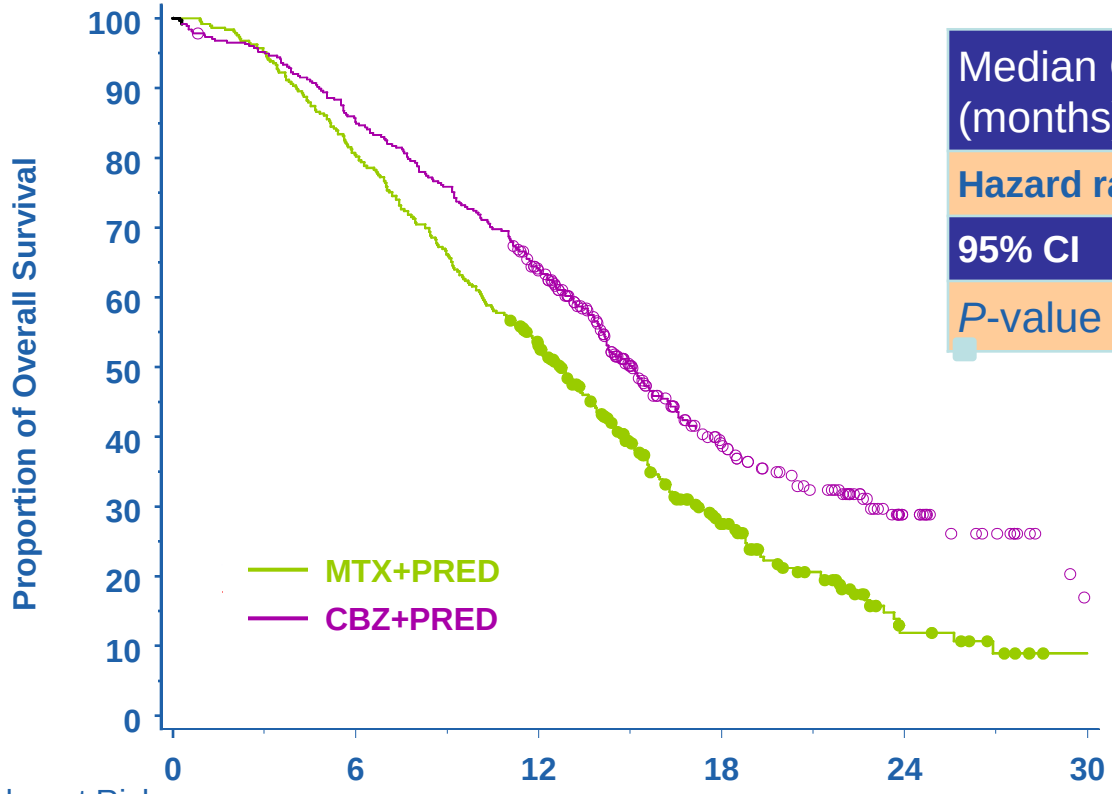


- *Stratification factor :*
  - ECOG PS (0,1 vs 2)
  - Mesurable/non_mesurable
- *Primary Endpoint:*
  - Overall survival
- *Secondary Endpoint:*
  - PSA response, PSA progression, PFS, RR, Pain progression, Safety, PK of cabazitaxel

Enrolment closed: 745/720 pts

Hypothesis: 25% Reduction in the risk of death
or median OS=10.67 months for cabazitaxel vs 8 months
511 events, duration 36 months

Cabazitaxel vs Mitoxantrone:Overall Survival



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	**0.72**	
95% CI	**0.61–0.84**	
P-value	<.0001	

28% risk of death reduction

Number at Risk

MTX + PRED	**377**	**300**	**188**	**67**	**11**	**1**
CBZ + PRED	**378**	**321**	**231**	**90**	**28**	**4**

Median FU: 13.7 mo

De Bono et al., Lancet 2010;376:1147-54

Active Cellular Immunotherapy (Sipuleucel-T)

Patient's white blood cells harvested

Short-term culture with protein "cassette"

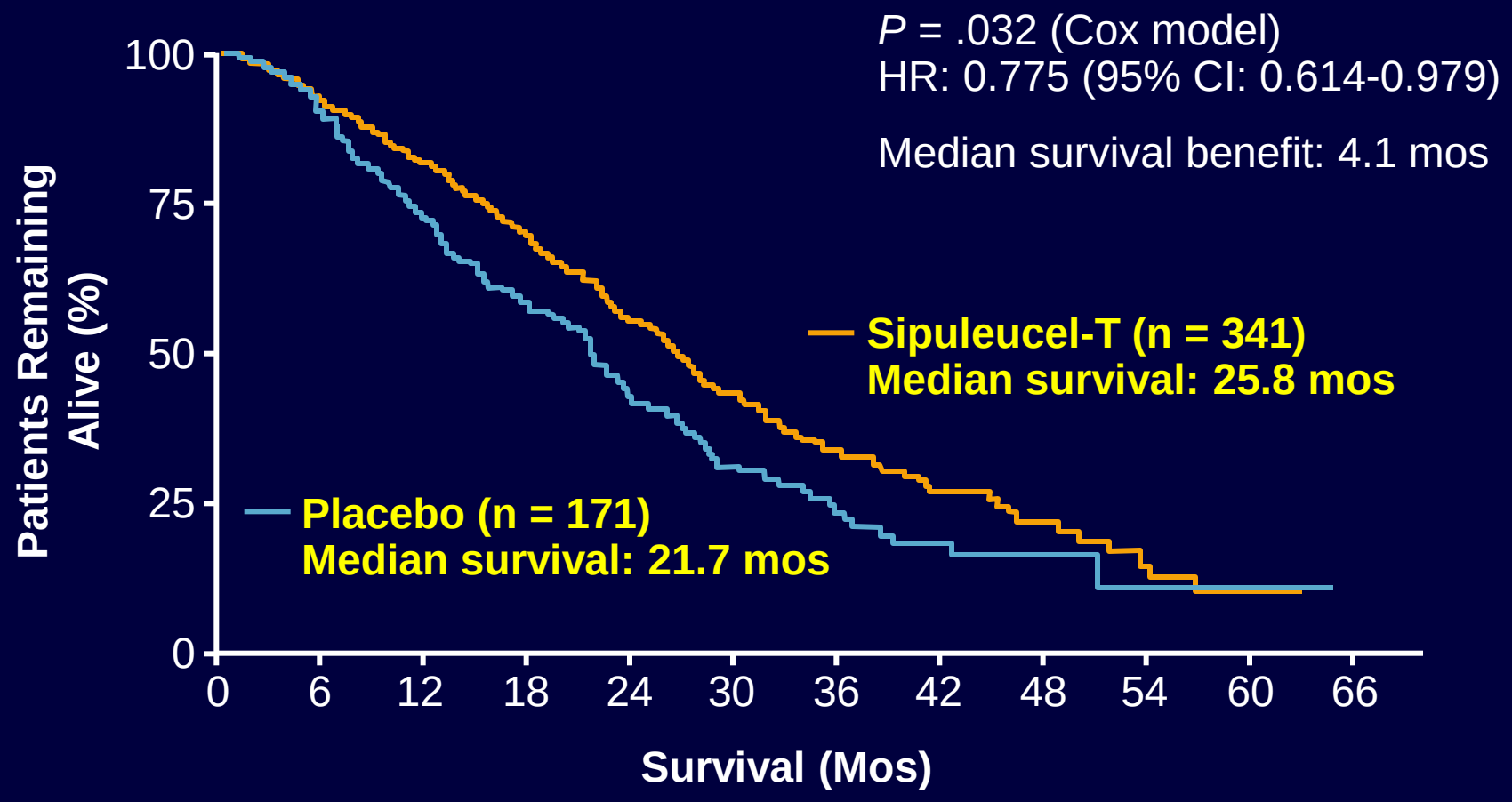
GM-CSF

Prostatic acid phosphatase

Shipping

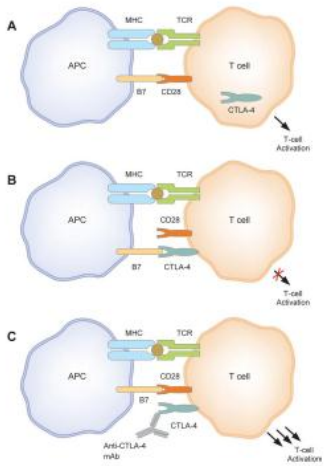
Cells infused back into patient (IV)

IMPACT Study: OS (ITT Population)



Kantoff PW, et al. N Engl J Med. 2010;363:411-422.

Targeting CTLA4: Ipilimumab



A, co-stimulation via CD28 ligation transduces T-cell activating signals; B, CTLA-4 ligation on activated T cells downregulates T-cell responses; C, blocking CTLA-4 ligation enhances T-cell responses[11]

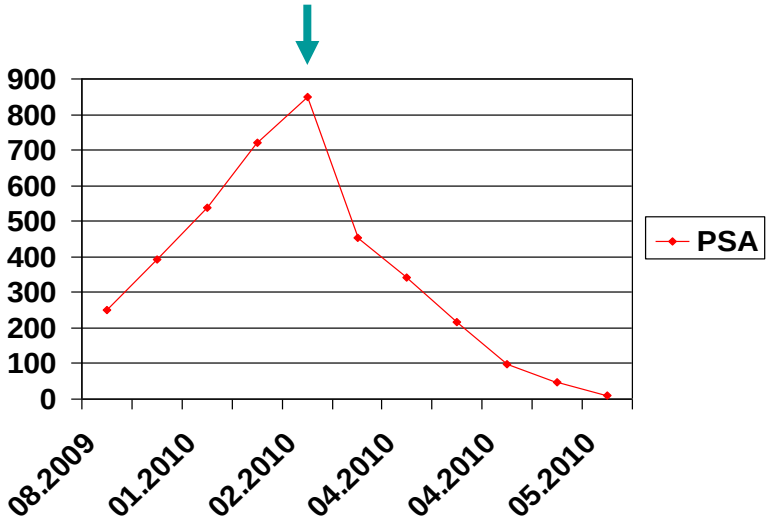
Docetaxel-naive patients: the « 95 » trial

R → 2 → Ipilimumab 10 mg/kg

R → 1 → Placebo

n= 600
OS (HR: 0.7)

Ipilimumab/Placebo + XRT



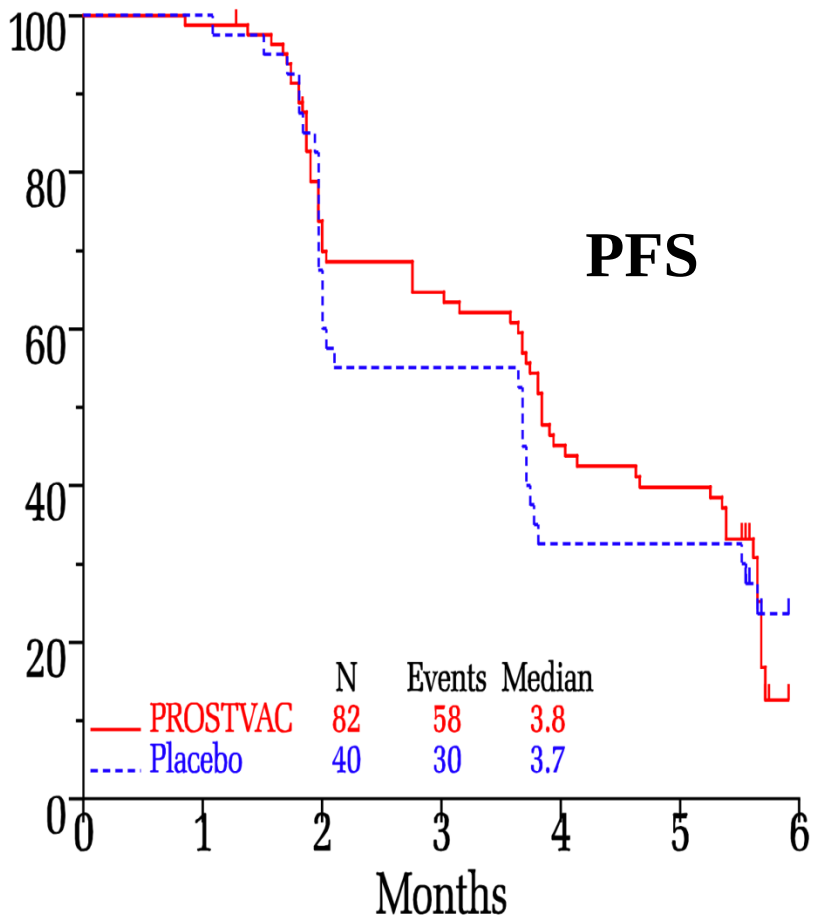
Docetaxel-pretreated patients: the « 43 » trial

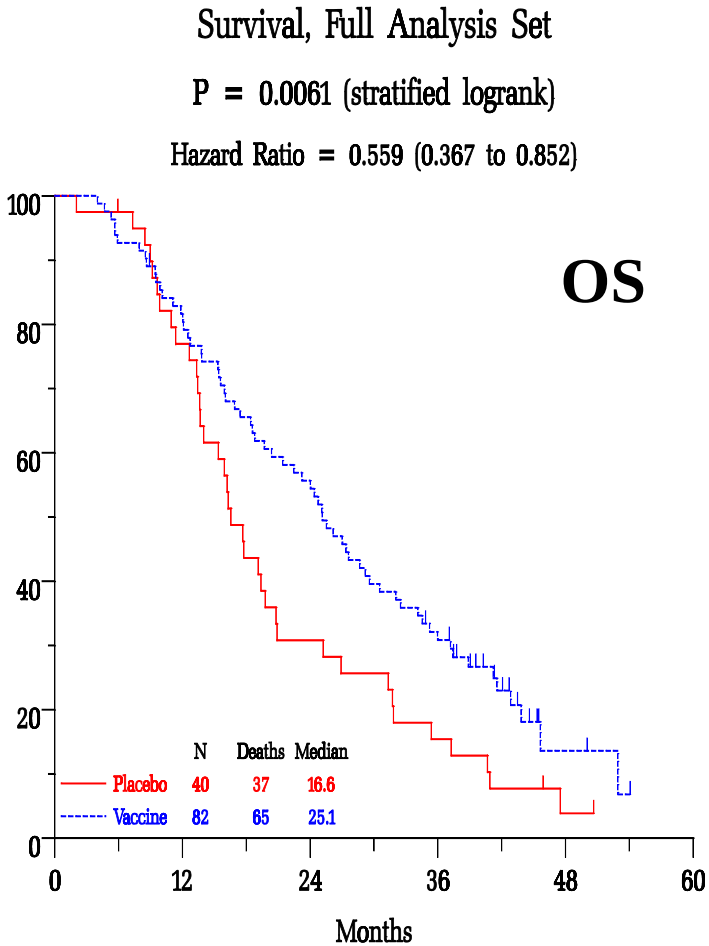
R → Ipilimumab + XRT to bone

R → Placebo + XRT to bone

n= 800
OS (HR: 0.76)

Prostvac: Poxviral-based PSA targeted immunotherapy



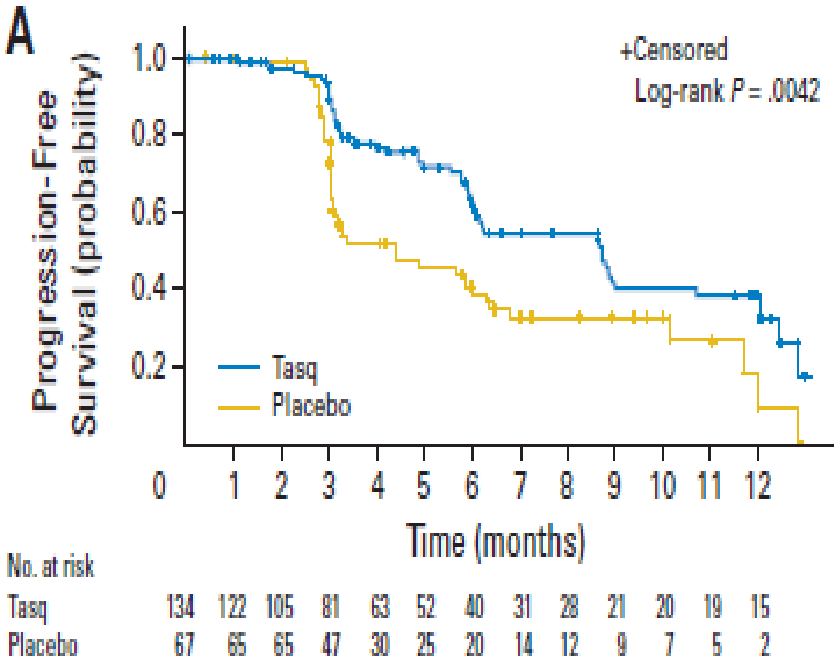


Kantoff P, J Clin Oncol 2010; 28: 1099-105.

Tasquinimod

Tasquinimod:
- Anti-angiogenesis (VEGF-dependent and independent)
- Immuno-modulation (Target: S100A9 protein)

n= 101 asymptomatic CRPC patients
Randomized phase II



Pili R, J Clin Oncol 2011, 29

Phase III trial asymptomatic CRPC

R → 2 → Tasquinimod
R → 1 → Placebo

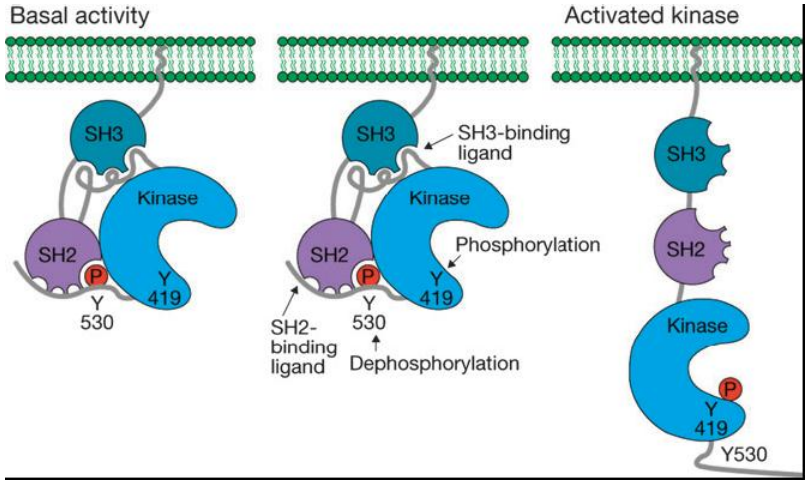
n= 1200
PFS (HR: 0.6)
+ OS

R-Phase II trial maintenance post-doce

R → Tasquinimod
R → Placebo

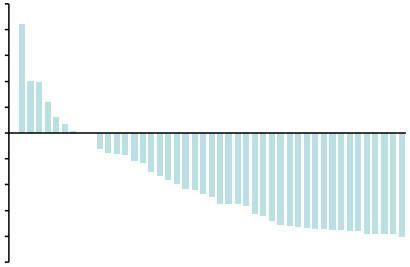
n= 140
PFS (HR: 0.59)

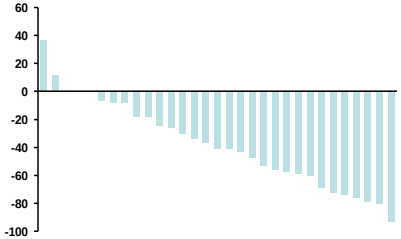
Targeting sRc: Dasatinib



Phase II Docetaxel-dasatinib
n= 46

PSA response:49% RECIST: 42%





Araujo et al., ASCO 2009, Abstr 5061
Fizazi K et al. Ann Oncol 18:1765-1773, 2007

Phase III « Ready » trial

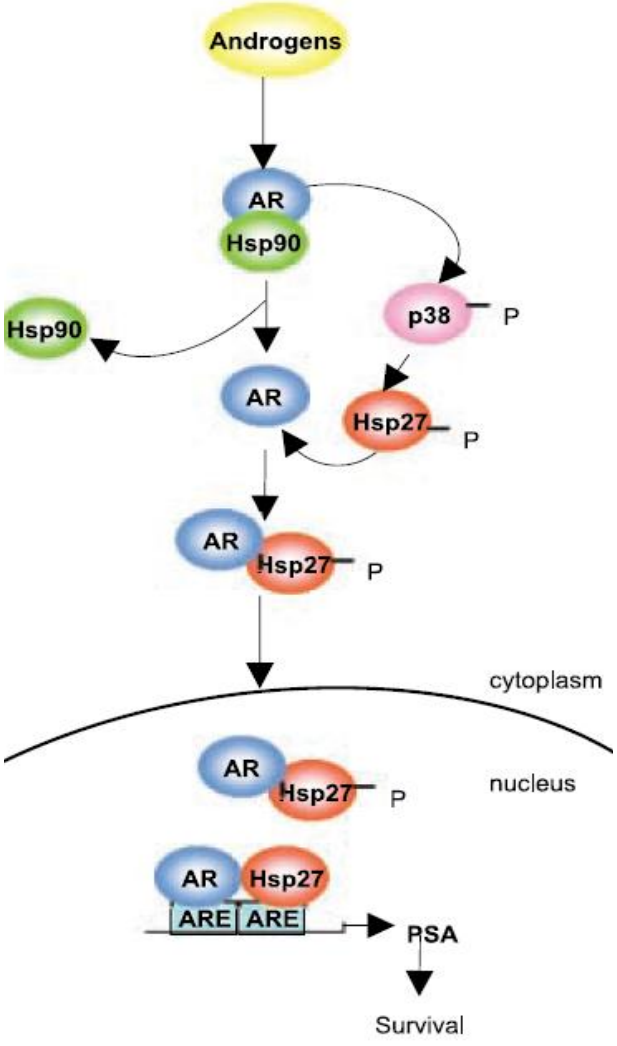
R → Docetaxel + Dasatinib

R → Docetaxel + Placebo

n= 1380
OS

Targeting Hsp27: OGX-427

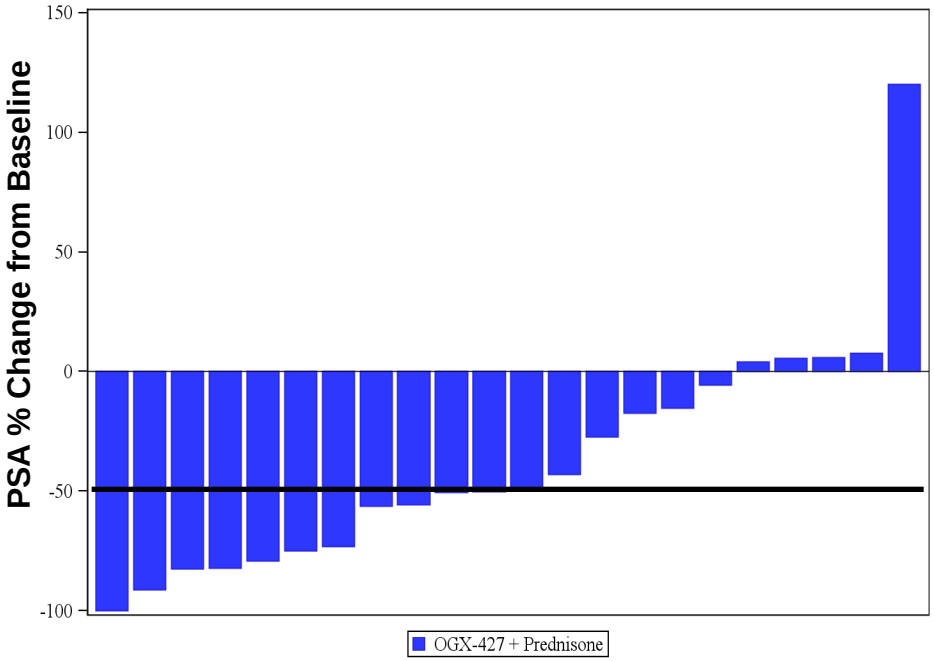
- Heat Shock Protein 27 (Hsp27)
  - Stress activated, small heat shock protein
  - Phospho-activated to form chaperoning oligomer which regulates multiple cell signaling and survival pathways
    - Inhibits apoptosis
    - Involved in proteasome mediated degradation
    - Facilitates normal protein folding and function
      - **Steroid receptors: AR, ER**
      - Growth factor: IGF-1, VEGF-1, FGF
      - Cytokine: IL-6, TGF-beta



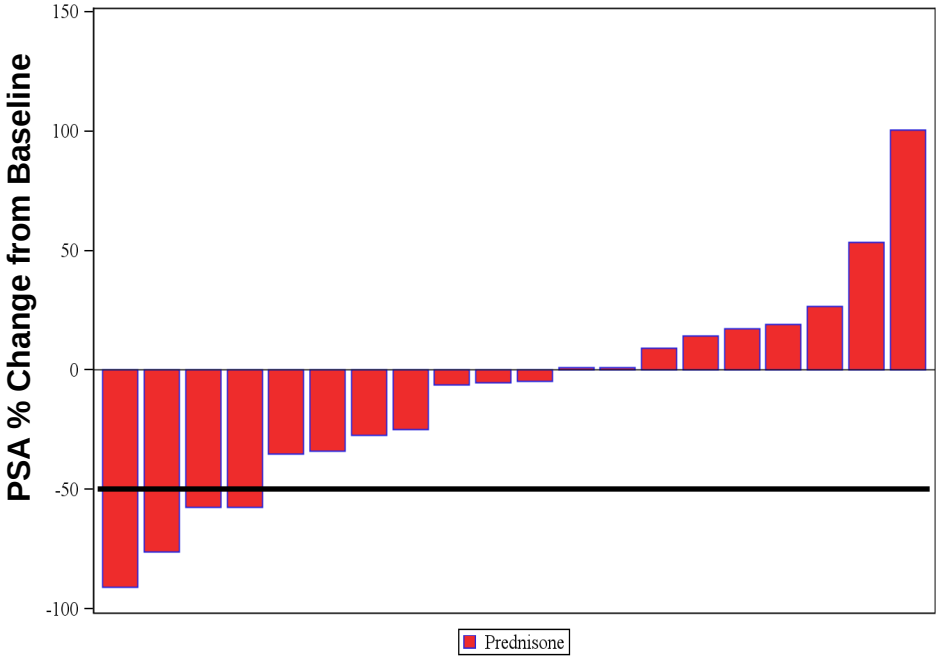
Rocci et al, Cancer Res, 65:11083, 2005;
Zoubeidi et al, Cancer Res, 67:10455, 2007

OGX-427 in CRPC: PSA Waterfall Plots

OGX-427 + Prednisone



Prednisone



+ activity reported on Recist, CTC conversion, cross-over

Chi K et al., ASCO 2012