XXV Congresso Nazionale AIRO

Simposio AIRO-AIMN: Trattamento delle Metastasi Ossee nel Paziente con Tumore della Prostata "Ormonorefrattario": - La Terapia Farmacologica -

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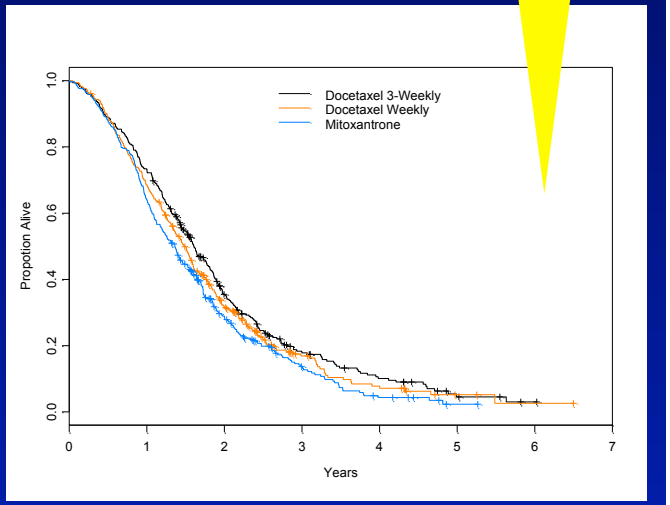
Rimini, 8 Novembre 2015

Advanced Prostate Cancer: From Treatment Sequencing to Algorythms

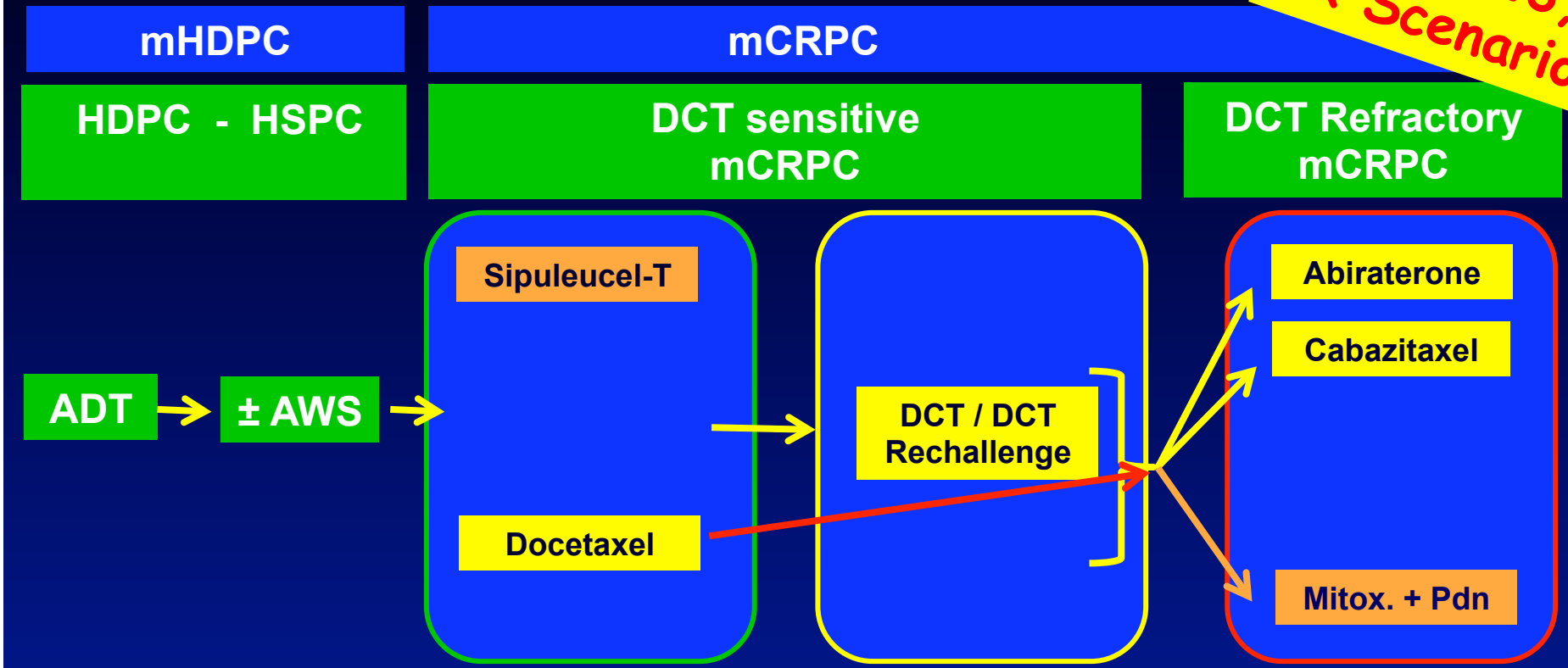
- ✓ **ADT (Androgen Deprivation Therapy) still the treatment of choice for advanced HSPC (Disease Control Rate: 80-85%).**
- ✓ **But, a sure progression to a CRPC status (Castration-Resistant Disease), mainly characterized by Bone Mets, will occur within 24-36 months from starting ADT (M+ disease).**
- ✓ ***Till yesterday,* Treatment Options in this setting limited only to a DCT-based CT, even if with significant improvements in median OS and disease control (TAX 327: *19.2 vs 16.3 m.*).**
- ✓ ***With …***



Berthold DR. et Al. J Clin Oncol. 2008;26:242-5.

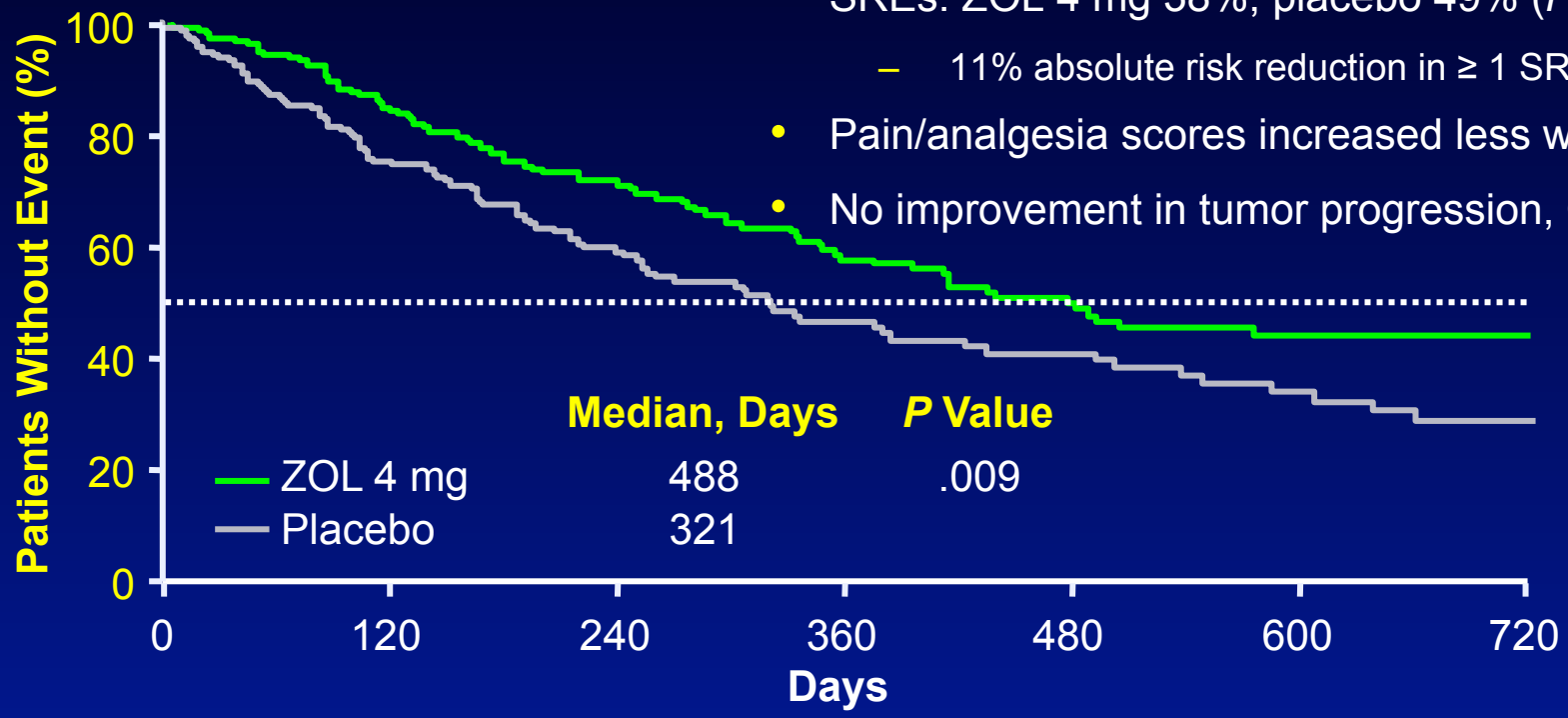
… the following Treatment Scenario until 2013 …..

The 2013, Rx Scenario



plus... Zoledronic Acid:

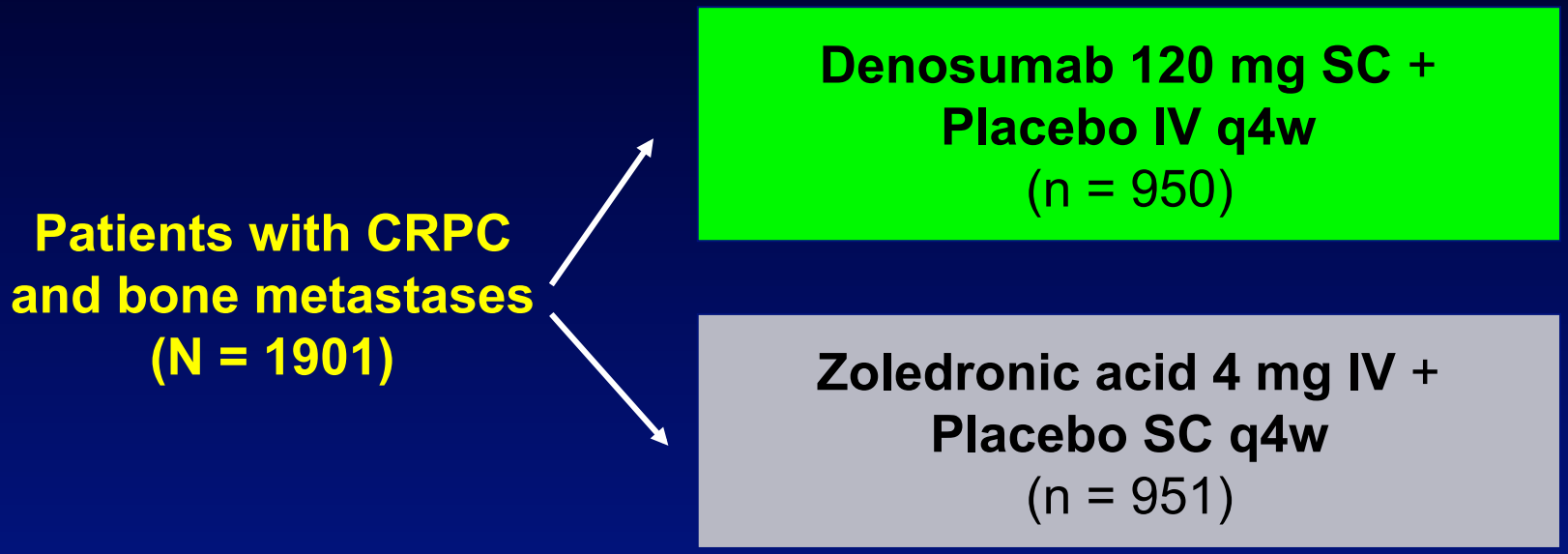
- **Time to First SRE in mCRPC**
- SREs: ZOL 4 mg 38%; placebo 49% (*P* = .028)
  - 11% absolute risk reduction in ≥ 1 SRE
- Pain/analgesia scores increased less with ZOL
- No improvement in tumor progression, QoL, OS



Pts at Risk, n						
ZOL 4 mg	214	149	97	70	47	35
Placebo	208	128	78	44	32	20

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. Saad F, et al. ASCO 2003. Abstract 1523.
Saad F, et al. J Natl Cancer Inst. 2004;96:879-882.

or… Denosumab (*Ph. III Study*):



- All patients received supplemental calcium and vitamin D
- Primary endpoint: time to first on-study SRE

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

Denosumab vs Zoledronic Acid: Efficacy Data in mCRPC

Outcome	Denosumab	Zoledronic Acid	HR (95% CI)	*P* Value
OS	19.4	19.8	1.03 (0.91-1.17)	.65
TTP	8.4	8.4	1.06 (0.95-1.18)	.30
Median time to first on-study SRE	20.7 mos	17.1 mos	0.82 (0.71-0.95)	.008

Fizazi K, et al. Lancet. 2011;377:813-822.

Potential Management Strategies for Metastatic Bone Disease

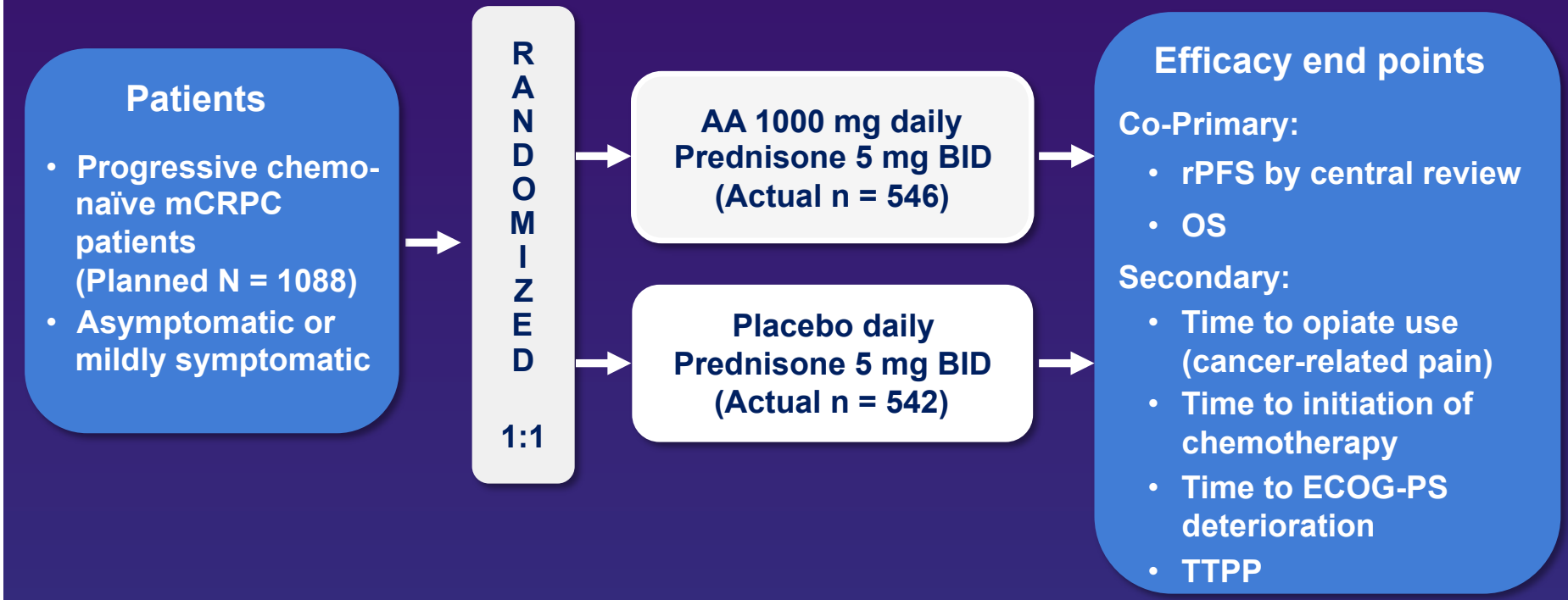
- **Treat underlying disease [1]**
  - Hormone (old & new) Therapy Options
  - Systemic Chemotherapy
  - External beam radiation therapy
  - Immunotherapy Options (?) [2]
- **Bone-directed therapy [3]**
  - Bisphosphonates
  - RANKL inhibitor
  - Bone-targeting radionuclides (*not a my task today !!*)

1. Horwich A, et al. Ann Oncol. 2010;21(suppl 5):v129-v133. 2. Drake CG. Nat Rev Immunol. 2010;10:580-593. 3. NCCN. Clinical practice guidelines in oncology. v.1.2014.

… recently, some changes in Decision Making derived from the "availability" of Efficacy Data for Abirat. and Enzalut. in the «so called» Pre-CT Setting

..Which Data ? …..

Overall Study Design of COU-AA-302

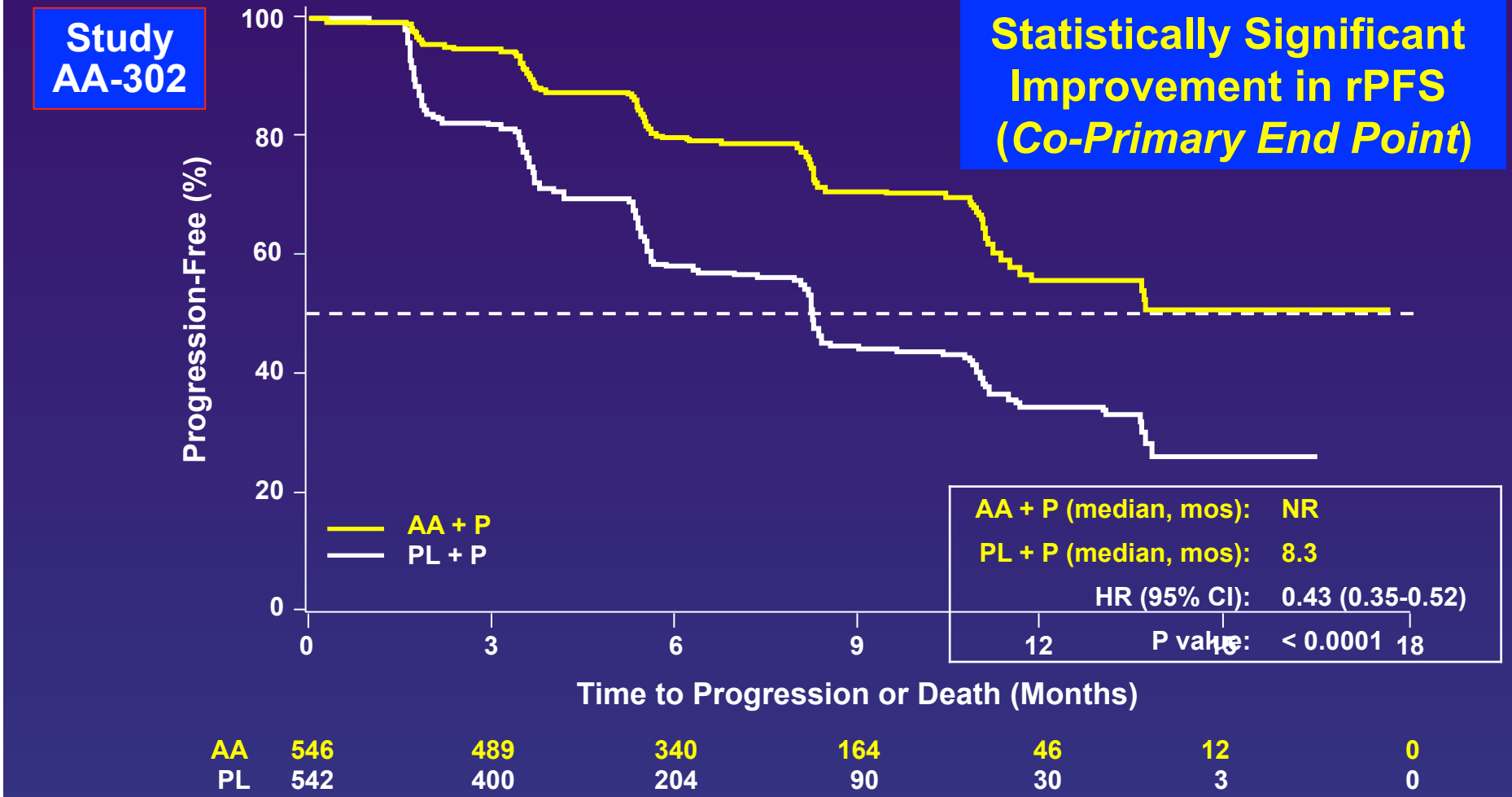


- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs. 1

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

COU-AA-302

Statistically Significant Improvement in Rx-PFS Co-Primary End Point



Data cutoff 20/12/2010

V4.0

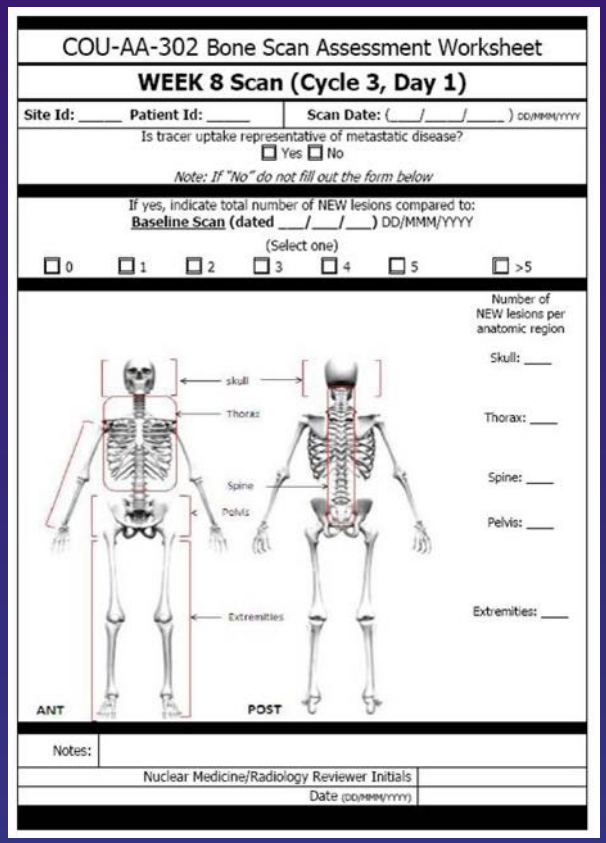
Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Adaptation of PCWG2 Consensus Criteria

COU-AA-302 Definition

- Progressive disease (PD) by bone scan: Adapted from PCWG2 consensus criteria1
  - Review < 12 weeks after randomization
    - ≥ 2 new bone lesions plus 2 additional lesions on a subsequent scan (“2+2”)
  - ≥ 12 weeks after randomization
    - ≥ 2 new bone lesions with new lesions confirmed at subsequent scan
- PD (soft tissue lesions) by CT/MRI by modified Response Evaluation Criteria in Solid Tumors (RECIST)
- Death from any cause

Prostate Cancer Clinical Trials Consortium (PCCTC) Bone Scan Form[2]



COU-AA-302 Bone Scan Assessment Worksheet

WEEK 8 Scan (Cycle 3, Day 1)

Site Id: _____ Patient Id: _____ Scan Date: (___/___/___) DD/MMM/YYYY

Is tracer uptake representative of metastatic disease?

☐ Yes ☐ No

Note: If "No" do not fill out the form below

If yes, indicate total number of NEW lesions compared to:
Baseline Scan (dated ___/___/___) DD/MMM/YYYY

(Select one)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5

Number of NEW lesions per anatomic region

Skull: ___

Thorax: ___

Spine: ___

Pelvis: ___

Extremities: ___

skull, Thorax, Spine, Pelvis, Extremities

ANT POST

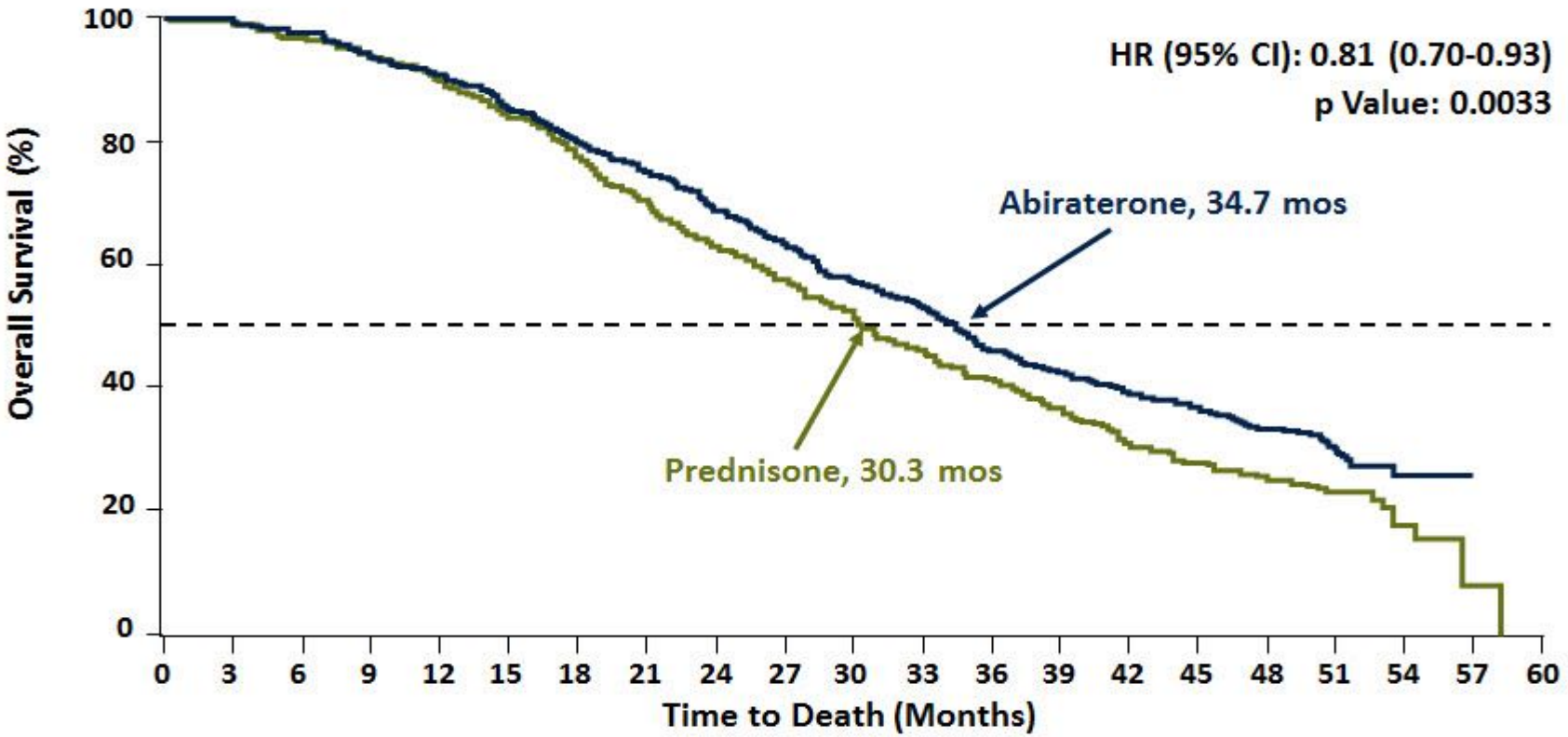
Notes:

Nuclear Medicine/Radiology Reviewer Initials

Date (DD/MMM/YYYY)

1. Scher HI, et al. *J Clin Oncol*. 2008;26:1148-1159.
2. Morris MJ, et al. *J Clin Oncol*. 2011;29(Suppl 7). Abstr 121.

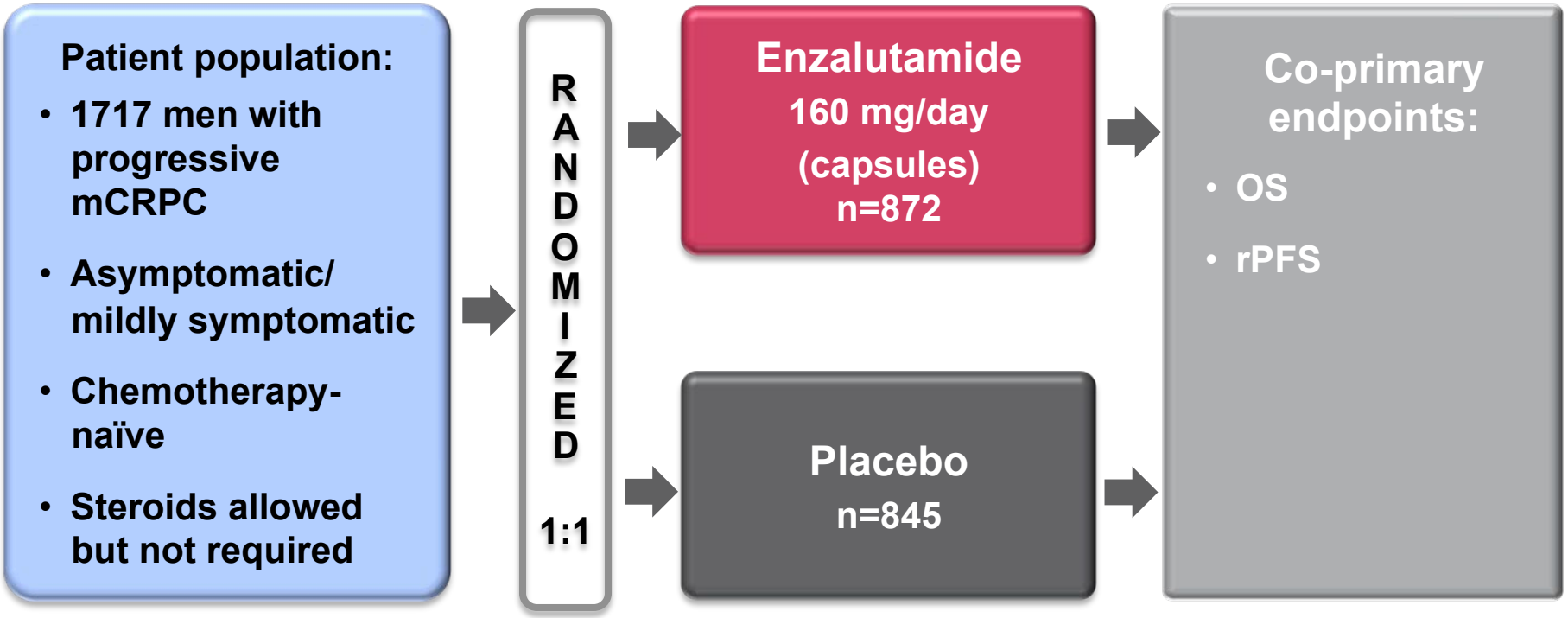
Final OS Analysis



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

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

PREVAIL: A Phase 3 trial of Enzalutamide after progression on ADT in men with mCRPC

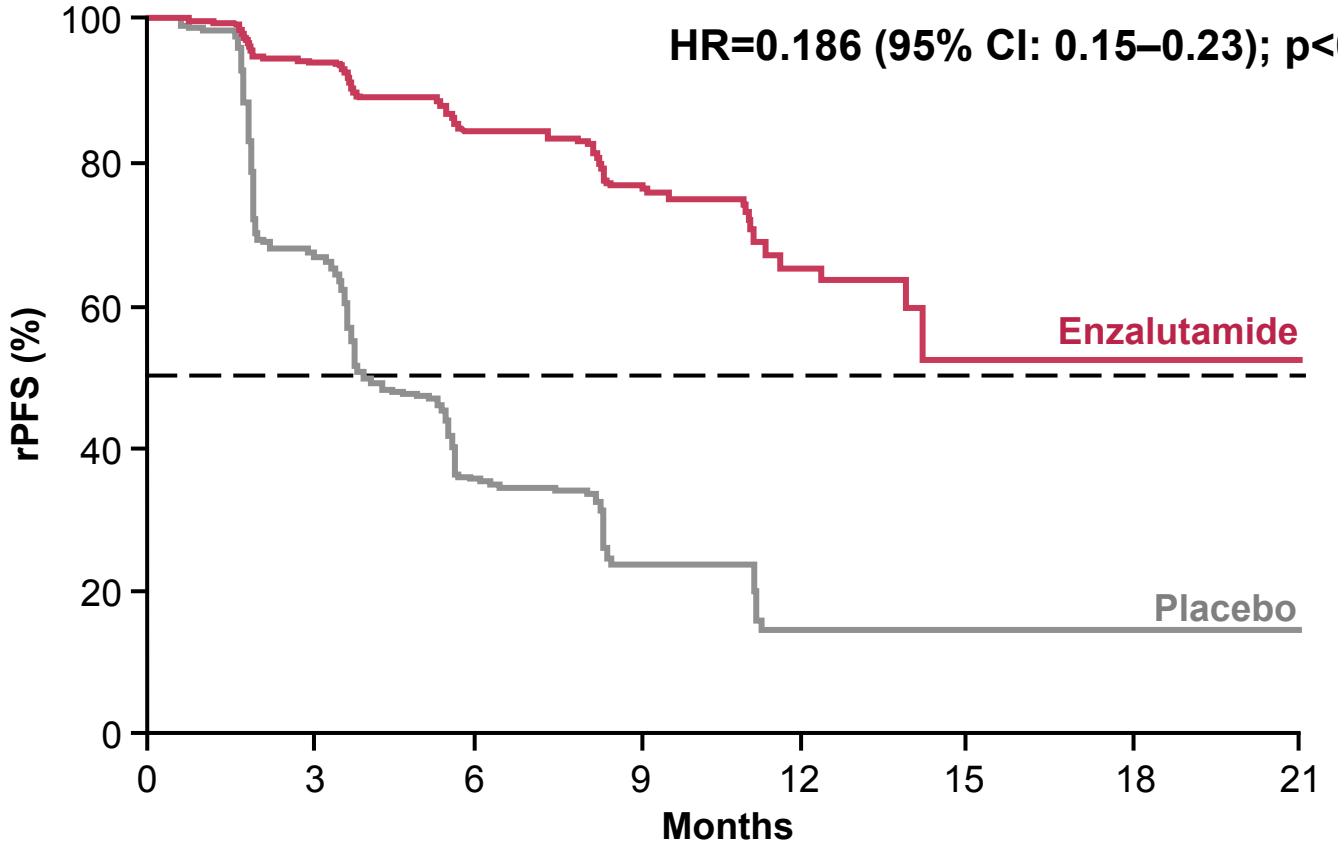


ADT=androgen-deprivation therapy; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; rPFS=radiographic progression-free survival.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation; ClinicalTrials.gov identifier: NCT01212991.

astellas
Leading Light for Life

PREVAIL:
prolonged Rx-PFS (*Co-Primary Endpoint*)



Enzalutamide, n	832	514	256	128	34	5	1	0
Placebo, n	801	305	79	20	5	0	0	0

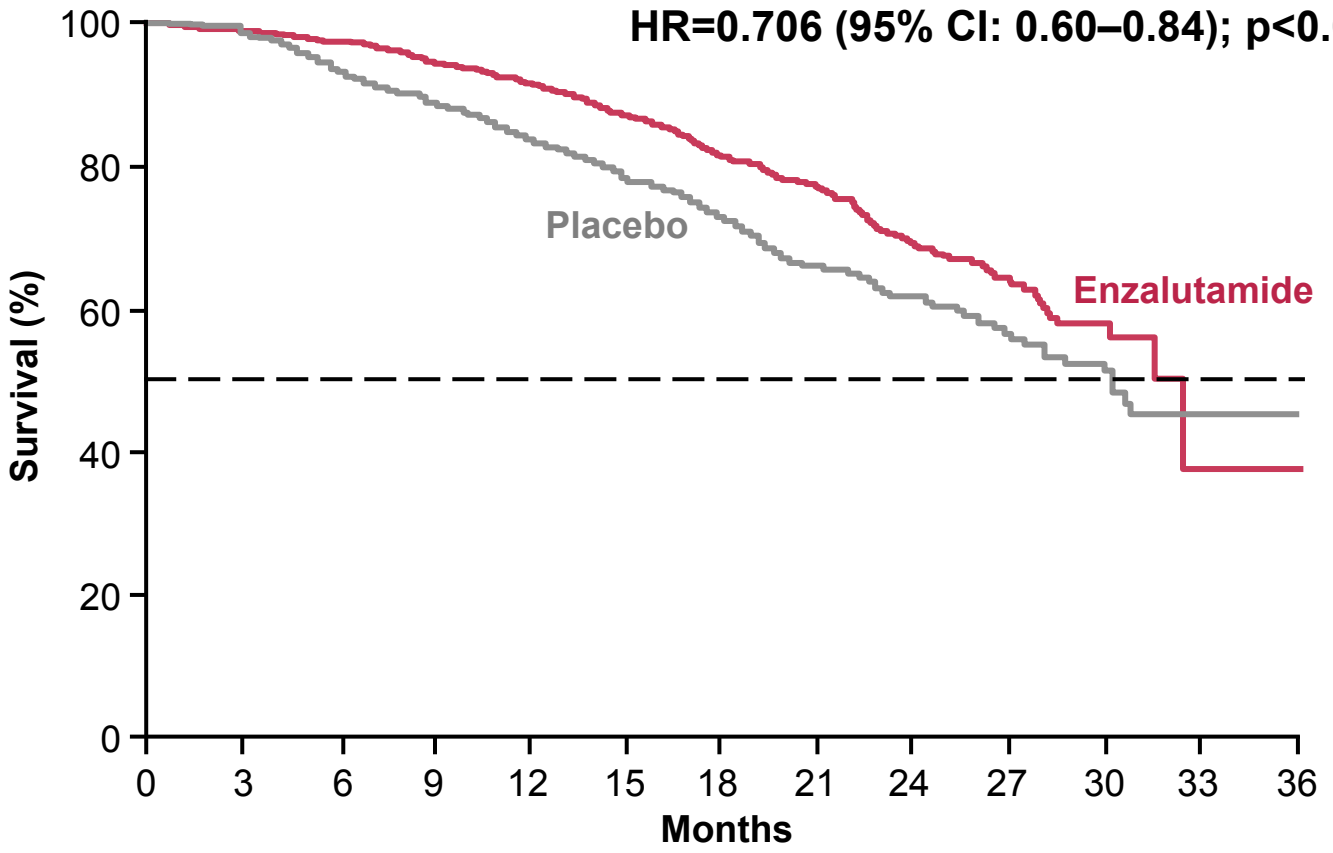
Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4)

NYR = Not Yet Reached

CI=confidence interval; HR=hazard ratio; rPFS=radiographic progression-free survival.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

PREVAIL:
reduced risk of death by 29%



Enzalutamide, n	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo, n	845	835	781	744	701	644	484	328	213	102	27	2	0

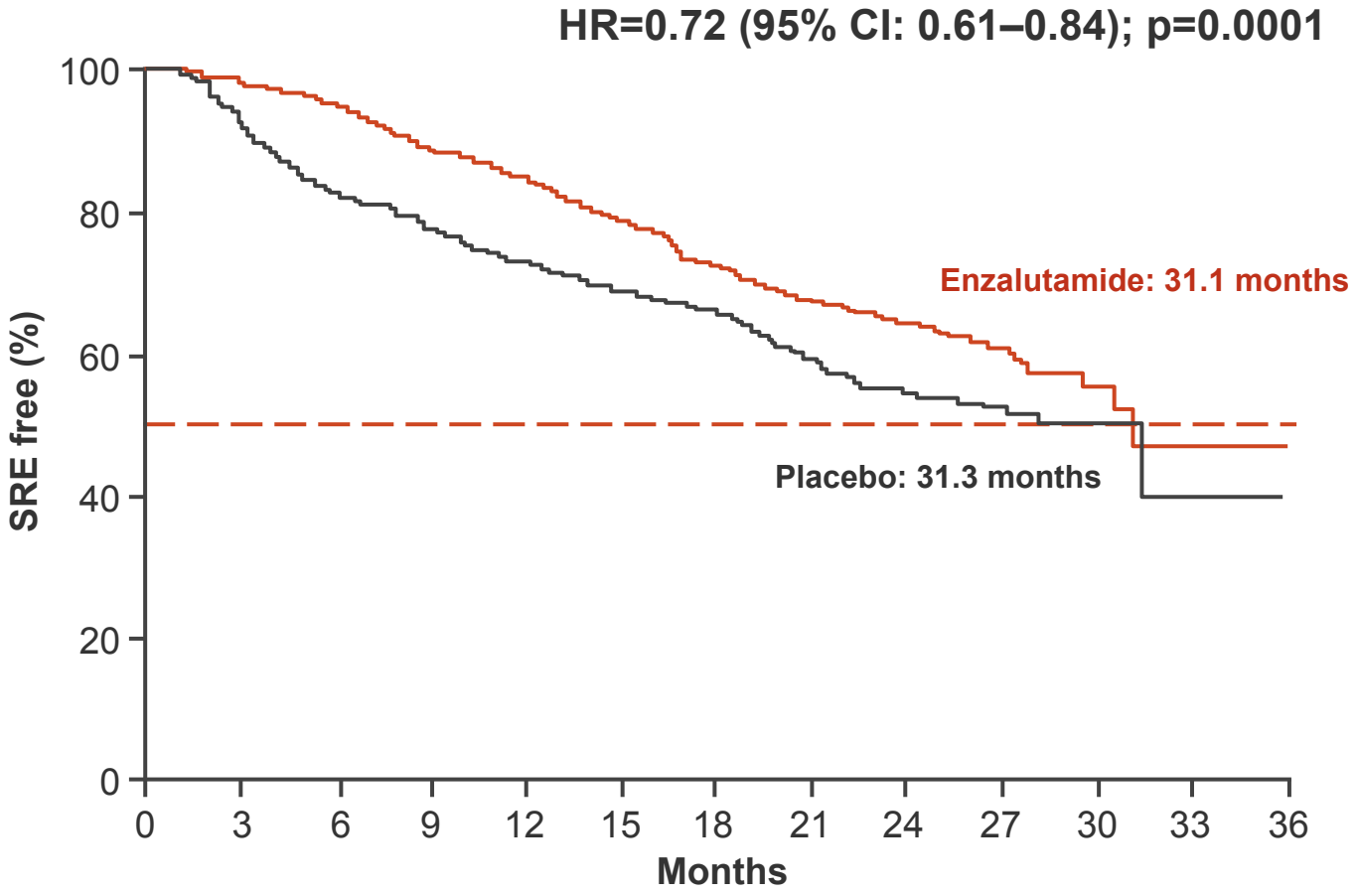
Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

NYR = Not Yet Reached

CI=confidence interval; HR=hazard ratio.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

PREVAIL: delayed time to first SRE*



Enzalutamide, n	872	843	797	732	674	605	447	286	183	90	24	1	0
Placebo, n	845	750	644	585	520	463	319	198	118	59	18	0	0

*Included radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression or change of antineoplastic therapy to treat bone pain from prostate cancer.
CI=confidence interval; HR=hazard ratio; SRE=skeletal-related event..
Armstrong AJ, *et al.* ASCO 2014; Oral presentation. Abstract 5007.

Pre-DCT and Post-DCT Setting Data

DCT

What's more ?

Pre-DCT and Post-DCT Setting Data

- The «Docetaxel» Spartiacque Dilemma -

DCT

Pre vs Post-DCT Data:

Will these spartiacque remain (direct sequencing in the future?) and how?

How to consider and place the actual post-DCT studies and data?

DCT Sensitive new Data:

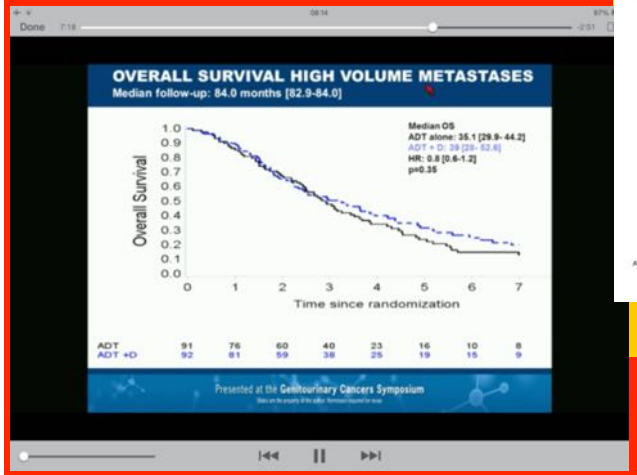
Will the CHAAARTED Data change clinical practice in mHDPC and, possibly, in the following mCRPC ?

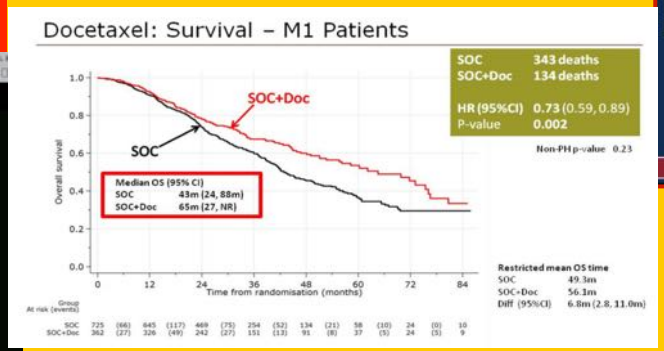
And which eventual optimal candidate patient' population?

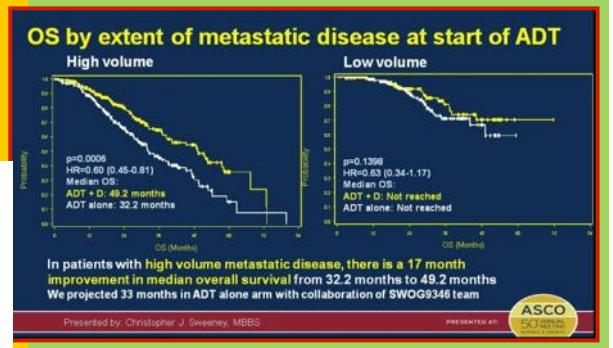
Controlled Trials of ADT+Chemo vs ADT alone
Who is the optimal candidate?

One negative and Two positive Trials for OS

But, three different definitions for the ideal Population !!

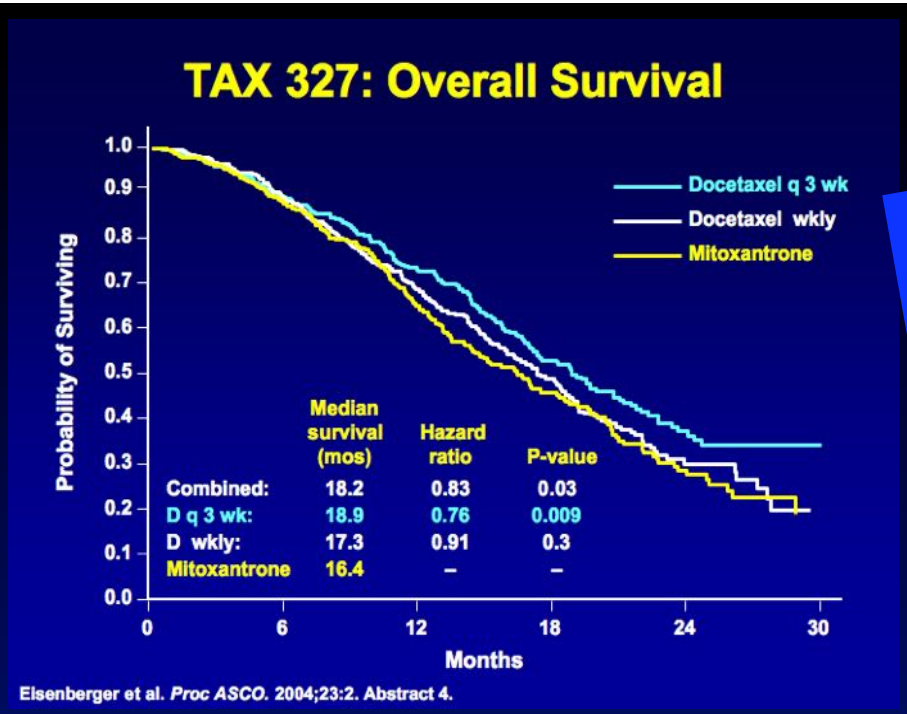






Probaly OK for Early DCT,

But Which Cases ?



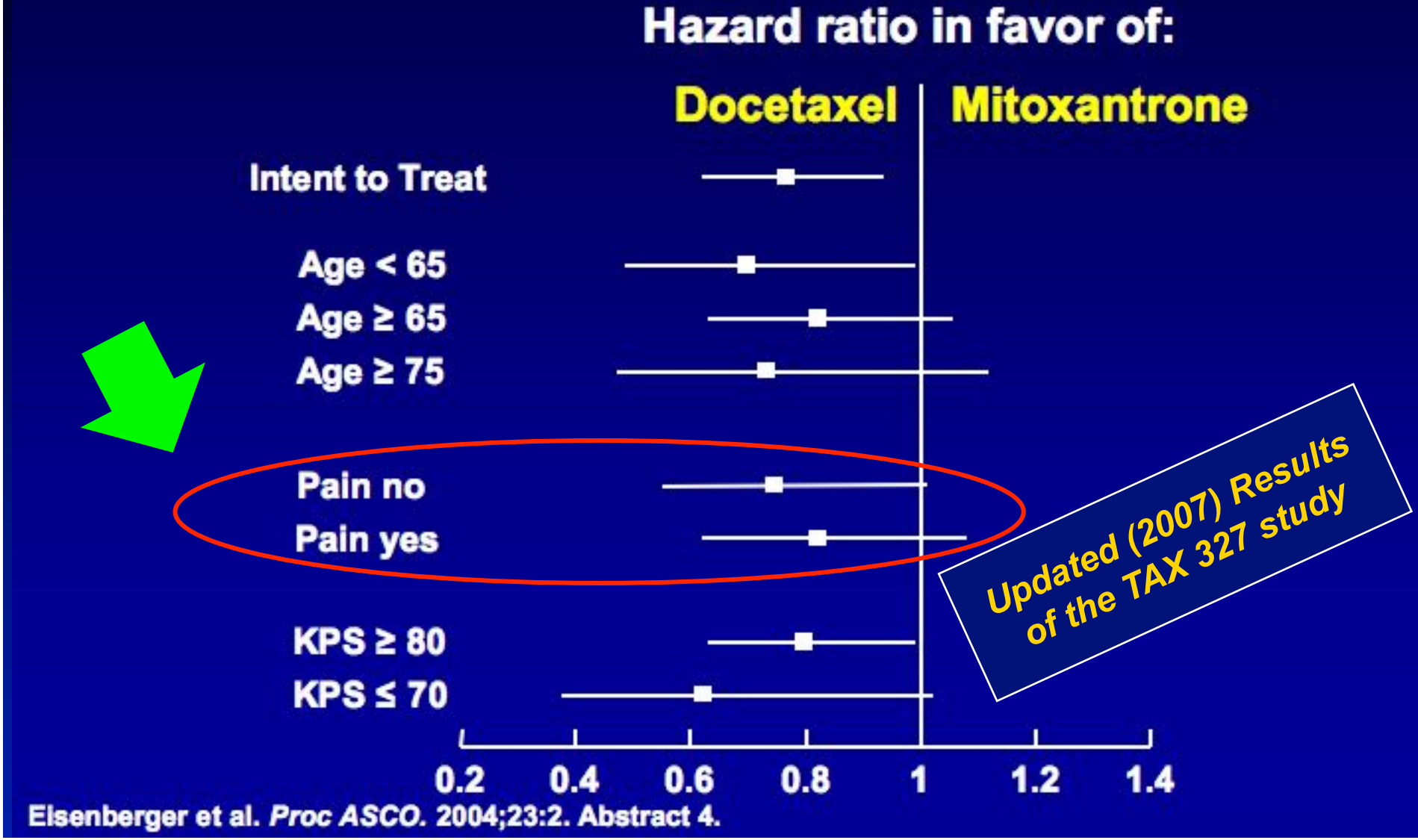
… but remembering also the «Old» TAX-327 Data …

OS = +2.5m

Docetaxel (q21),
significantly improves:

- **OS (18.9 vs 16.5 m)** p =.009)
  (*24% ↓ in the risk of death, HR=0.76, 95% CI 0.62-0.94*)
- **PSA response**: 45 vs. 32%, p = .0005
- **Objective *response*:** *12 vs 7%, p = 0.11*
- **Pain response**: 35 vs. 22%, p = .01
- **Quality of Life** (FACT-P): 22 vs 13%, p = .009
- ***Safe*** *but with ↑ toxicity (Grade 3/4 neutropenia: 32 vs 21.%)*

TAX 327: Survival in Subgroups
Docetaxel q 3 wk vs Mitoxantrone



Updated (2007) Results of the TAX 327 study

Eisenberger et al. *Proc ASCO.* 2004;23:2. Abstract 4.

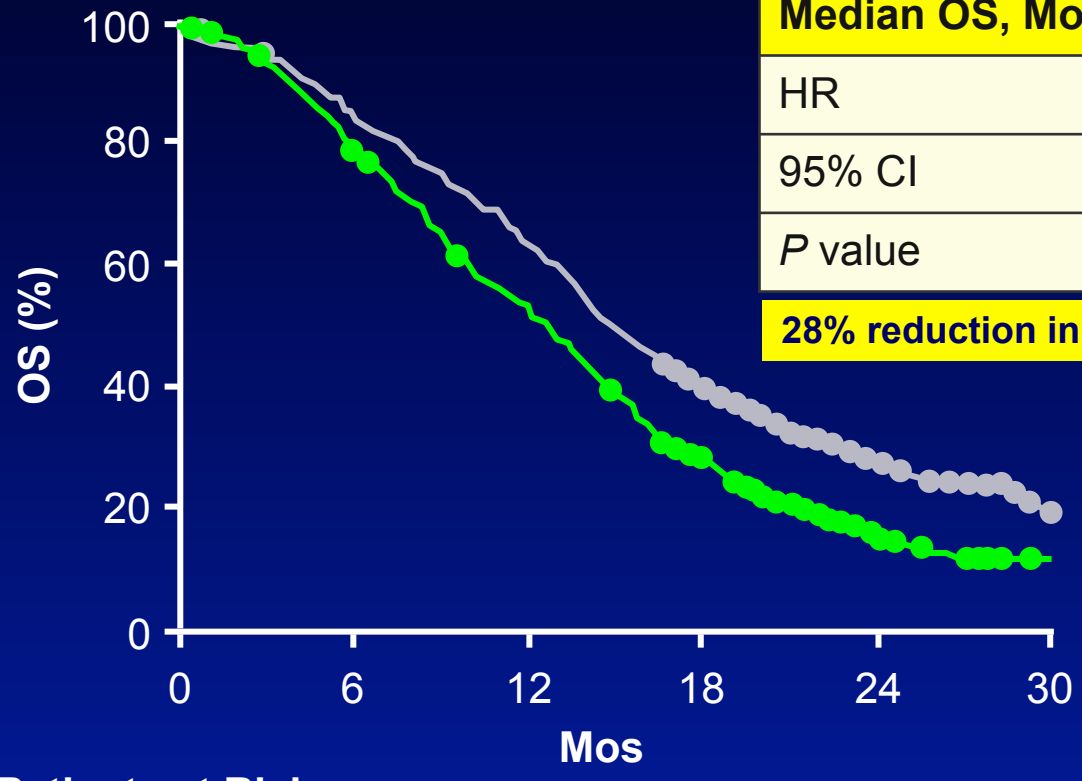
Cabazitaxel (TROPIC Phase III Study)
Primary Endpoint: OS (ITT Analysis)

+2.4 m

De Bono JS, et al

	MP	CBZP
Median OS, Mos	**12.7**	**15.1**
HR	0.70	
95% CI	0.59-0.83	
P value	< .0001	

28% reduction in risk of death



Combined median follow-up: 13.7 mos

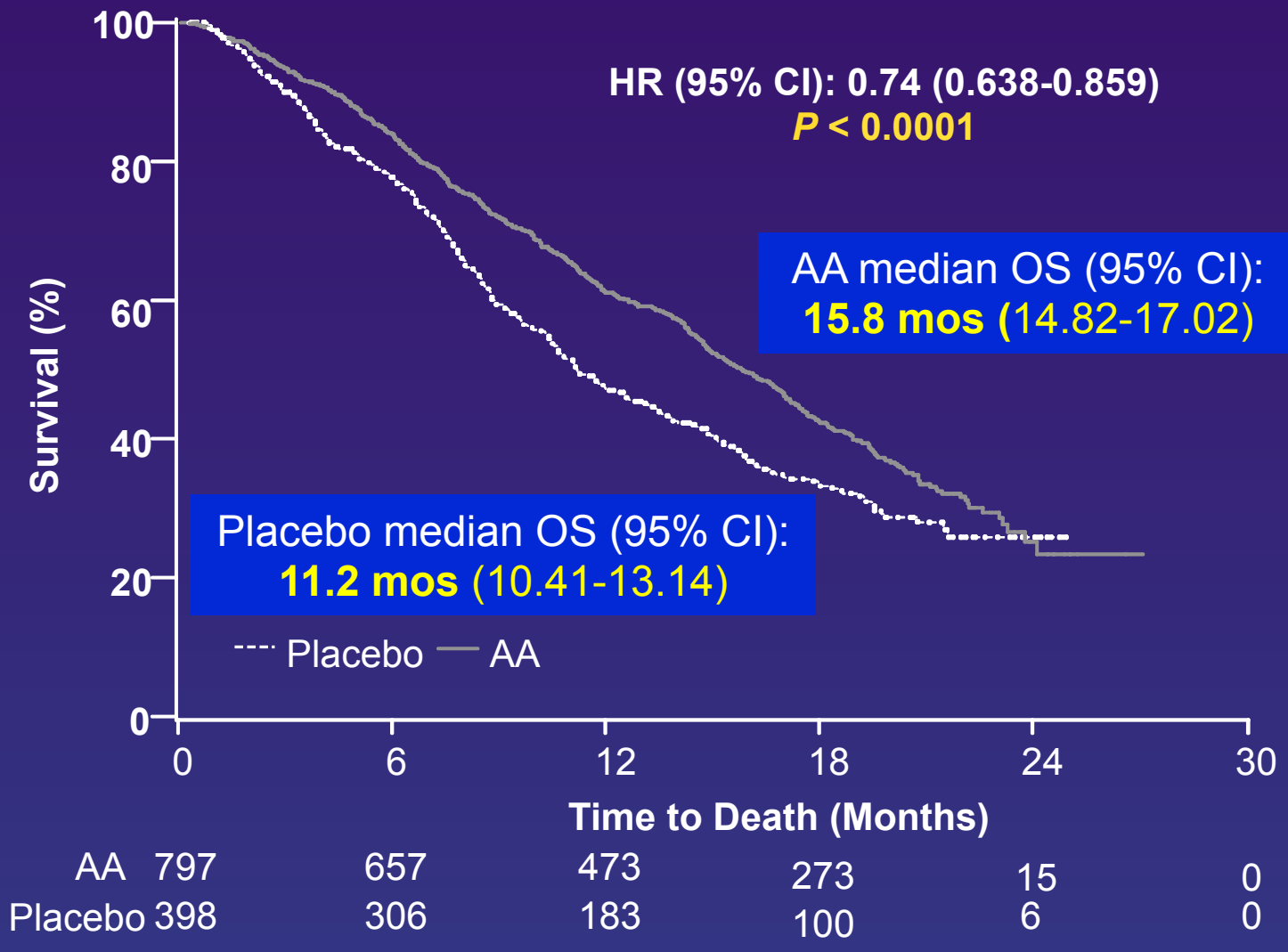
30% risk reduction

Patients at Risk, n

MP	377	299	195	94	31	9
CBZP	378	321	241	137	60	19

28% of patients still alive at 2 years with cabazitaxel vs 17% with mitoxantrone

Abiraterone Acetate (Study 301)
(2nd pre-planned analysis, mOS >from 3.9 to 4.6m)

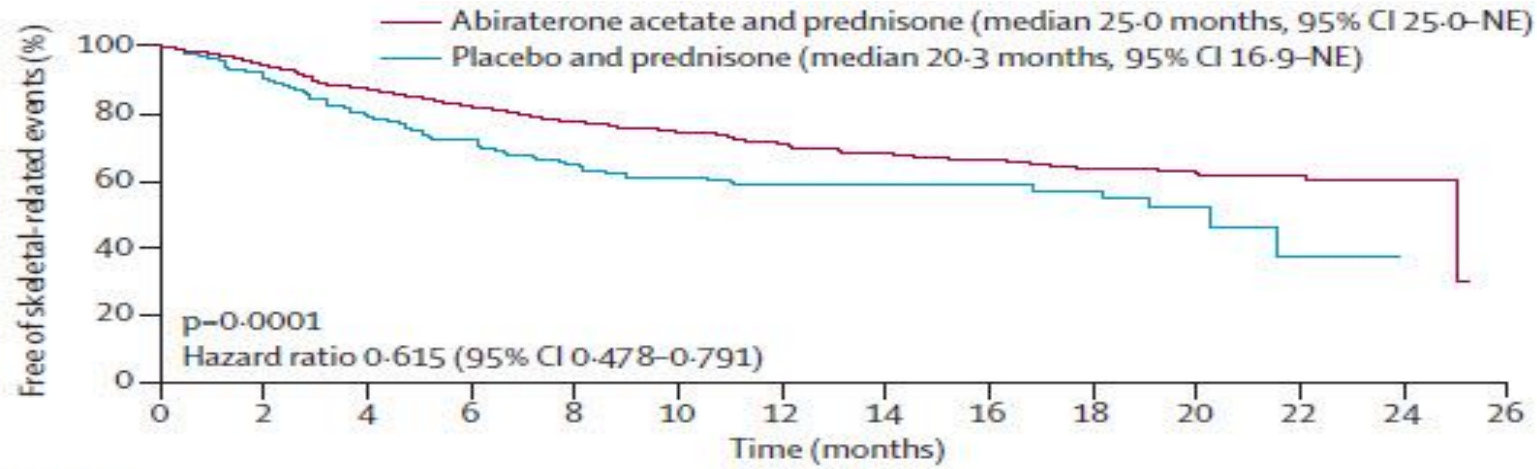


Scher et al. J Clin Oncol 2012; 29 (suppl): Abs A4517 (oral presentation)

V2.0

Abiraterone Acetate (COU-AA-301 Study) (*Post DCT Setting*): Time to SRE

- SREs were documented in 22.6% of patients in the abiraterone + prednisone arm and 24.6% in the placebo + prednisone arm
- Abiraterone + prednisone significantly delayed the time to SREs

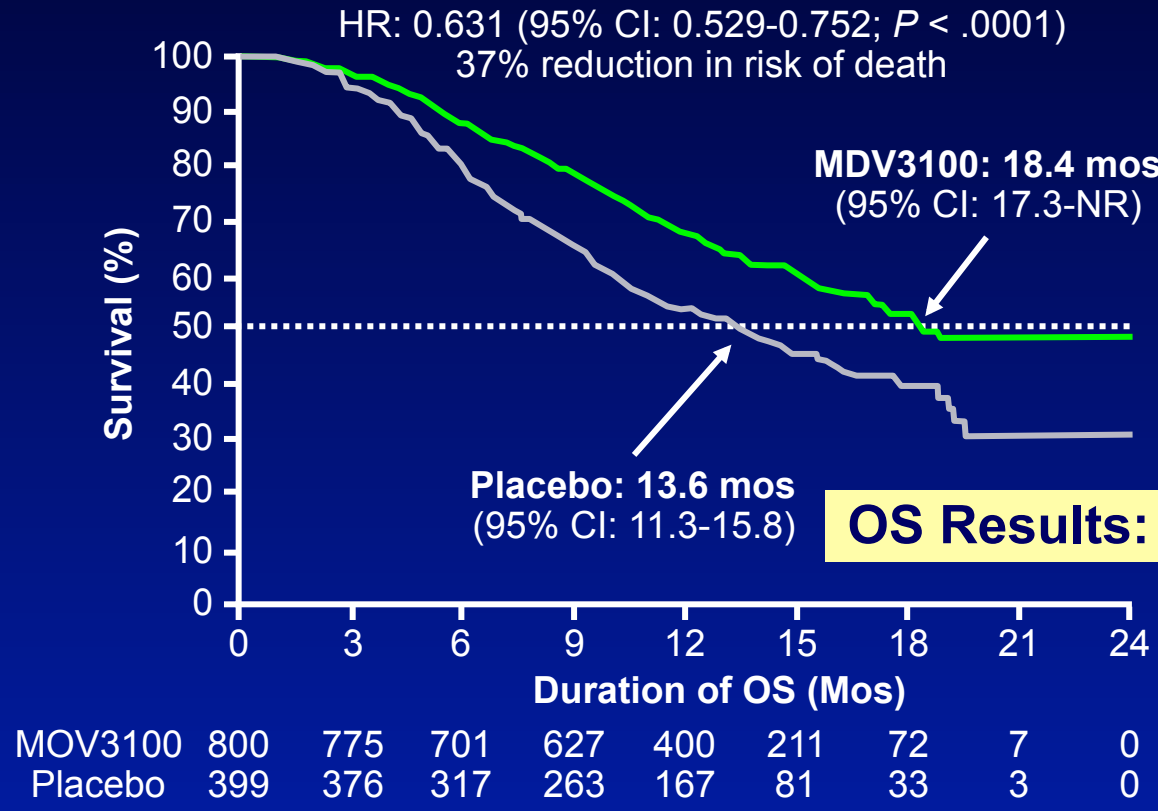


Number at risk					
Abiraterone acetate and prednisone	797	399	204	111	7
Placebo and prednisone	398	114	53	25	0

Logothetis et al. Lancet Oncol 2012: 2012; 13: 1210–17

Enzalutamide (AFFIRM Study) (post-DCT setting): median OS

- OS improved with MDV3100 vs placebo
  - Median follow-up: 14.4 mos

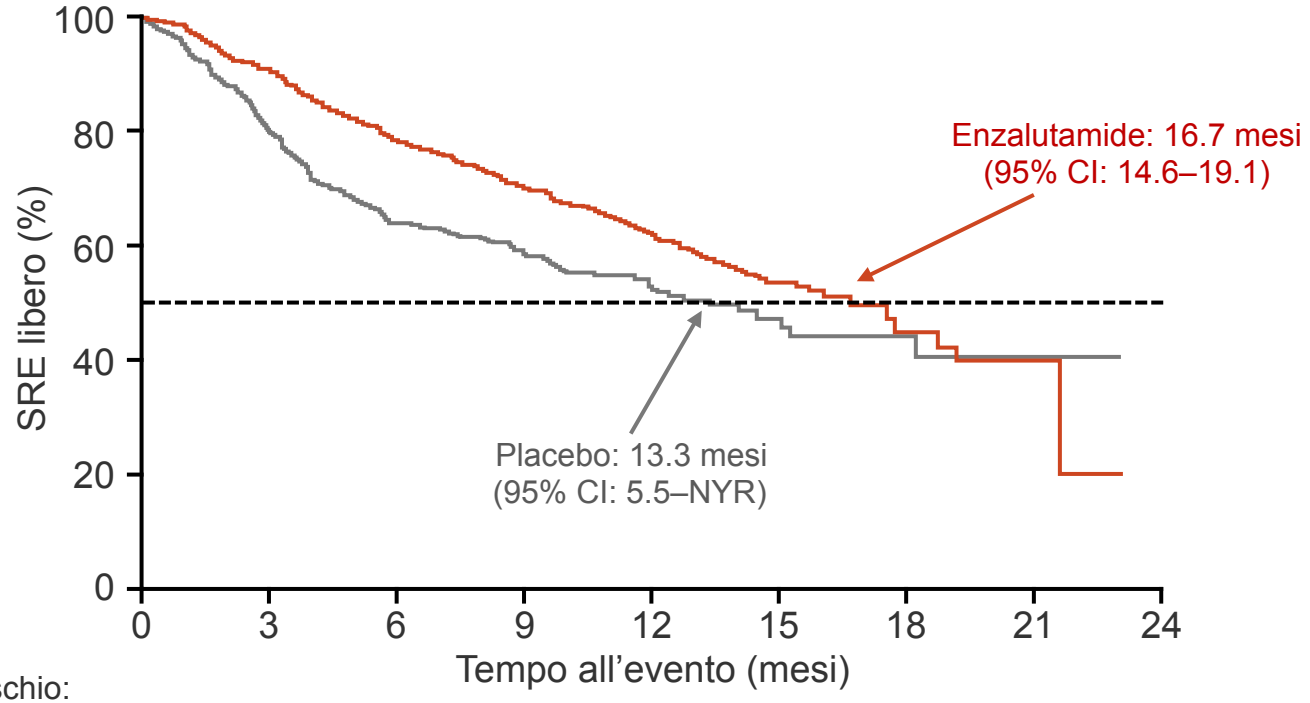


OS Results: 18.4 vs 13.6m

Scher HI, et al. ASCO GU 2012. Abstract LBA1.

AFFIRM Study: Time to first SRE (secondary endpoint)

- Tempo di insorgenza del primo SRE significativamente ritardato da enzalutamide rispetto a placebo:
  - 16.7 versus 13.3 mesi (HR=0.69, 95% CI: 0.57–0.84; p<0.001)
  - 31% riduzione del rischio di SRE



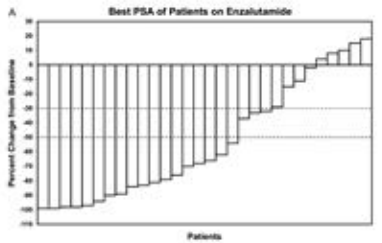
N. a rischio:									
Enzalutamide, n=	800	676	548	379	209	87	19	2	0
Placebo, n=	399	278	196	128	68	33	11	0	0

Tempo al primo SRE definito come il tempo di radioterapia, chirurgia ossea, fratture ossee patologiche, compressione del midollo spinale o il cambiamento di terapia antineoplastica per trattare il dolore osseo.
CI= intervallo di confidenza; HR= rapporto di rischio; NYR= non ancora raggiunto; SRE= eventi scheletrici correlati.
De Bono J, *et al.* Presented at ASCO 2012; Oral presentation 4519.

What's more ?

- **The Sequencing problem & AR variants: Abi-Enza or Enza-Abi?**
  (*Again … !! Remembering RCC…*)

PSA decline in patients on (A) enzalutamide and (B) abiraterone.



Noonan K L et al. Ann Oncol 2013;24:1802-1807

Resistance to Enzalutamide

- Overexpression of CYP17

Resistance to Abiraterone

- Overexpression of AR

Prevalence of AR-V7 in CRPC (n=62)

- Pre-Enza, Pre-Abi : 11.6%
- Post-Enza *only* : 25.0%
- Post-Abi *only* : 51.2%
- Post-Enza *and* Post-Abi : 66.7%

ASCO 50 ANNUAL MEETING

Which Agent first?
Any sure data !!!
And what's about CT ?

Emmanuel Antonarakis, 2014 ASCO Annual and ESMO Meetings

Conclusions

- in **mCRPC with Bone Mets**, We have now a number of ***new*** and ***efficacious Rx Options.***

- A relevant number of these Rx Options are ***quickly moving in earlier Phases*** of the Disease.
- Other Options are coming back (DCT-CT) or leave the Rx Scenario for lack of efficacy

- We are "***RUNNING***" from the "**Old Sequential Strategy**" to a new, ***but till now"Strongly Experience-based", Algorythm (due to the lack of validated Predictive Factors ..)***

sb