

Discussion

Bertrand TOMBAL

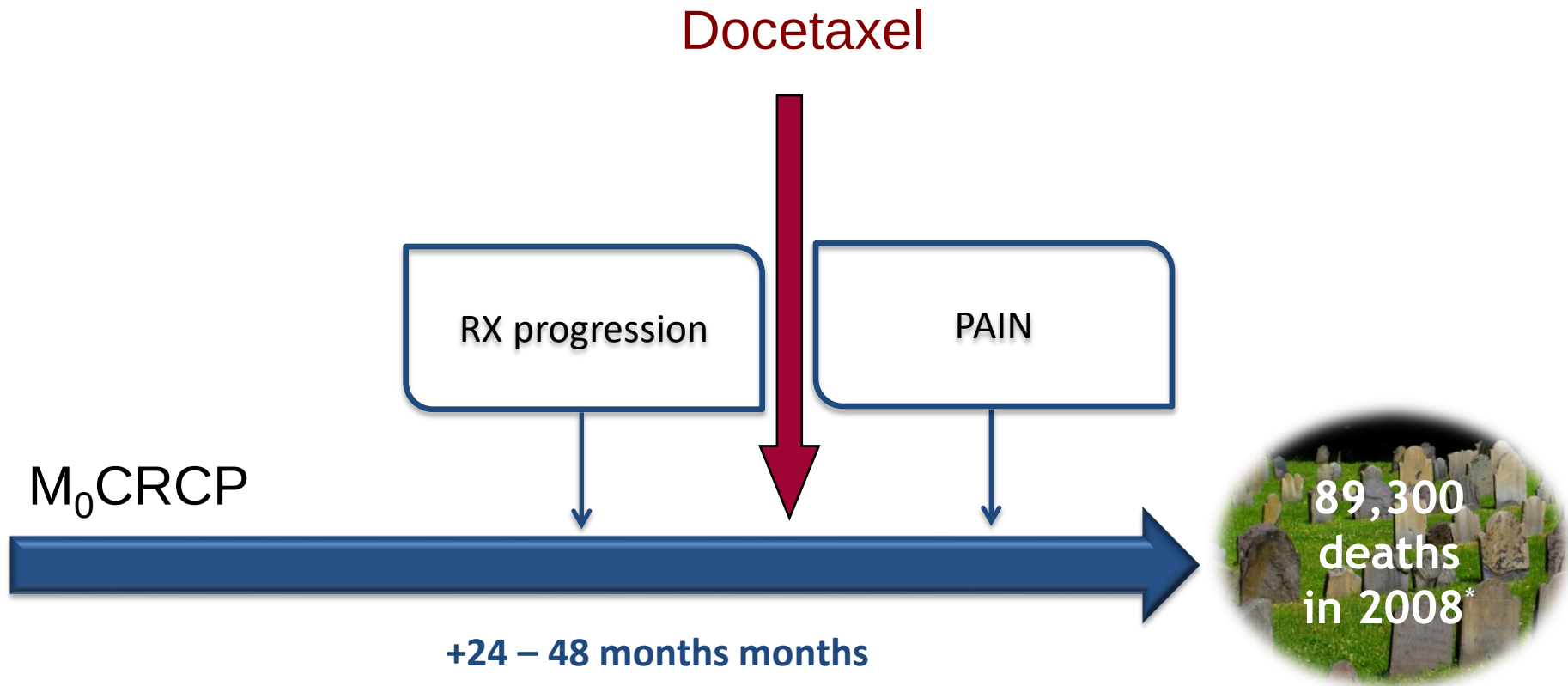
Cliniques universitaires Saint-Luc

Brussels, Belgium

Disclosure slide

- Advisor or investigator for Amgen, Astellas, Bayer, Medivation, Millenium, Sanofi-Aventis.
- Member of Steering Committee: MDV3100 Prevail and 9785-CL-0321 trials.

Natural history of CRPC



Ferlay J et al. Eur J Cancer 2010;46:765-81

A portfolio of new drug...

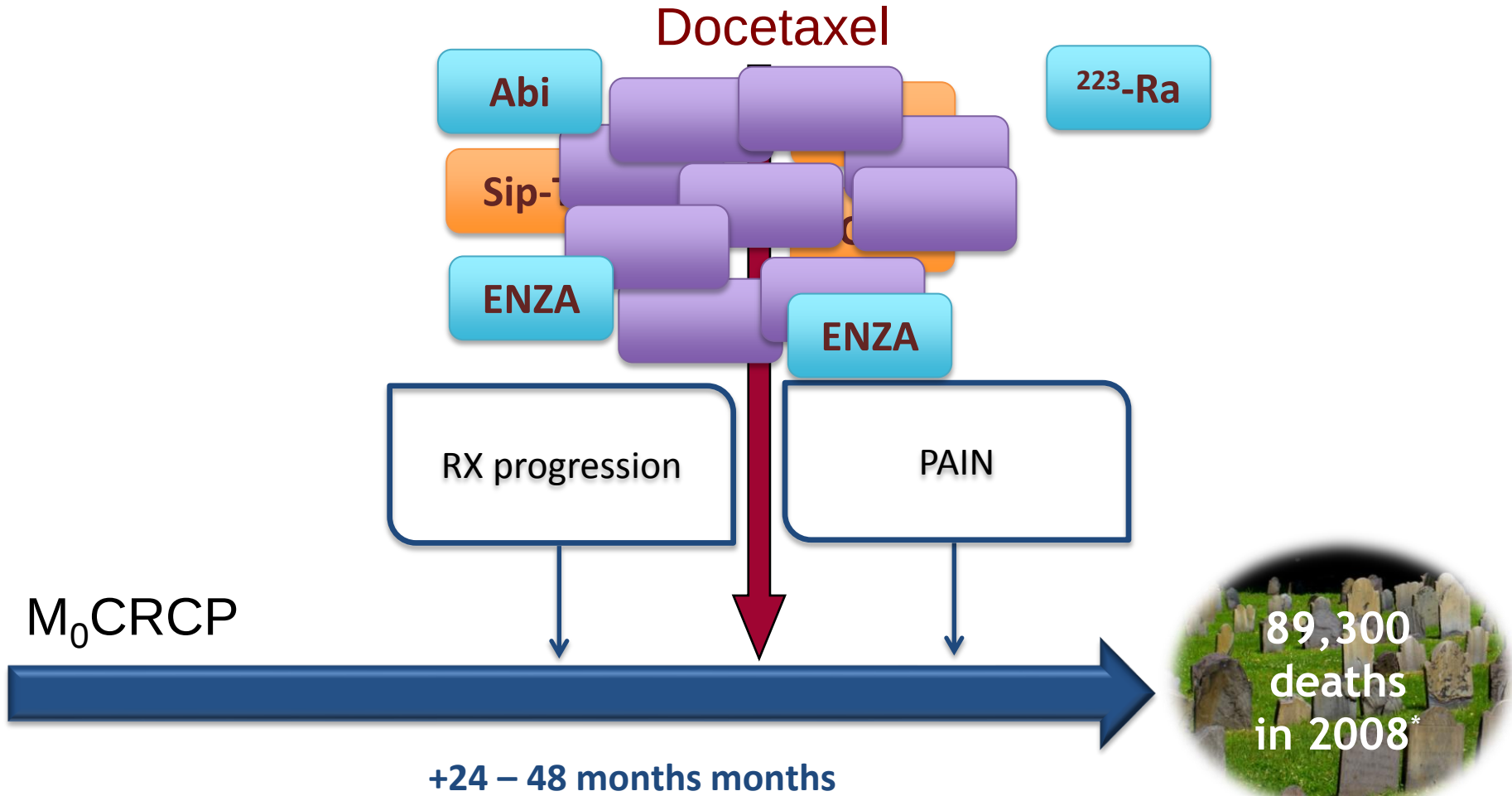
	Increase in median survival	Relative reduction in risk of death	Hazard ratio (P-value)
Abiraterone/P vs placebo/P ¹	3.9 months	35%	0.65 (P < 0.001)
MDV3100 vs placebo ^{2*}	4.8 months	37%	0.63 (P < 0.0001)
Docetaxel (Q3W)/P vs Mitoxantrone/P ³	2.4 months	24%	0.76 (P = 0.009)
Cabazitaxel/P vs. mitoxantrone/P ⁴	2.8 months	30%	0.70 (P < 0.0001)
Sipuleucel-T vs. placebo ⁵	4.1 months	22%	0.78 (P = 0.03)
Alpharadin vs. placebo ⁶	2.8 months	31%	0.70 (P = 0.00185)

1. de Bono JS, et al. N Engl J Med 2011;364:1995–2005; 2. Medivation Press Release AFFIRM 3rd November 2011;

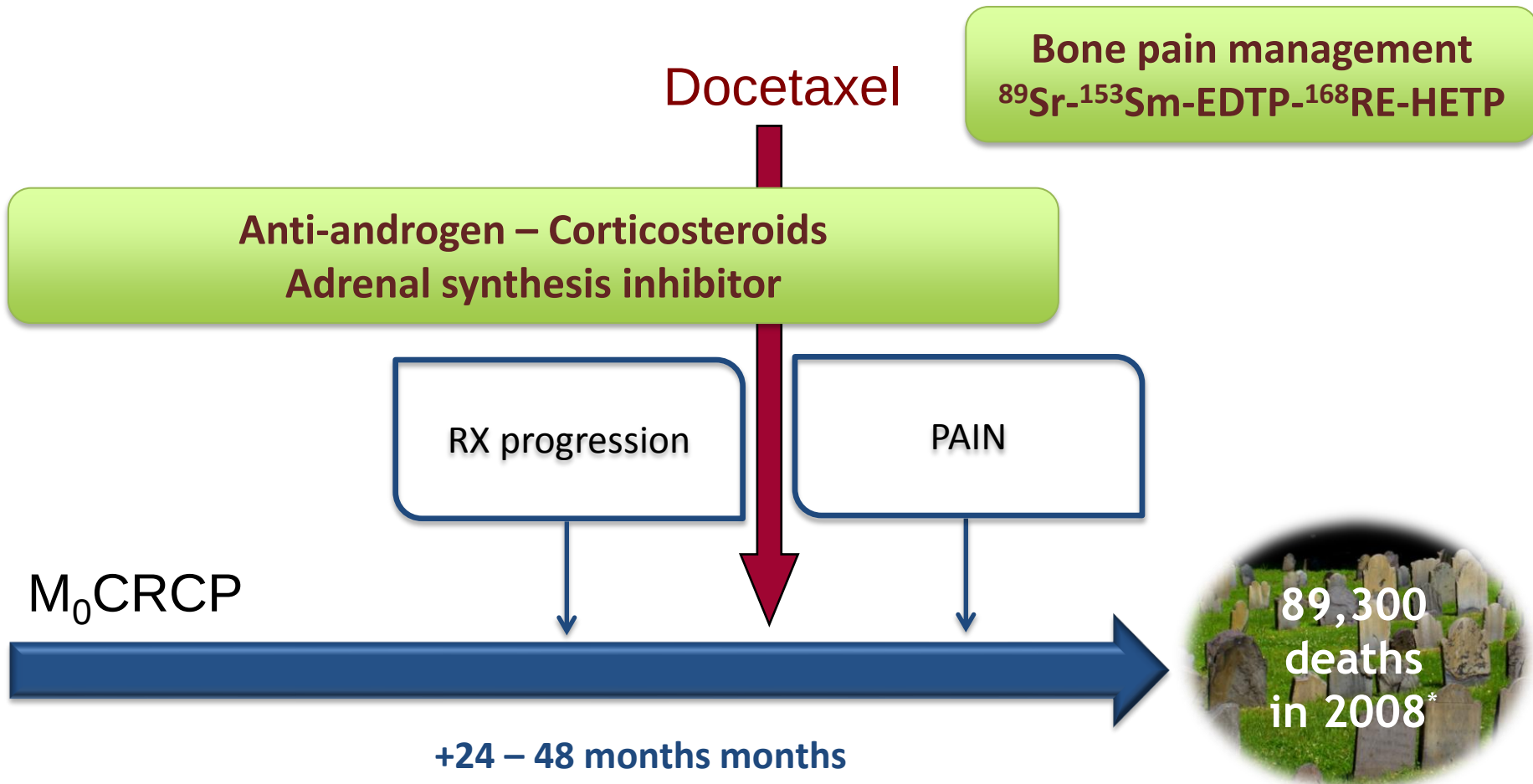
3. Tannock IF, et al. N Engl J Med 2004;2351:1502–12; 4. de Bono JS, et al. Lancet 2010;76:1147–545;

5. Kantoff PW, et al. N Engl J Med 2010;363:411–22; 6. Bayer Press Release ALSYMPCA 24th September 2011.

Natural history of CRPC



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A portfolio of new drug... substitutes for older but extensively used drug ?

	Substitute for	PSA or PAIN data	OS powered trials	Comparative trials
Abiraterone/P vs placebo/P ¹	Ketoconazole	yes	no	no
MDV3100 vs placebo ^{2*}	Bicalutamide	yes	no	no
Docetaxel (Q3W)/P vs. Mitoxantrone/P ³				
Cabazitaxel/P vs. Mitoxantrone/P ⁴				
Sipuleucel-T vs. placebo ⁵				
Alpharadin vs. placebo ⁶	⁸⁹ Sr- ¹⁵³ Sm-EDTP- ¹⁶⁸ RE-HETP	yes	no	no

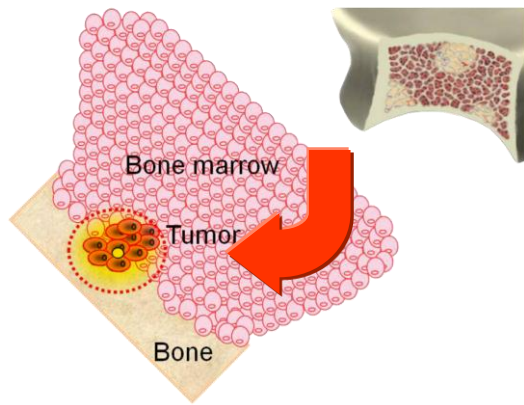
1. de Bono JS, et al. N Engl J Med 2011;364:1995–2005; 2. Medivation Press Release AFFIRM 3rd November 2011; 3. Tannock IF, et al. N Engl J Med 2004;2351:1502–12; 4. de Bono JS, et al. Lancet 2010;76:1147–545; 5. Kantoff PW, et al. N Engl J Med 2010;363:411–22; 6. Bayer Press Release ALSYMPCA 24th September 2011.

P, prednisone.

Updated Survival, Quality Of Life (QOL), and Safety Data of Radium-223 Chloride (Ra-223) in Patients with Castration-resistant Prostate Cancer (CRPC) with Bone Metastases from the Phase 3 Double-blind, Randomized, Multinational Study (ALSYMPCA).

C. Parker et al., 898PD.

Radium-223 Targets Bone Metastases



Ra²²³

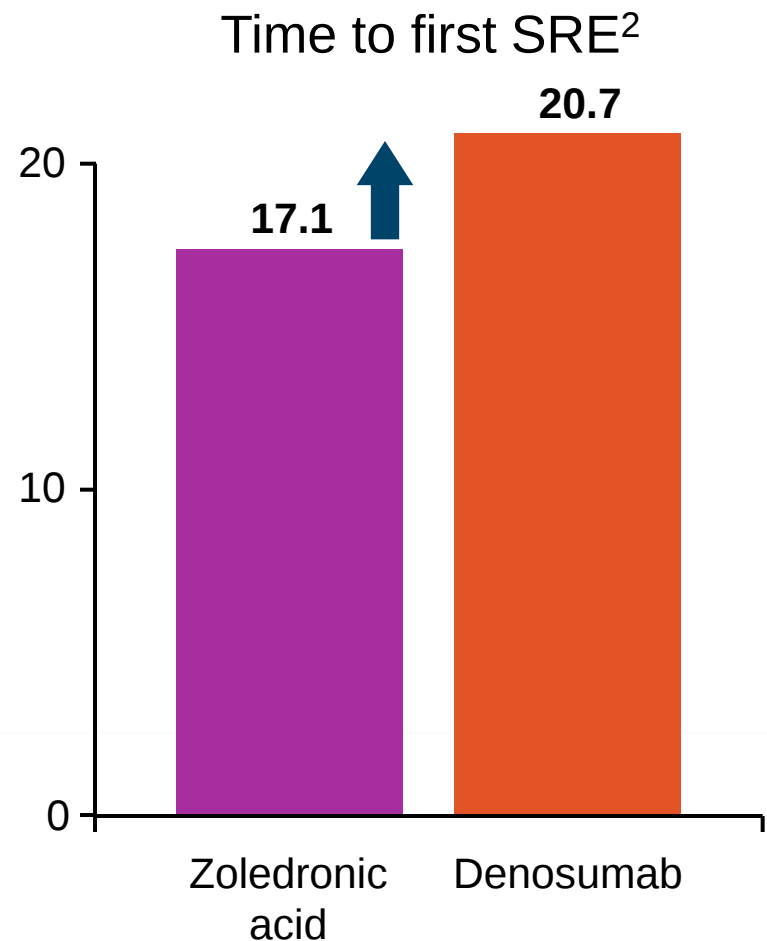
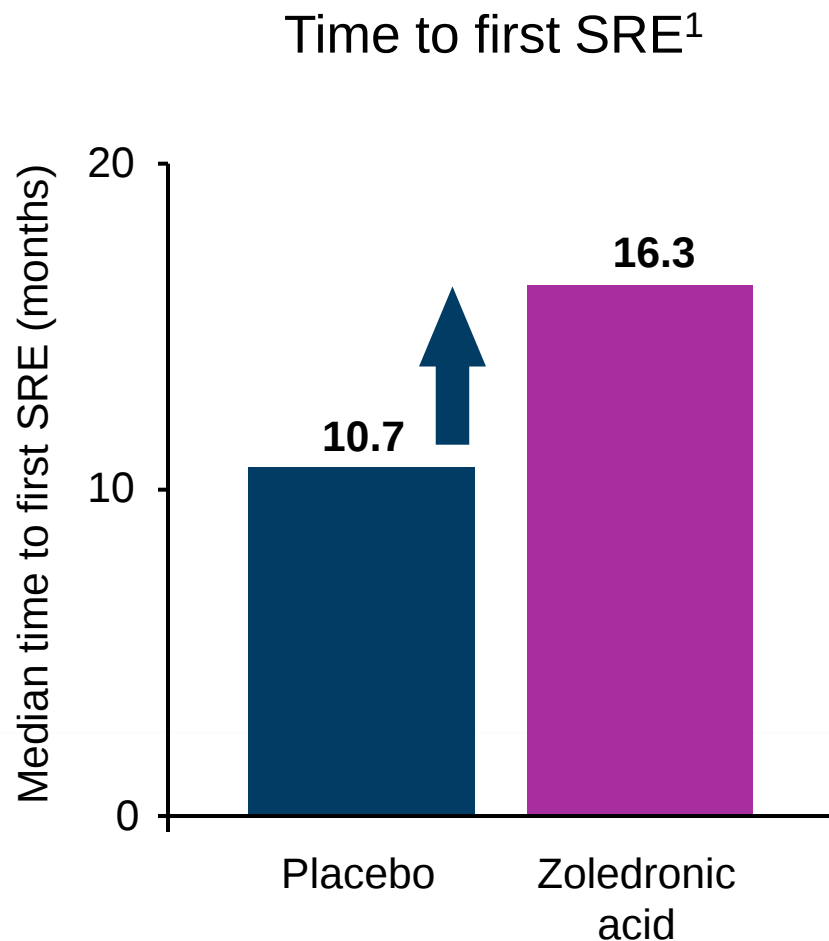
- Direct effect on tumor is questionable
 - PSA ↓ in only 6% of patients
- Major effect on osteoblast
 - PAlc ↓ 30%: 47%
 - PAlc ↓ 50%: 27%
 - PAlc normalization: 34%

^{223}Ra is a bone targeted agent...

- That increases overall survival from 11.2 months in 268 placebo patients to 14.0 months in 541 ^{223}Ra patients (0.00185)
- Zoledronic acid 0.4 mg increased OS from 15,6 (n=208) to 18.2 months (n=214) (p: 0.103)
- In association with KAVE, ^{89}Sr extended OS from 16.8 months (placebo, n=36) to 27.7 months (n=36)

^{223}Ra is a bone targeted agent...

- That delays the first SRE by 6 months (6.7 to 12.2 months)



The population is extremely advanced

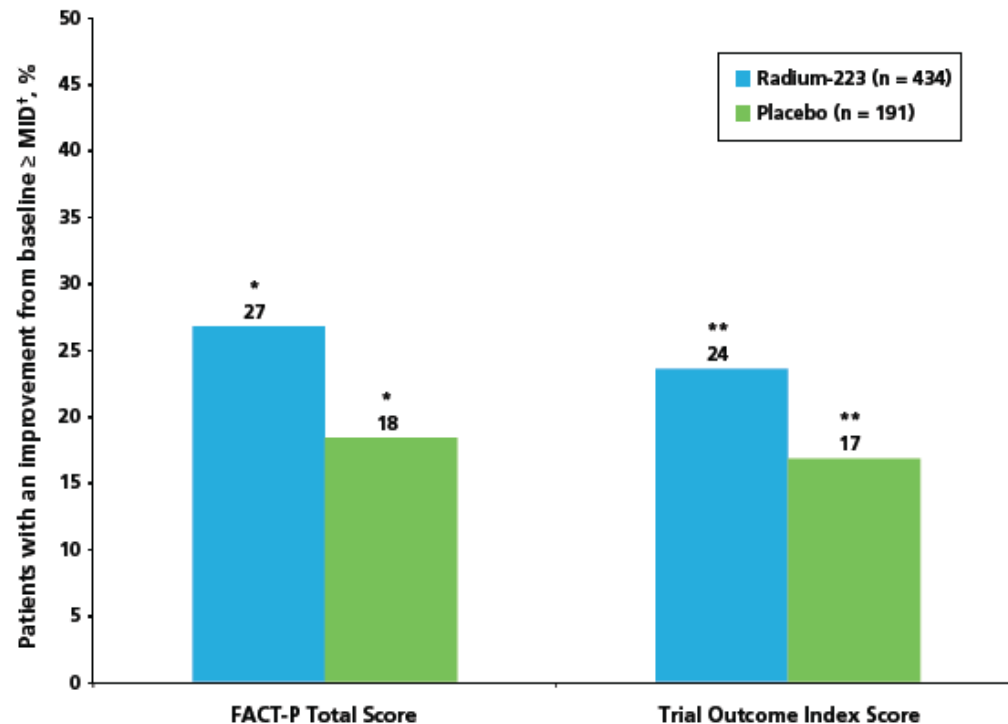
- In the placebo arm,
 - 40% have > 20 metastases
 - Although only 40.4% receive bisphosphonates
 - 56% have WHO pain ladder stage ≥ 2
 - 57% have received docetaxel
 - ALP average 223 (29-3856) $\mu\text{g/ml}$
 - PSA average 173 (1;5-14500) ng/ml
 - **Survival is only 11,2 months**

Is increasing OS and delayed SRE so important in these patients ?

Semantic...

- In patients patient reported outcomes (PROs) studies, the Minimally Important Difference (MID) is the smallest change in a measure that is perceived by patients as beneficial or that would result in a change in treatment

(A) Responder Analysis Based on Changes in FACT-P Summary Scores



* $P < 0.05$

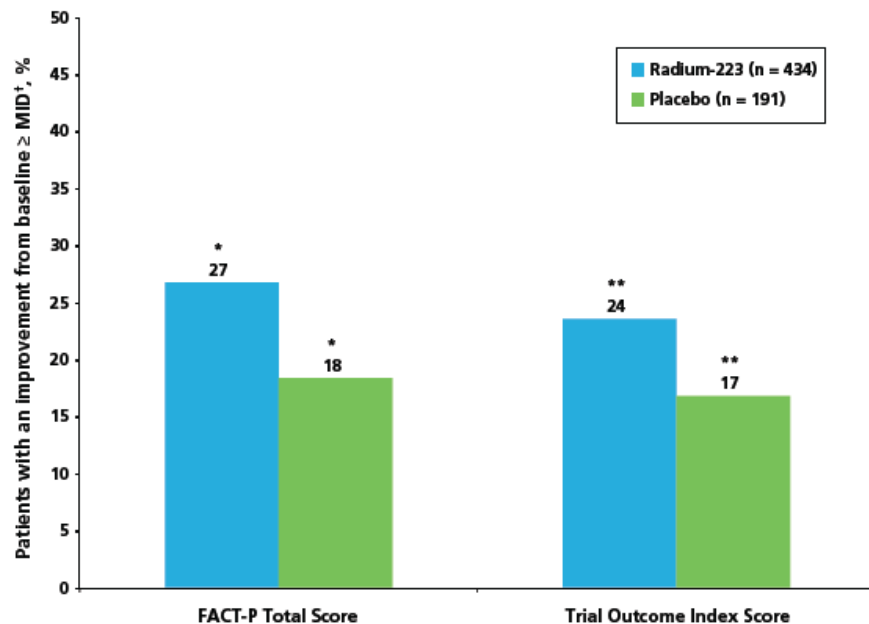
** $P < 0.1$

*FACT-P MID = 10 points; TOI MID = 9 points

FACT-P MID = 10 points;
TOI MID = 9 points

^{223}Ra has benefit on QoL

(A) Responder Analysis Based on Changes in FACT-P Summary Scores

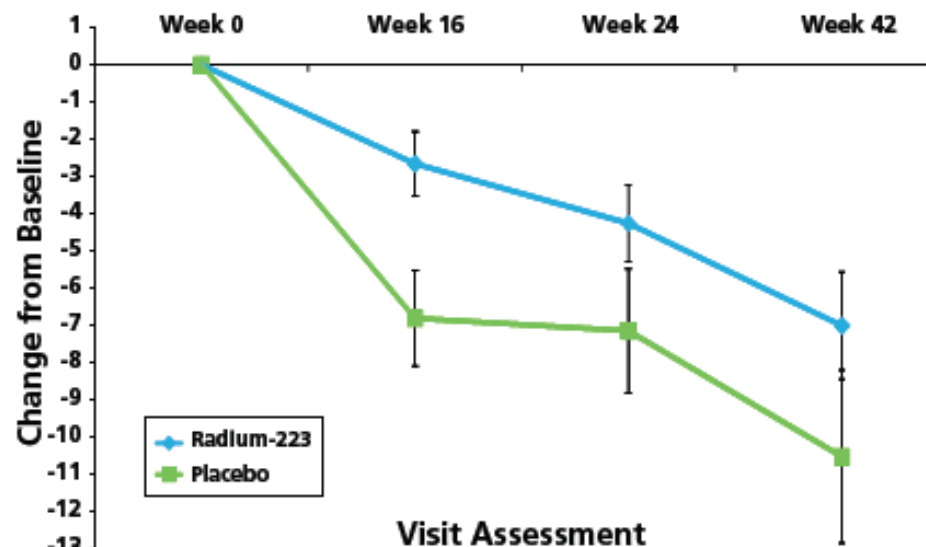


* $P < 0.05$

** $P < 0.1$

[†]FACT-P MID = 10 points; TOI MID = 9 points

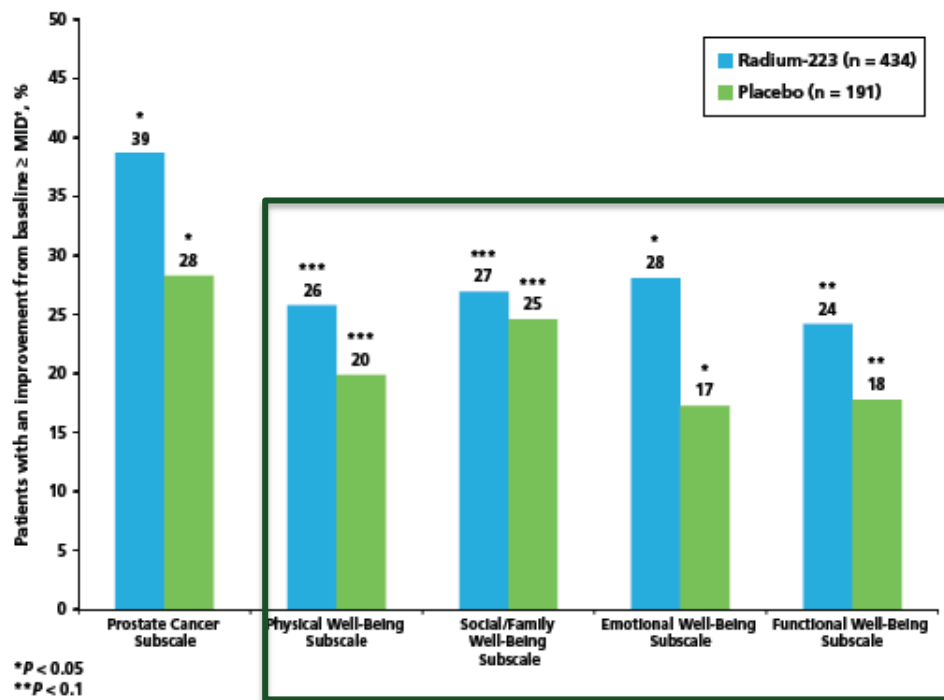
(A) FACT-P Total Score



^{223}Ra has benefit on QoL

- There was not benefit of QoL for Zometa (Fact-G) and this has not been released for denosumab.

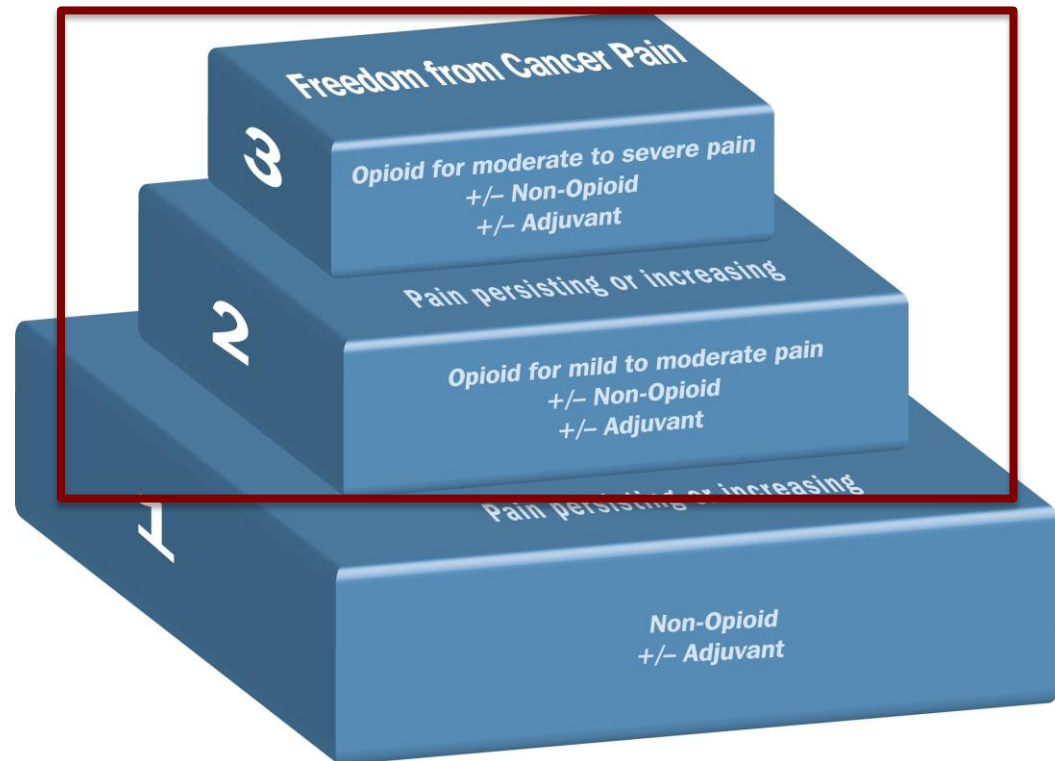
(B) Responder Analysis Based on Changes in FACT-P Subscale Scores



* $P < 0.05$
** $P < 0.1$
***Not significant
*For each subscale, MID = 3

Fact-G

^{223}Ra and pain



WHO's ladder pain

^{223}Ra and pain

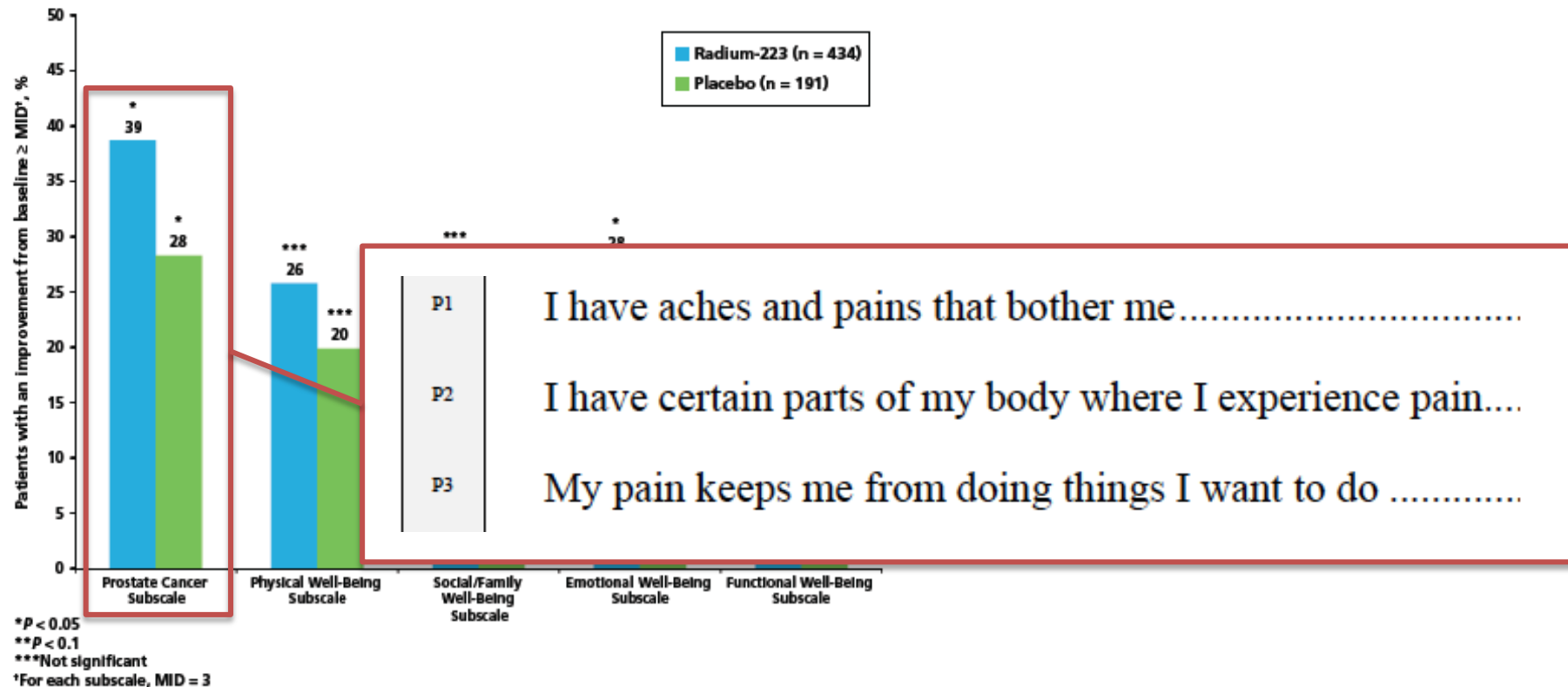


• ?

	Pain response	Pain free
^{188}Re -HEDP,	77	16
^{186}Re -HEDP,	67	13
^{153}Sm -EDTMP	73	13
^{89}Sr	72	17

^{223}Ra and pain

(B) Responder Analysis Based on Changes in FACT-P Subscale Scores



Updated Survival, Quality Of Life (QOL), and Safety Data of Radium-223 Chloride (Ra-223) in Patients with Castration-resistant Prostate Cancer (CRPC) with Bone Metastases from the Phase 3 Double-blind, Randomized, Multinational Study (ALSYMPCA).

C. Parker et al., 898PD.

- ^{223}Ra targets the bone remodelling unit (more than the tumor)
- Used in a very advanced population (including patients unfit for chemo), it was able to extend survival (highlighting the importance of the bone in survival)
- Parker reports that QoL benefits are in line with OS and previous SRE
- However we do regret the absence of Pain relief data in that specific niche of patients, although it is of critical importance

Updated Survival, Quality Of Life (QOL), and Safety Data of Radium-223 Chloride (Ra-223) in Patients with Castration-resistant Prostate Cancer (CRPC) with Bone Metastases from the Phase 3 Double-blind, Randomized, Multinational Study (ALSYMPCA).

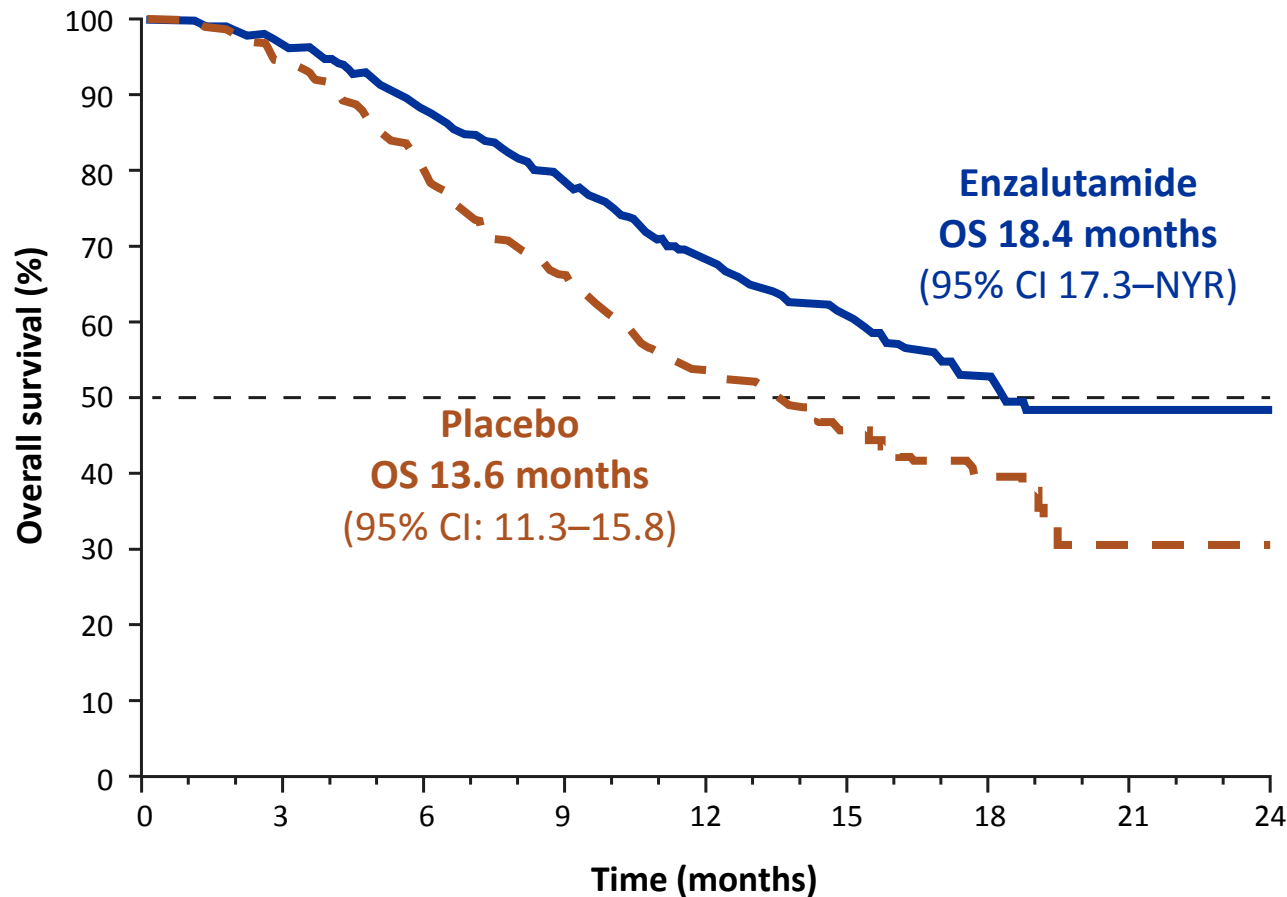
C. Parker et al., 898PD.

- Is Placebo the correct comparator in that study ?
- FACT-P and EQ-5D are QoL/HTA-HE tools, but what is the standard practice comparator ?

Association of Baseline Corticosteroid with Outcomes in a Multivariate Analysis of The Phase 3 Affirm Study of Enzalutamide (ENZA), an Androgen Receptor Signaling Inhibitor (Arsi)

H.I. Scher et al., 899PD.

2012: Enzalutamide improves survival versus placebo post-docetaxel



Hazard Ratio 0.63
(95% CI, 0.53-0.75)
P<0.001

T/ portfolio in CRPC

- Corticosteroids are standard of care in CRCP.

	Corticosteroid	Dose
Ketoconazole	hydrocortisone	40 mg
Docetaxel	prednisone	10 mg
Cabazitaxel	prednisone	10 mg
Abiraterone	prednisone	10 mg
Enzalutamide	none	
Sipuleucel T	none	

Potential interaction !!!

Does previous prednisone has an impact on ENZA benefit

- ENZA consistently superior to placebo with respect to overall survival

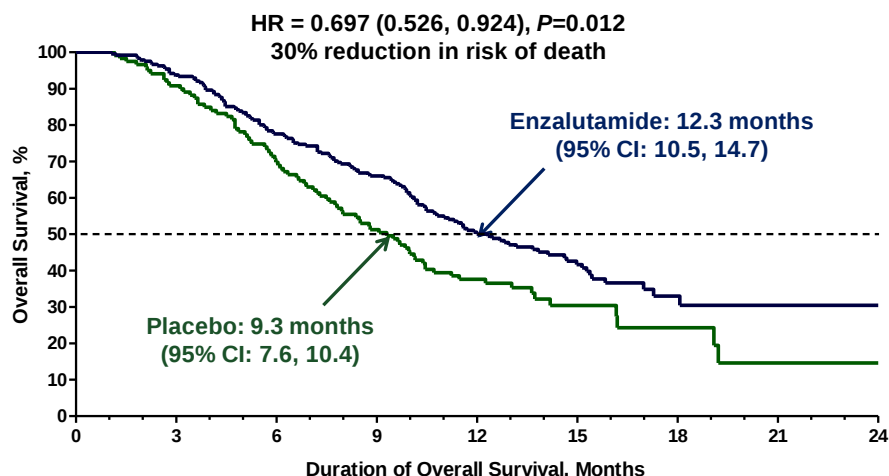
Baseline corticosteroid use	HR (95%CI)	OS benefit Months	P
No	0.593 (0.471-0.746)	NR in ENZA	<0.001
yes	0.697 (0.526-0.924)	3	0.012

Does previous prednisone has an impact on ENZA benefit

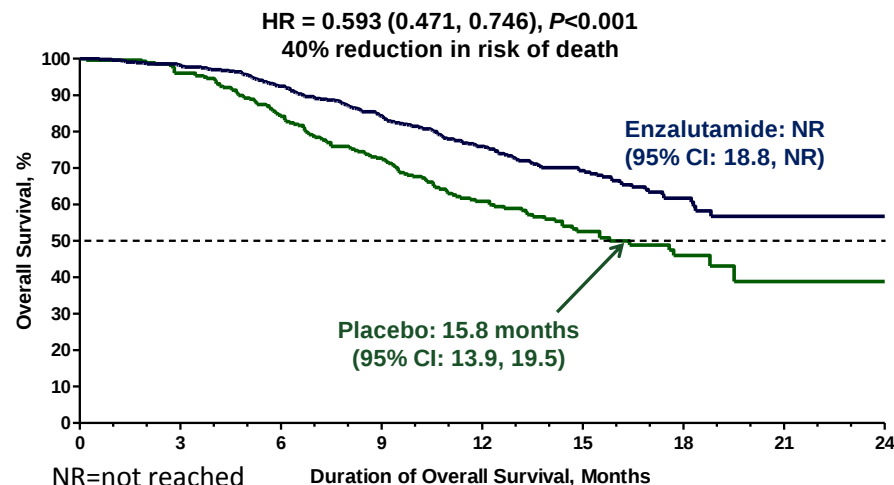
	Patients with baseline corticosteroid use	Patients with NO baseline corticosteroid use
	(n =360)	(n=839)
Overall Survival		
Median (95% CI), months	10.8	NR
	(10.0, 12.5)	(18.3, NR)
Radiographic Progression -Free Survival		
Median (95% CI), months	5.2	8.0
	(4.0, 5.5)	(6.1, 8.3)
Time to PSA Progression		
Median (95% CI), months	4.6	5.7
	(4.6, 5.5)	(5.6, 8,3)

Patients Receiving Corticosteroids At the Start of Therapy Had Inferior Survival Times Adjusting for Baseline Factors

On Baseline Corticosteroids



No Baseline Corticosteroids



Results of Stepwise Multivariate Analysis of Overall Survival

Variable	Parameter Estimates		HR for Death (95% CI ²)
	Coefficient	P-value	
Treatment (ENZA vs PBO)	-0.54±0.090	<0.0001	0.58 (0.49-0.70)
Mean pain score: <4 vs. ≥4	-0.26±0.098	0.0091	0.78 (0.64-0.94)
Progression at study entry: PSA only vs radiographic	-0.35±0.094	0.0002	0.70 (0.59-0.85)
Visceral disease at screening (No vs Yes)	-0.42±0.097	<0.0001	0.66 (0.54-0.80)
Baseline hemoglobin result	-0.03±0.003	<0.0001	0.97 (0.97-0.98)
Baseline lactate dehydrogenase (LDH) result	0.002±0.000	<0.0001	1.002 (1.001-1.002)
Baseline corticosteroid use (No vs Yes)	-0.62±0.091	<0.0001	0.54 (0.45-0.64)

Baseline corticosteroid and reduced survival ?

- Imbalance in risk factor ?
- Result of chronic toxicity ?
- Corticoid mediated activation ?

Imbalance in risk factors

	Patients with baseline corticosteroid use		Patients with NO baseline corticosteroid use	
	Enzalutamide	Placebo	Enzalutamide	Placebo
	n=241 (30%)	n =119 (30%)	n=559 (70%)	n = 280 (70%)

Baseline Characteristics

Age				
Median, yrs	69	67	69	70
ECOG = 2	14.5%	4.2%	6.3%	9.6%
BPI $\geq$ 4 on Question 3	31.5%	36.1%	26.8%	25.7%

Disease Burden

Median PSA (ng/mL)	199.7	174.5	89.1	111.5
Median Hb (g/L)	116.5	117.0	122.0	120.5
Median ALP(U/L)	145.0	122.0	137.5	107.0
Median LDH (U/L)	245.0	239.0	197.0	208.0
% Abnormal (>234 U/L)	53.1%	52.5%	31.3%	35.5%
> 20 BM at screening	49.0%	47.1%	32.9%	33.9%

Months from initial diagnosis (Median)	66	56	75	76
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Halabi nomogram

Nomogram Halabi Applet

<https://www.calgbapps.org/Nomogram/CRPCv1p1.html>

Duke University Medical Center
CRPC Nomogram

FirstName Initial LastName Initial PatID

Questions:

- ? Visceral Disease
- ? Gleason Score
- ? Performance Status
- ? Baseline PSA
- ? LDH
- ? Alkaline Phosphatase
- ? Hemoglobin

Site Visits: 1457

Additional Information

Median OS (95% CI)	Visceral Metastases	
	No	Yes
No baseline CS	16 (14-18)	14 (12-17)
Baseline CS	14 (12-16)	12 (11-15)

Halabi nomogram is based on mostly steroids trials....

Why these patients receive steroids ?

- Prescribed alone for pain reduction, appetite, PSA response ?

Total	Drug	Patients (n)	50% PSA response	Duration (months)
Tannock et al., 1989 ¹	Prednisone (7.5 - 10 mg sid)	81	22	4
Fossa et al., 2001 ²	Prednisone (5 mg bid)	101	21	4,2
Sartor et al., 1998 ³	Prednisone (10 mg bid)	29	34	2.0
Fossa et al., 2007 ⁴	Prednisolone (10 mg bid)	50	26	4
Small et al., 2000 ⁵	Hydrocortisone (40 mg qd)	230	16	2.3
Kantoff et al., 1999 ⁶	Hydrocortisone (30/10 mg qd)	78	14	2.3
Kelly et al., 1995 ⁷	Hydrocortisone	30	20	4
Morioka et al., 2002 ⁸	Dexamethasone (1.5 mg sid)	27	59	NA
Saika et al., 2001 ⁹	Dexamethasone (1.5 mg sid)	19	28	NA
Storlie et al., 1995 ¹⁰	Dexamethasone (0.75 bid)	38	61	NA
Debruyne et al., 1998 ¹¹	Lyarozole (300 mg bid)	160	20	NA

% PSA response: % of patients achieving 50% decrease in PSA.

Why these patients receive steroids ?

- Left over from first combination

	Corticosteroid	Dose	Median Duration (months)	Prednisone equivalent Dose (mg)
Ketoconazole	hydrocortisone	40 mg	8.6	2580
Docetaxel	prednisone	10 mg	6.5	1950
Cabazitaxel	prednisone	10 mg	4.1	1230
Abiraterone	prednisone	10 mg	8.0	2400

T. B. Dorff^{1*} & E. D. Crawford, Annals of Oncology, 2012

Corticosteroid toxicity

Table 2. AEs associated with corticosteroid use

AE	Corticosteroid type and dose for AEs attributable to use in mCRPC
Hyperglycemia/diabetes [8, 14, 15*, 16*]	Low-dose dexamethasone (0.5–2 mg/day)*; low-dose prednisone (10 mg/day)
Infection [8, 10, 13]	
Myopathy/muscle loss [8, 16*]	Low-dose prednisone (10 mg/day)*
Insomnia [17, 18]	
Osteoporosis/avascular bone necrosis [19–21]	
Edema [13, 16]	Low-dose prednisone (10 mg/day)*
Weight gain [13]	
Dyspnea [13, 16*]	Low-dose prednisone (10 mg/day)*
Cushingoid facies [13]	
Posterior subcapsular cataracts [15*, 22]	Low-dose dexamethasone (0.5–2 mg/day)*

Notes: Choice of corticosteroid, as well as dose, duration, and therapeutic indication varies for each study. AEs shown to be attributable to corticosteroid use in mCRPC are denoted with an asterisk, with steroid type and dose noted; corresponding studies are also denoted with an asterisk.

AE, adverse events; mCRPC, metastatic castration-resistant prostate cancer.

Conclusion

- AFFIRM (Enza) raise a very provoking question on the benefit of CS
- Despite clearly reported limitations and imbalance in risk factors
- Will delay use of CS an important endpoint ?