“Clinical Effects” of Androgen Signaling Inhibition in Metastatic Castrate Resistant Prostate Cancer (mCRPC)

Eleni Efstathiou, M.D., Ph.D.

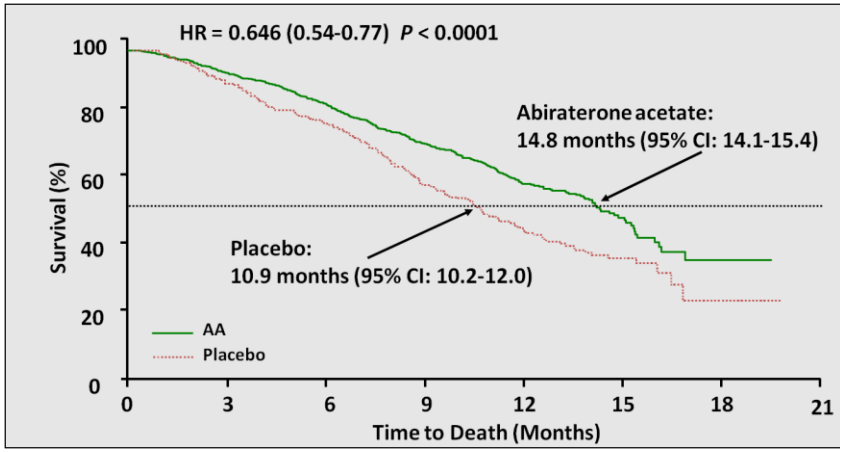
Abstract Discussion

8950 – Basch et al

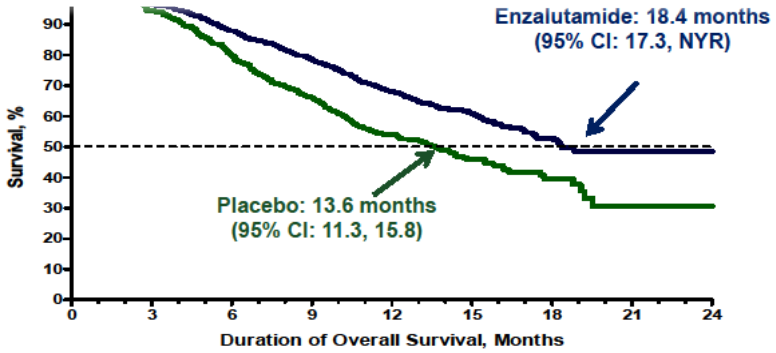
8960 – Fizazi et al

Further Androgen Signaling Inhibition Prolongs Survival of Men with CRPC

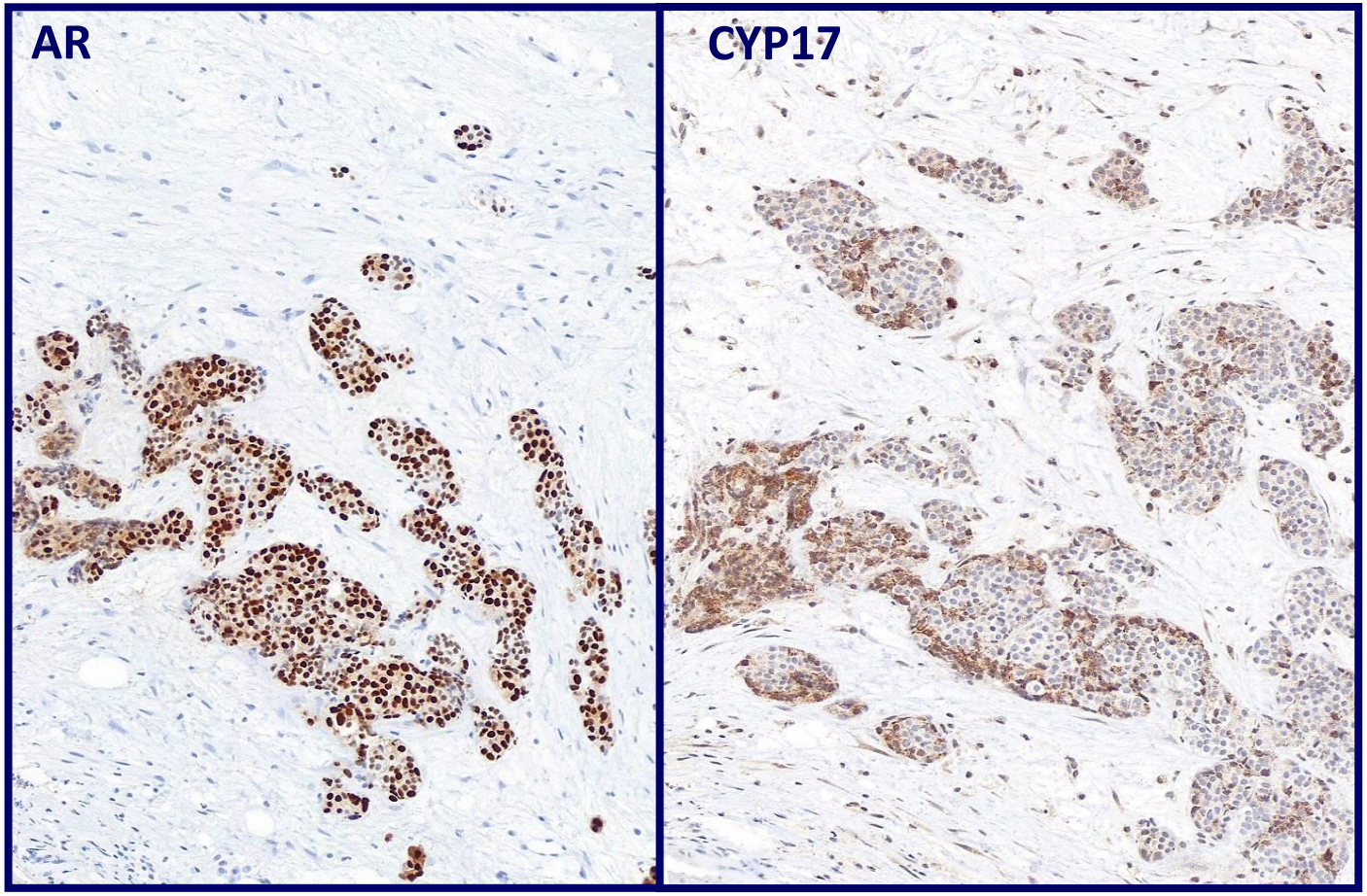
Abiraterone Acetate + Prednisone



Enzalutamide

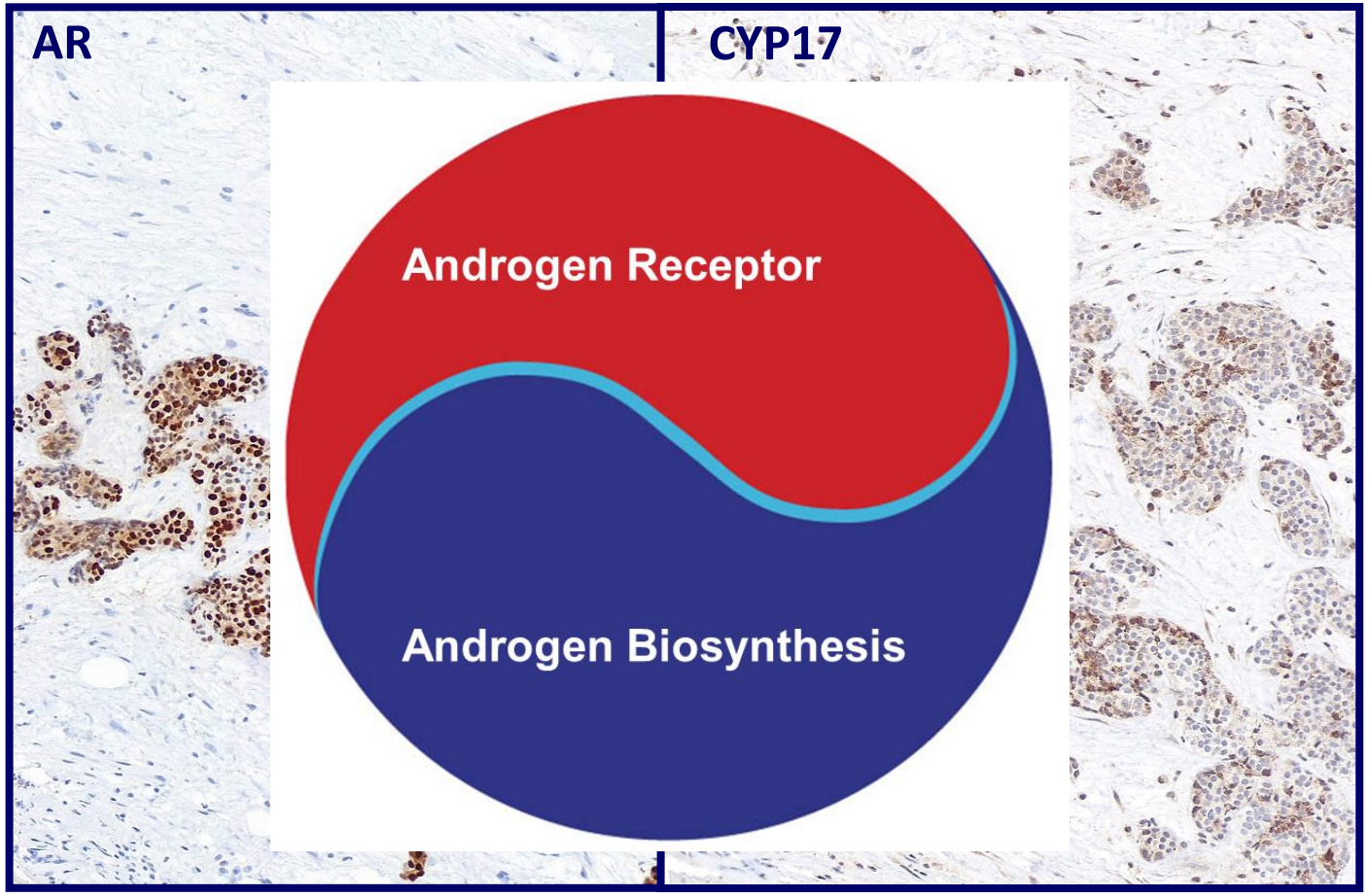


Persistent Androgen Signaling in CRPC With Bone Metastases



Efstathiou et al JCO 2012

Persistent Androgen Signaling in the CRPC infiltrated bone microenvironment



Addressing the Clinical Challenge of Prostate Cancer Bone Metastases

Proof of Principle established:

- ✓ Targeting Prostate Cancer bone metastases cancer prolong survival (*Tu et. al., Parker et al)*
- ✓ Treatment of metastatic CRPC in bone with androgen biosynthesis inhibitors reduces pain and increases functionality (*Logothetis et al in Press*)

Abstract 8950

The Impact of Abiraterone Acetate Therapy on Patient-Reported Pain and Functional Status in Chemotherapy-Naïve Men with mCRPC

Basch, et al.

Initial Analysis of Patient Reported Outcomes (PRO) in Chemonaive Asymptomatic/Oligosymptomatic Men with mCRPC

- PRO and time to opiate use included in study endpoints.
- Predefined pain response and functional change definitions.
- Study, though large, Not powered to address specific endpoints.

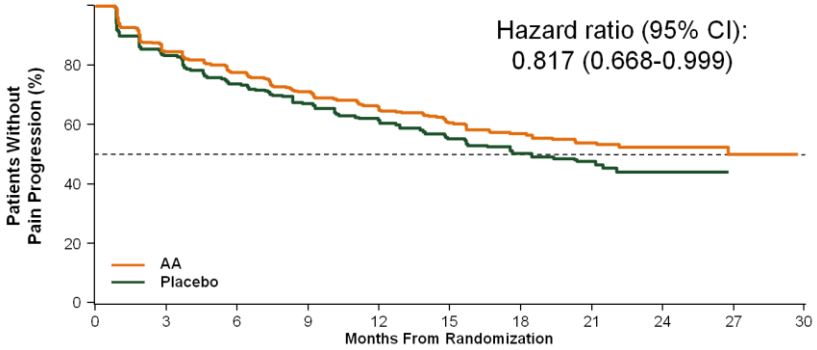
	AA + P (n = 546)	Placebo + P (n= 542)
Baseline average pain intensity, mean (SD)	0.8 (1.12)	0.8 (1.11)
Baseline worst pain intensity, mean (SD)	1.2 (1.67)	1.2 (1.61)
Baseline FACT-P total score, mean (SD)	122 (17.00)	123 (17.69)
Asymptomatic patients at baseline	69%	65%
Median duration of follow-up	22.2 months	
Median no. of therapy cycles (range)	15 (1-33)	9 (1-31)

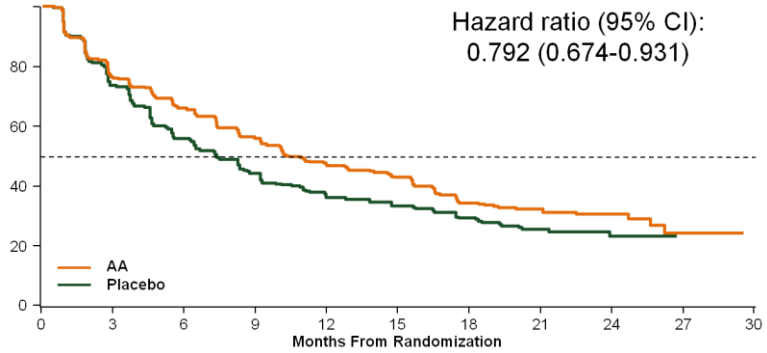
P, prednisone; SD, standard deviation.

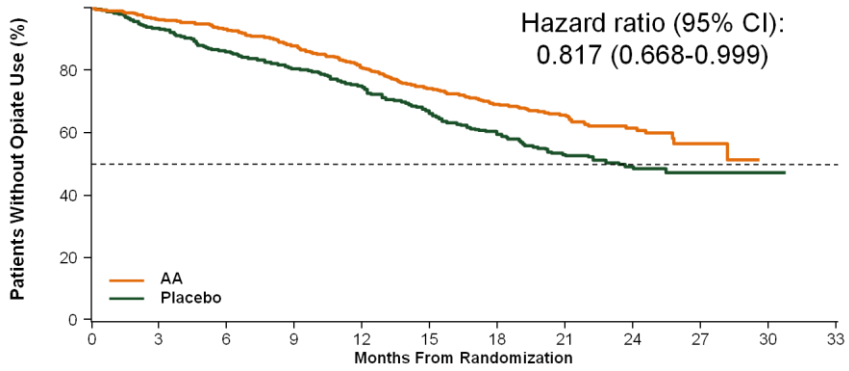
Per Study Design/ Eligibility

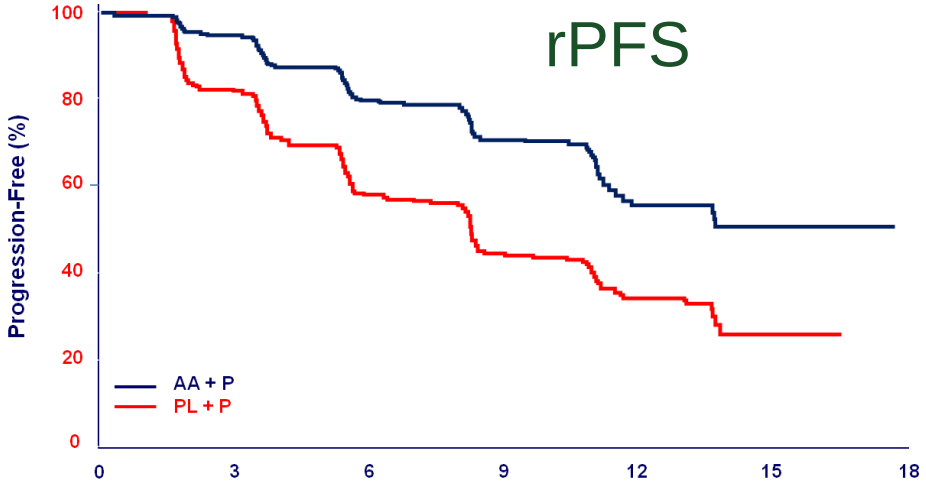
- Minimal Pain Present
- ~70% Asymptomatic pts

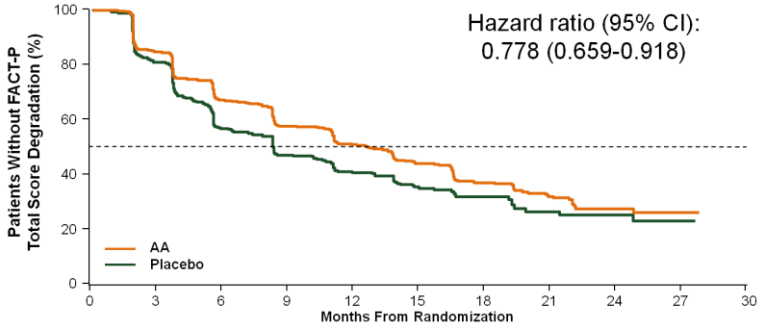
Delay in Pain Progression, Use of Opiates and Functional Decline in Line with Reported rPFS Findings









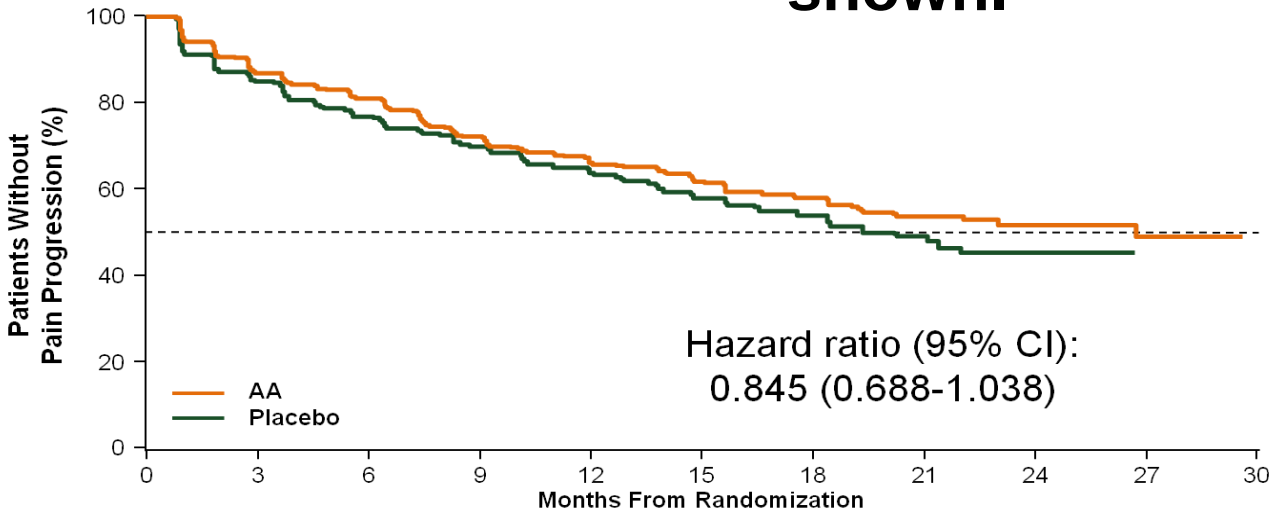


VIENNA 2012 ESMO congress

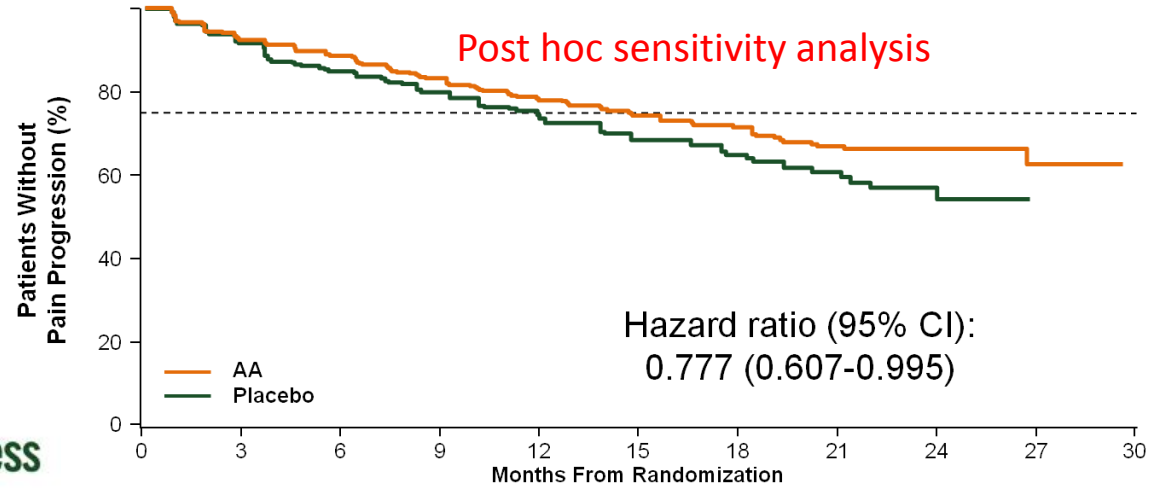
www.esmo2012.org

However…

No meaningful difference in *worst pain intensity* was shown.



Post hoc sensitivity analysis



Abstract 8950 - Basch, et al. Conclusions - Take Home Message

- Abiraterone Acetate +Prednisone delays pain progression, opiate use and functional decline in asymptomatic / oligosymptomatic chemotherapy-naive men with mCRPC.

- However, severe clinical symptoms may not be reduced proportionally to the effect observed in men with in modest or no symptoms.

Abstract 8960

Impact of Enzalutamide, an Androgen Receptor Signaling Inhibitor, on Time to First Skeletal Related Event (SRE) and Pain in the Phase 3 AFFIRM Study

Karim Fizazi,
Howard I. Scher, Fred Saad, Cora N. Sternberg, Kurt Miller, Peter Mulders, Kim N. Chi, Ethan M. Basch, Mohammad Hirmand, Johann S. de Bono

Analysis Endpoint:
Assessment of Clinical Effects of Enzalutamide In Chemotherapy treated mCRPC

This is the first report of the clinical impact of Enzalutamide in mCRPC

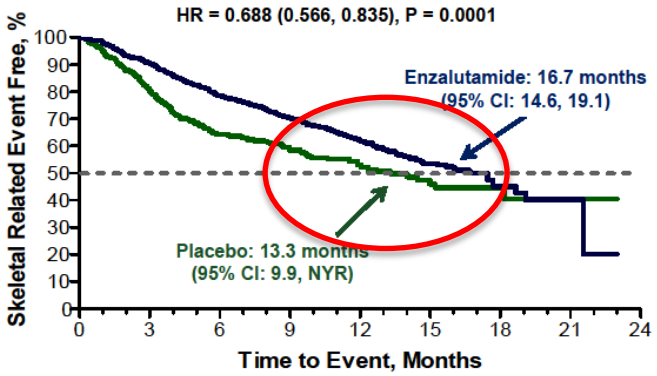
Provision for analysis made in study design though not powered to address secondary aims addressed in the investigation reported today

Baseline Characteristics

	Enzalutamide (n = 800)	Placebo (n = 399)
Age (median in yrs)	69	69
ECOG Performance Status = 2	8.8%	8.0%
Mean Pain Score ≥4	**28.3%**	**28.8%**
Bone Disease	91.3%	91.2%
Soft Tissue Disease	70.9%	68.9%
Visceral disease: liver/lung	24.5%	20.6%
≥ 3 Lines of prior hormonal therapy	49.1%	53.1%
≥ 2 Regimens of prior chemotherapy	27.6%	25.8%
Bisphosphonate use	**43%**	**43%**

- One third of patients were symptomatic
- Almost all had bone disease *though extent of burden is not known*
- Approximately half on biphosphonates

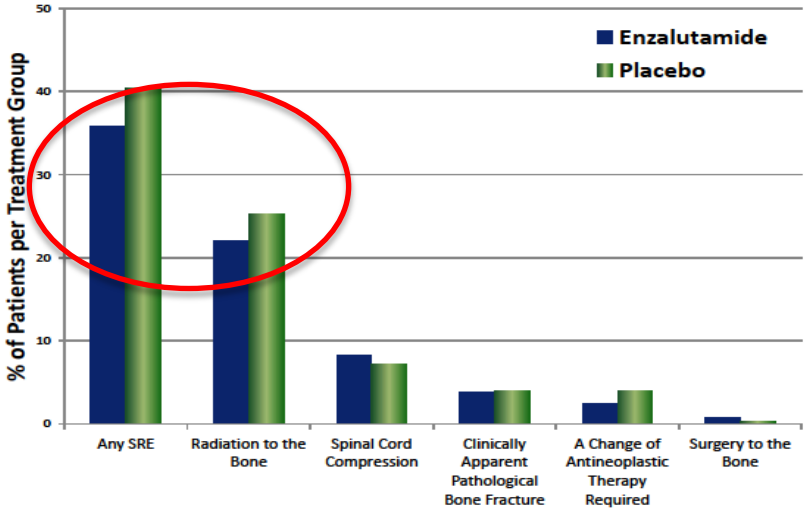
Time to First Skeletal Related Event: 31% risk reduction



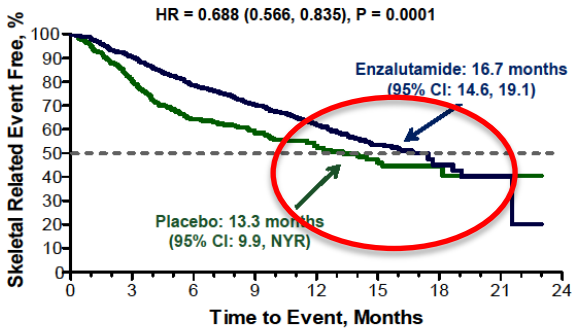
Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33	11	0	0

Significant reduction of Skeletal Related Event risk

Distribution of First SRE

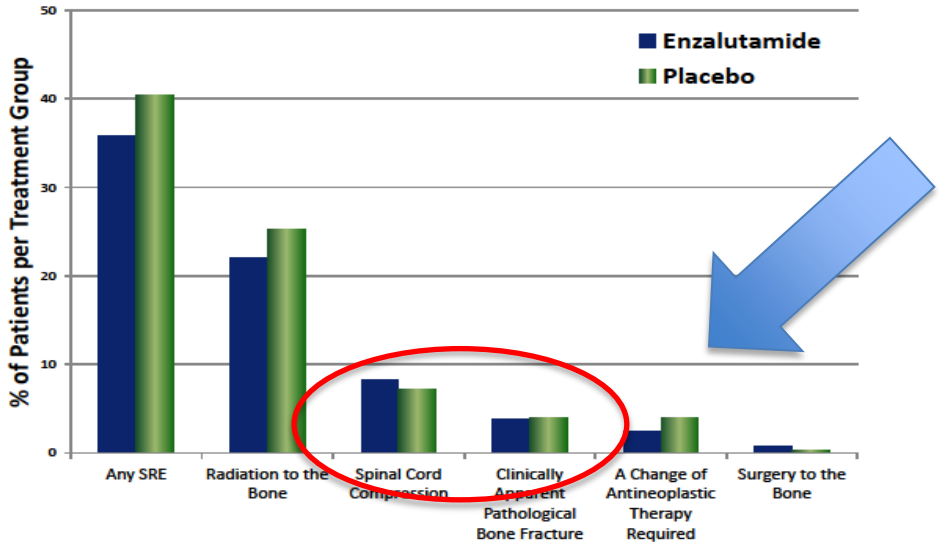


Time to First Skeletal Related Event: 31% risk reduction



Enzalutamide	800	676	548	379	209	87	19	2	0
Placebo	399	278	196	128	68	33	11	0	0

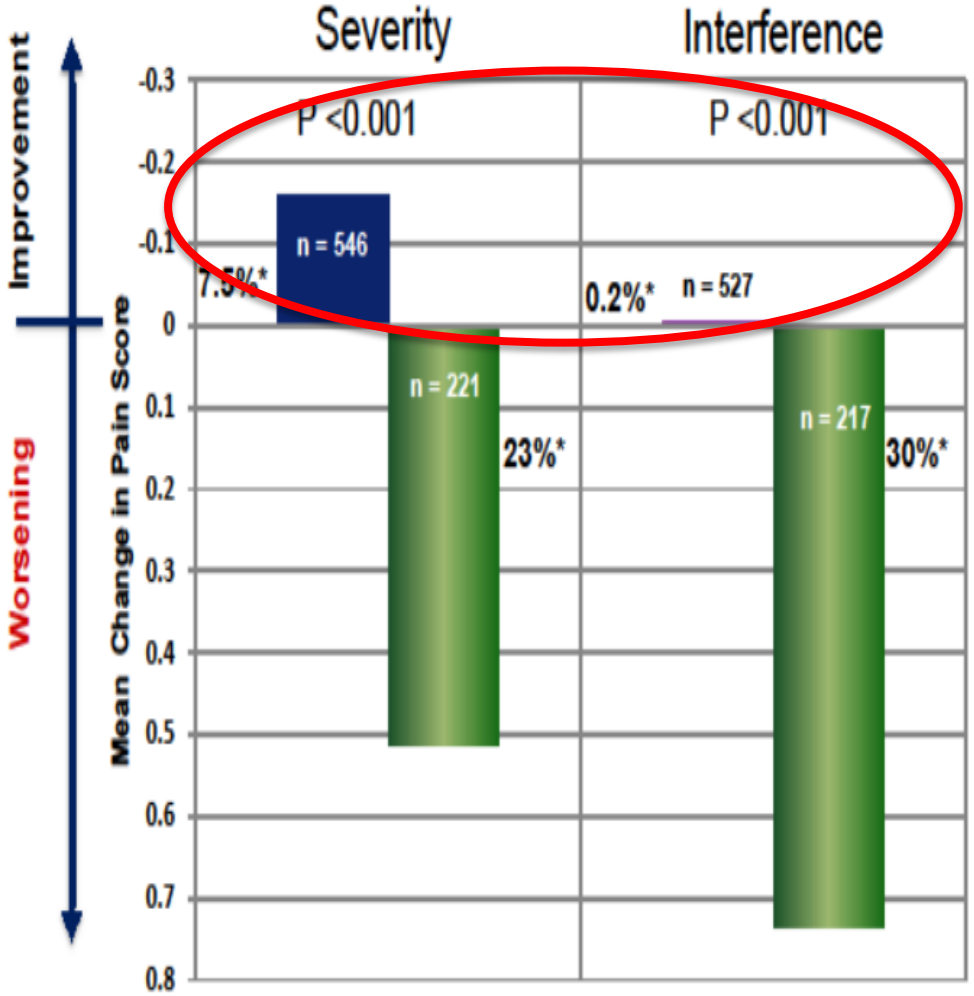
Distribution of First SRE



But "severe" complications of bone metastases not avoided!

VIENNA 2012 ESMO congress
www.esmo2012.org

Change in Pain (BPI-SF) from Baseline to Week 13

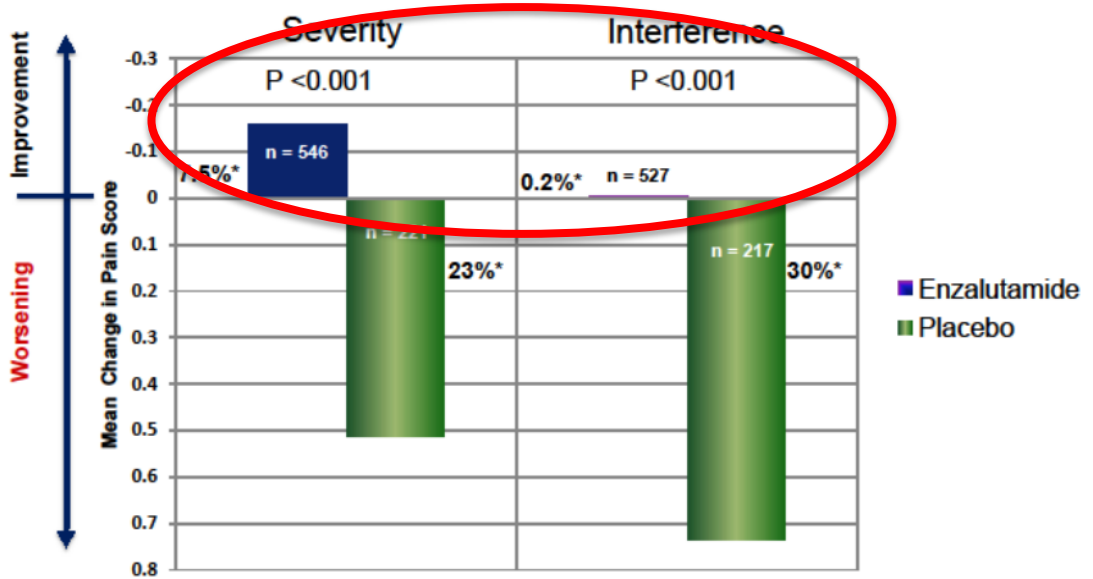


Reduced pain & sustained "functionality" is aligned with survival prolongation:

- Enzalutamide
- Placebo

<u>Enzalutamide a good drug!</u>

Change in Pain (BPI-SF) from Baseline to Week 13



Pain Palliation (Pain Diary) at Week 13

	Enzalutamide	Placebo
Number of evaluable pts	49	15
N (%) with pain palliation	22 (**45%**)	1 (**7%**)
95% CI	(31% to 60%)	(0.2% to 32%)
P-Value	**0.0079**	

Though Pain Palliation (PRO) conclusion is based on few patients !

Abstract 8960 : Fizazi et al Conclusions-Take Home Message

- ✓ Prolongs life
- ✓ ***Reduces Risk of Skeletal Related Events***
- ✓ ***Improves quality of life / functionality***
- ✓ ***Relieves pain and delays pain progression***

- ➢ No evidence that severe complications of bone metastases are modified.

Data in line with those reported for Abiraterone Acetate in similar setting *(Iogothetis et al in press).*

Conclusion

Androgen signaling inhibition

not only prolongs, but also ameliorates bone metastases associated symptoms

in men with mCRPC

Conclusion

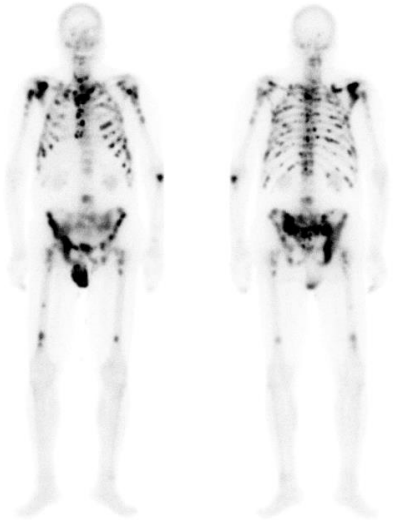
Androgen signaling inhibition prolongs and improves lives of mCRPC patients by delaying or alleviating symptoms.

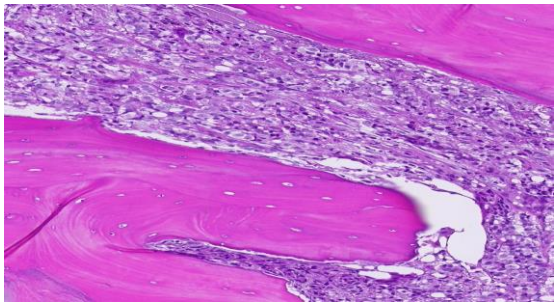
However

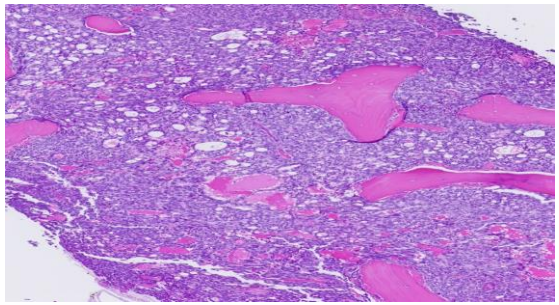
Severe clinical events may remain unaltered and the reported benefit in the advanced setting is still short lived.

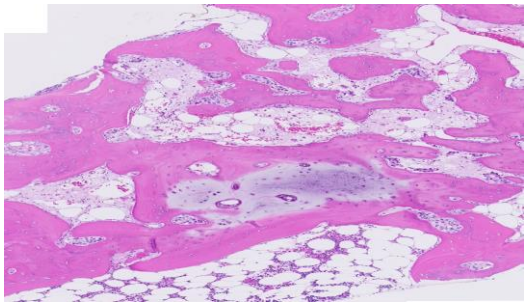
Moving Forward

- To effectively build on bone targeting therapy we must link the understanding of prostate cancer progression in bone to clinical decision making!
- Studies should focus on understanding the mechanism(s) of prostate cancer progression in bone to develop algorithms to anticipate this development.









Studies focusing on PROs should be pursued further.

Challenges:

Establishing continuous variables out of symptoms

- Properties of selected instruments;
- Using a score/ delta to describe clinically meaningful benefits

Logistics

- Missing data and patient compliance
- Expense

Prespecified analysis

- Limited *a priori* specification of Patient reported outcome (PRO) analytic plans
- Lack of statistical power for PRO endpoints

Trial Design

- Failure to engage regulatory agencies in the planning stages of trial development
- Limited involvement of PRO experts in trial design

Keeping always in mind..

Symptom development is devastating to the patient and associated with a worse outcome and increased cost

A symptomatic debilitated patient values quality of life in the short term

over extension of survival