

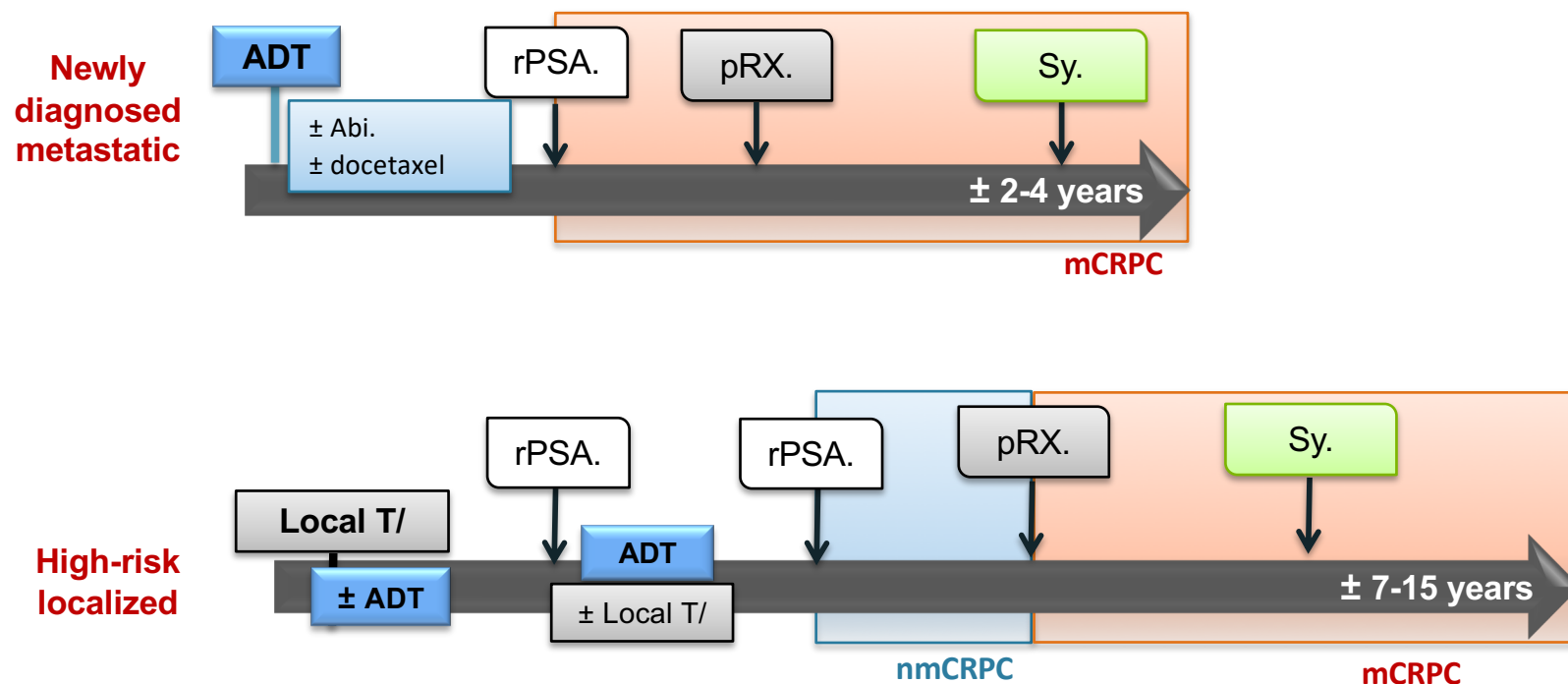
**Antiresorptive therapy to reduce SRE risk in men with
bone-metastatic CRPC.**
For the majority of men with CRPC and bone metastases

Bertrand Tombal, MD, PhD
Cliniques universitaires Saint-Luc
Université catholique de Louvain
Brussels, Belgium

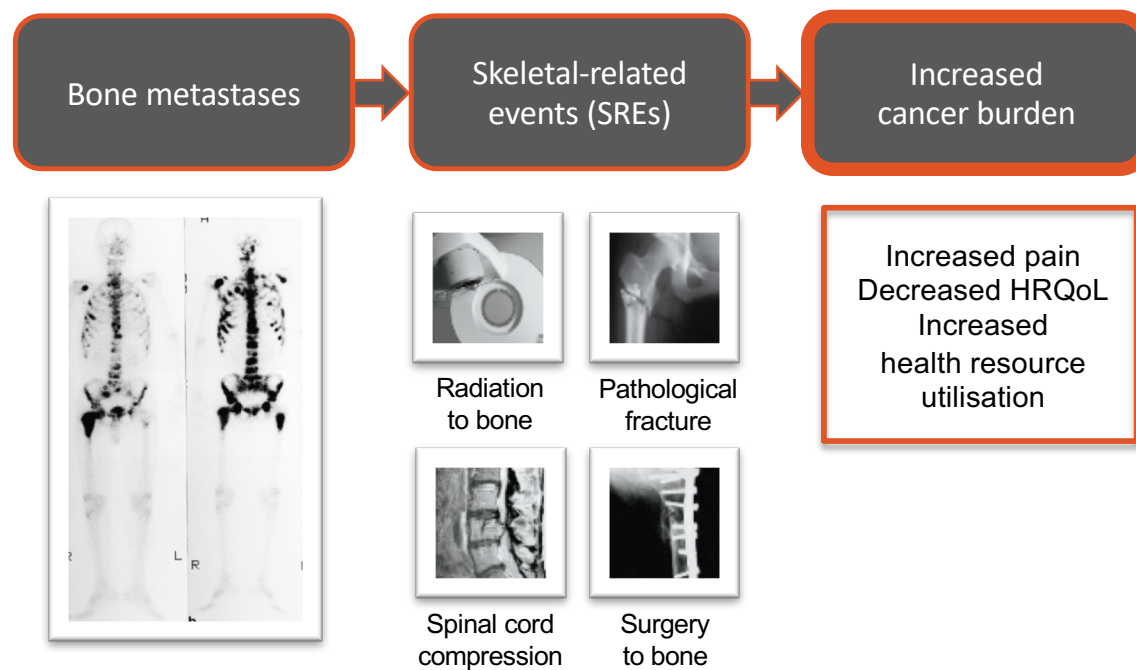
Credentials and conflict of interests

- Professor and Chairman, Division of Urology, Cliniques universitaires Saint Luc, Brussels, BE
- PI investigator and paid advisor for Amgen, Astellas, Bayer, Janssen, Ferring, Pfizer, Sanofi, Myovant.
- This presentation reflects the personal view of Bertrand TOMBAL
- BPA (bone protecting agent): zoledronic acid or denosumab at the SRE prevention dose.

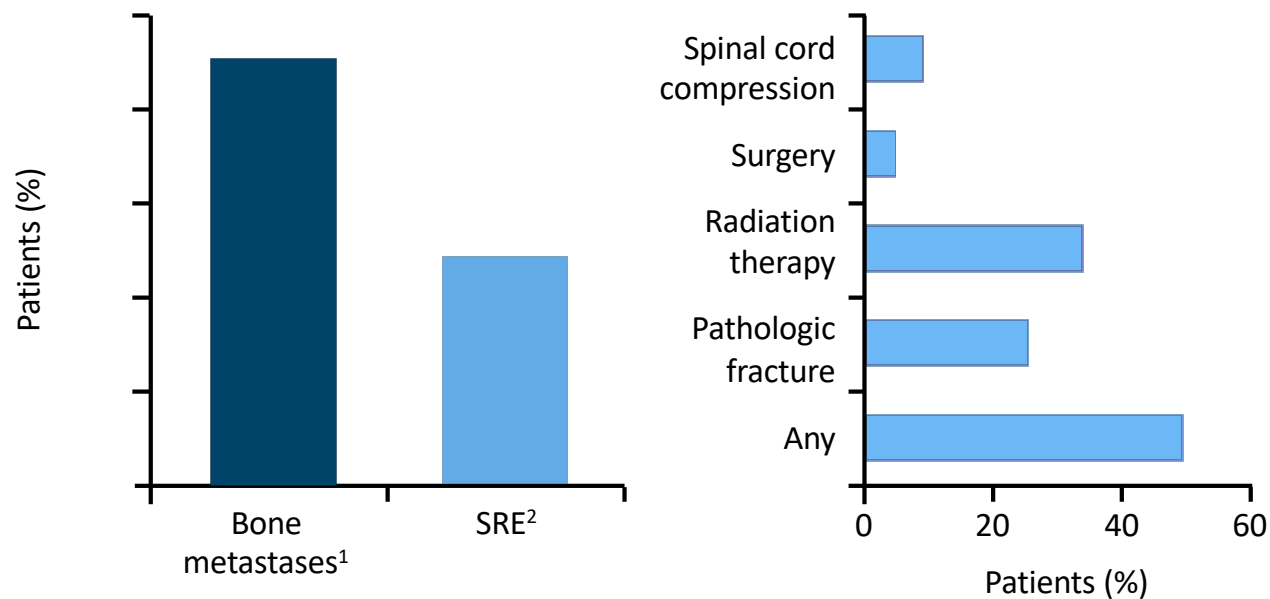
Advanced PCa landscape in 2019



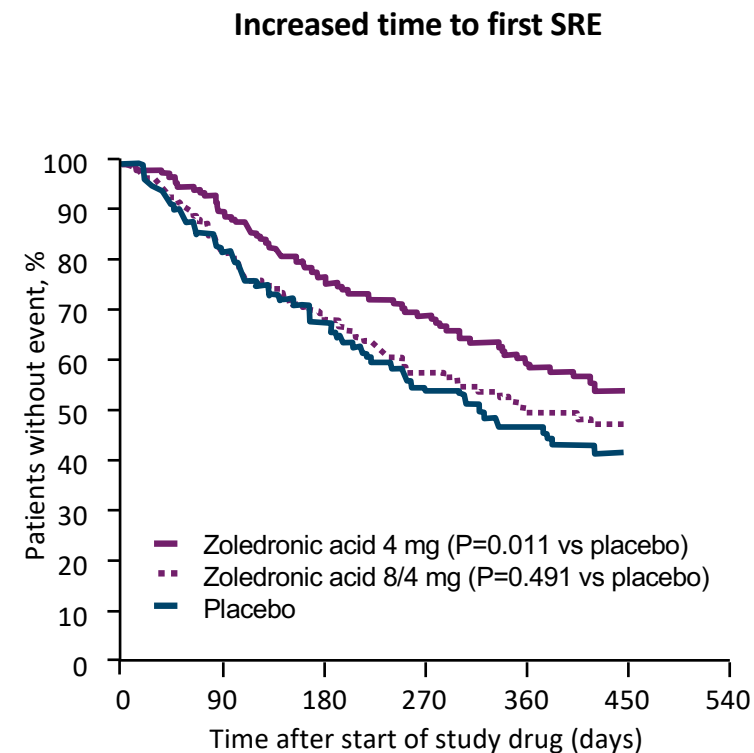
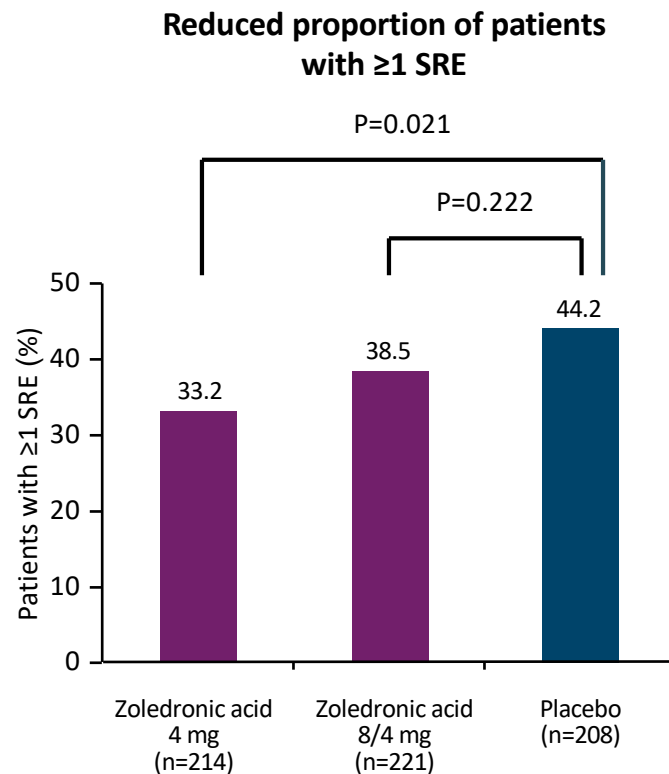
The concept of Skeletal-related events



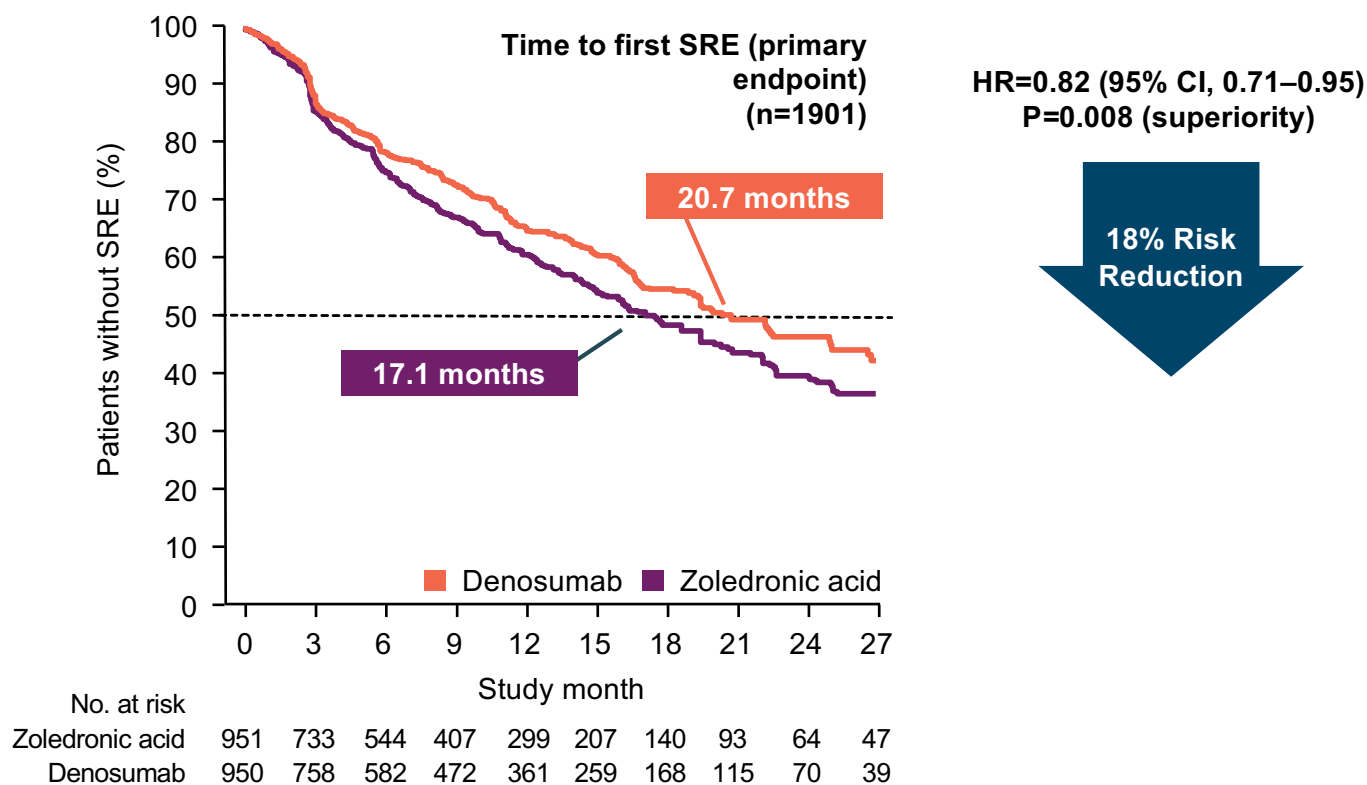
Patients with bone metastases from CRPC are at high risk of developing SREs



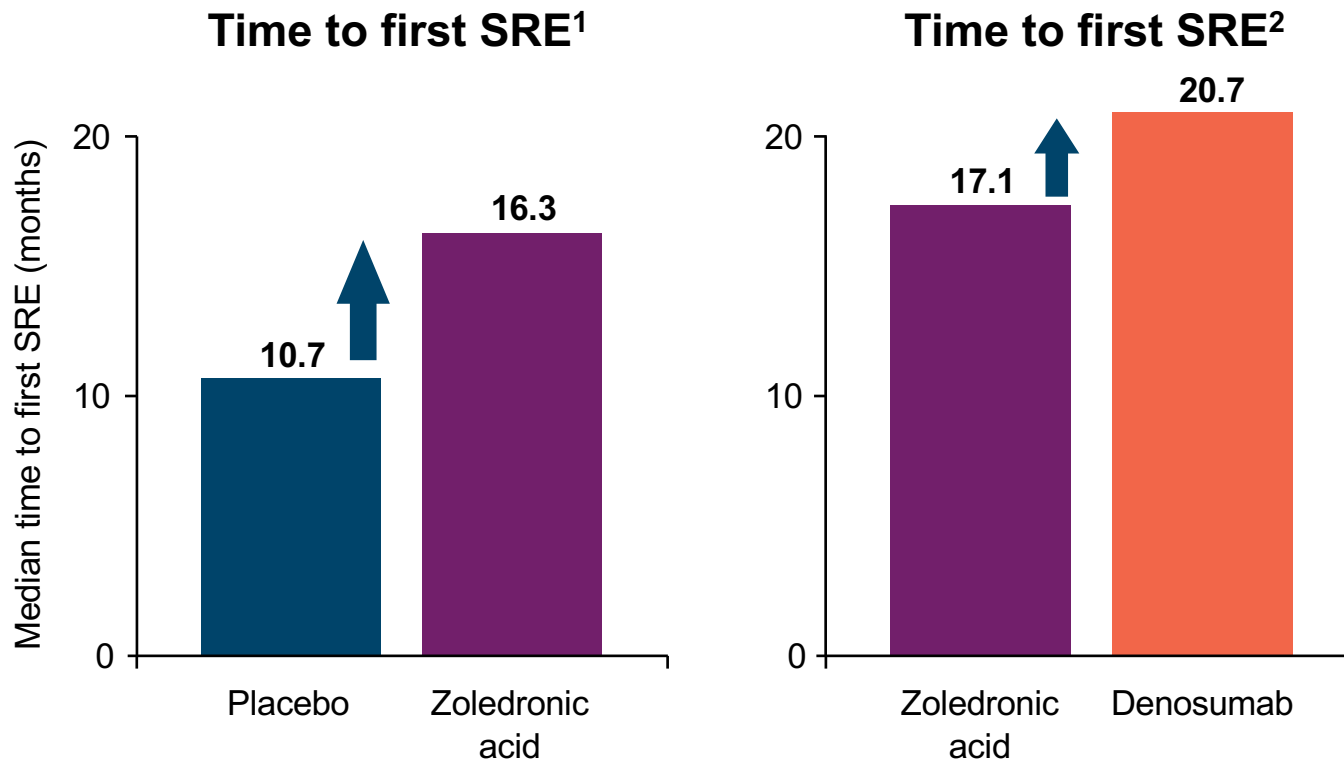
Zoledronic acid delays the onset of first and subsequent SREs



Denosumab vs. zoledronic acid for the prevention of SRE in men with mCRPC



Benefit of BPA on the 1st on-study SRE



BPA are recommended by many guidelines.



EAU/EANM/ESTRO/ESUR/SIOG

- Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.

NCCN

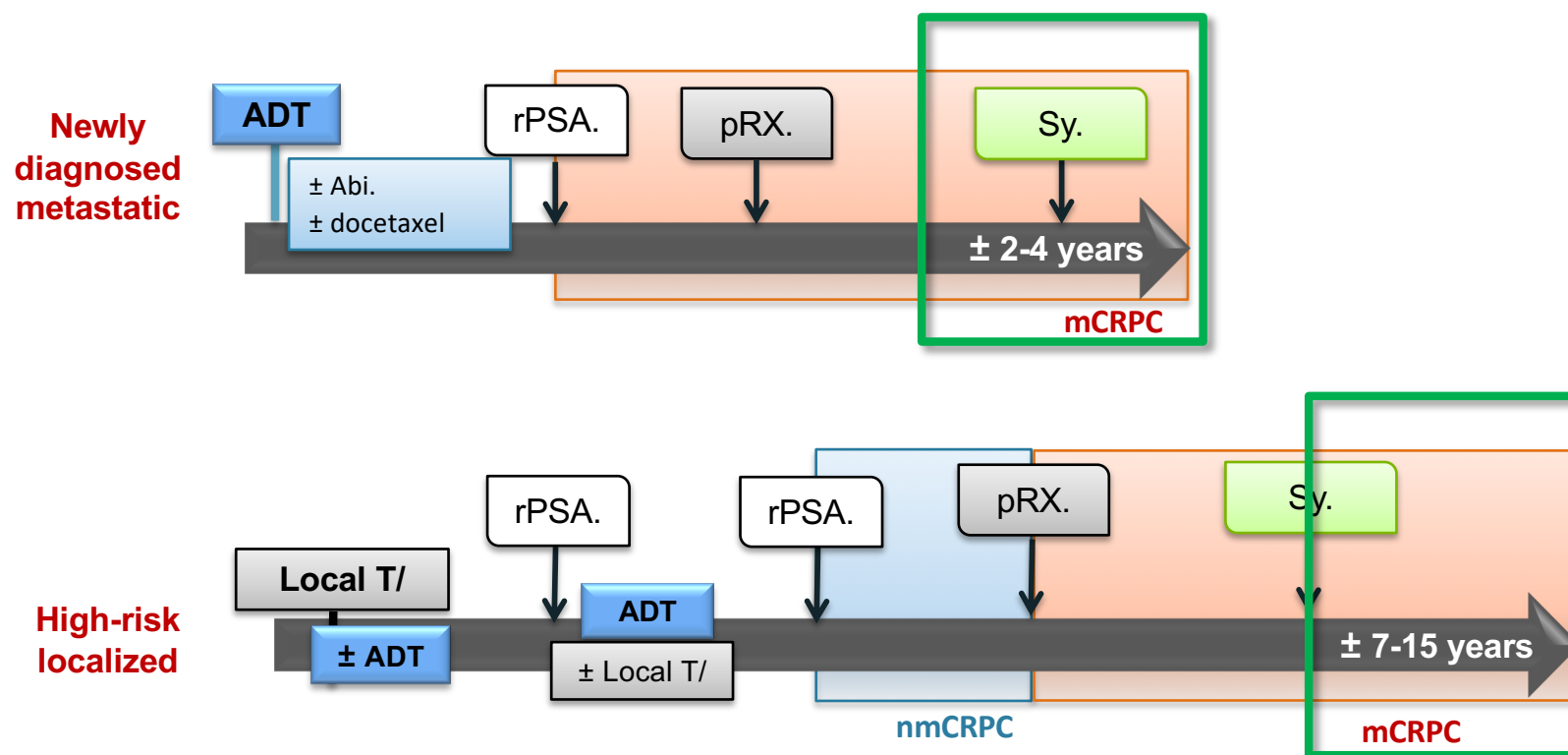
- Recommended in CRPC patients with bone metastases

But,...These we are mostly speaking of very late patients

	Zoledronic Ac. Vs. Placebo ⁽¹⁾	Denosumab vs. Zoledronic Acid ⁽²⁾
Average number of bone metastases	4,2	
Previous SRE	30%	24%
Time since first bone metastasis	23.8 months	5.19 months
Pain at baseline	72.5 %	

No abiraterone, enzalutamide, and others

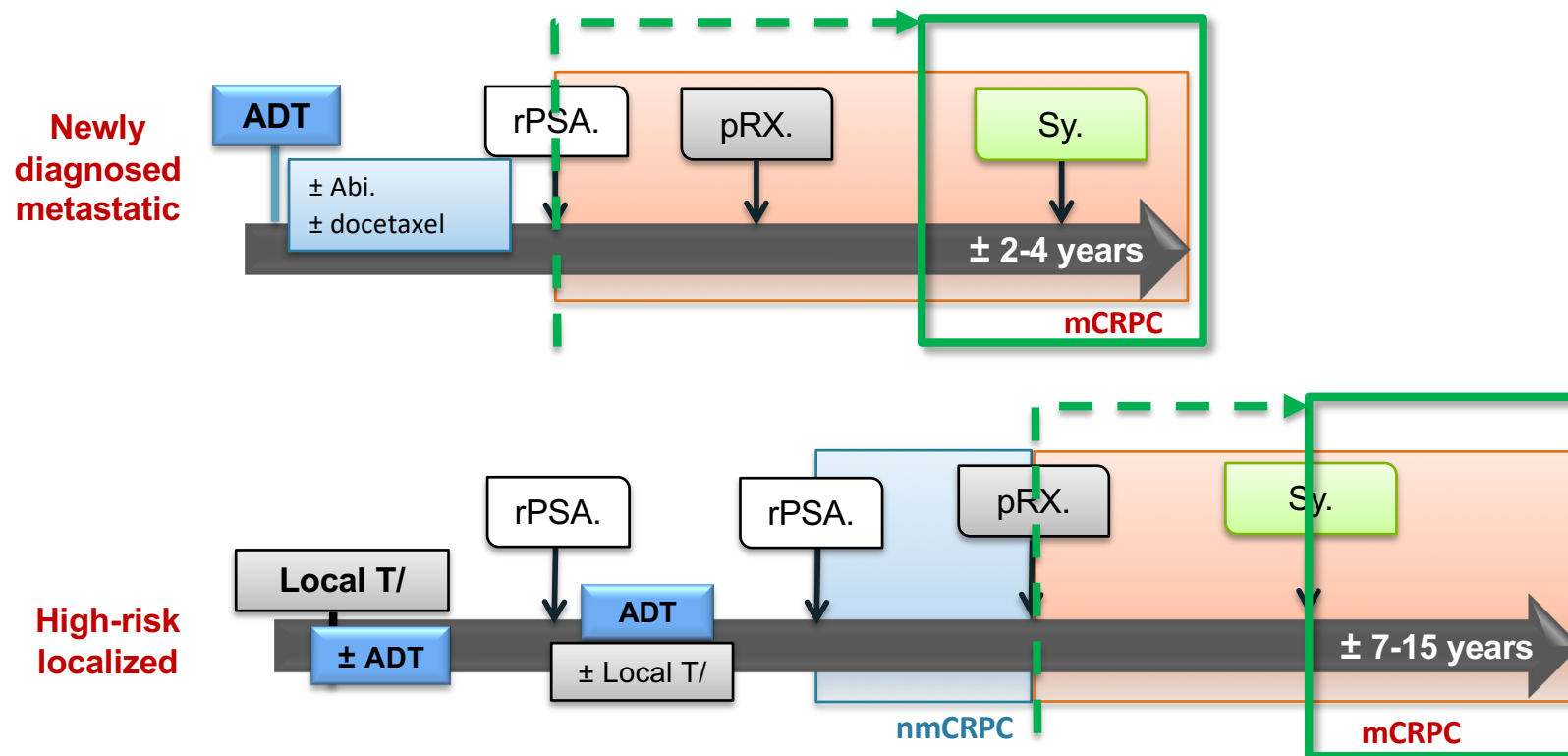
Advanced PCa landscape in 2019



When to start BPA acid at SRE protection dose ?

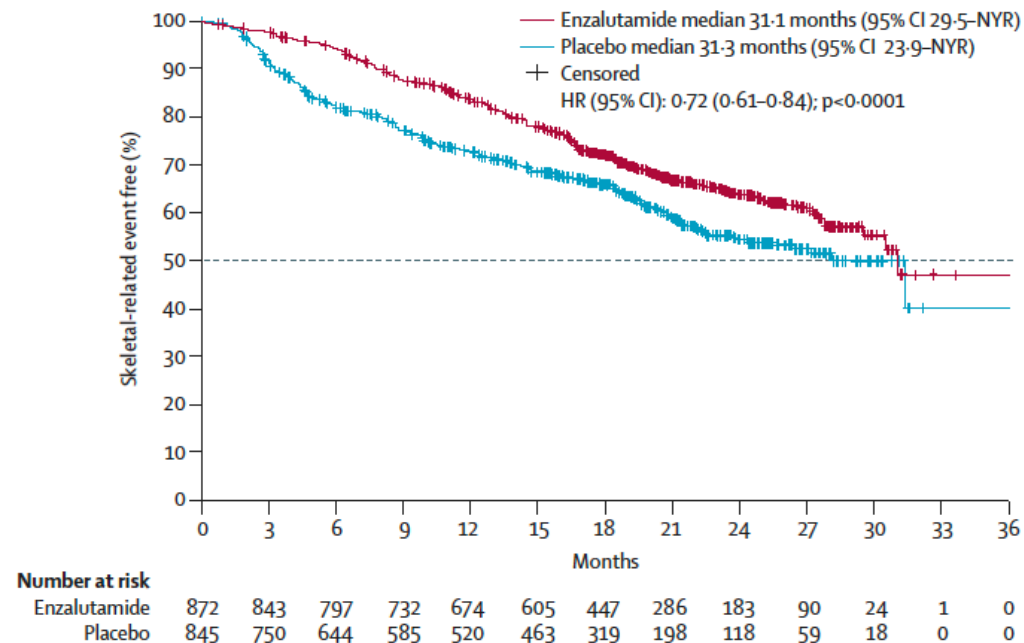
- There is clear evidence that for advanced patients, with multiples bone metastases, having experience previous SRE, BPA are recommended at the SRE preventing dose
- But what for PREVAIL and COU-AA-302 patients ?
 - ✓ Patients have a low bone metastatic burden, are usually SRE free, and low pain

Advanced PCa landscape in 2019



SRE still happen on enzalutamide and abiraterone.

- 278 (32%) have experienced SRE at the time of analysis on 28% of death.



Incidence of SRE in Patients with CRPC: An Observational Retrospective Cohort Study in the US.

- Incidence rates of first SREs in a 2.234 men with CRPC in the SEER-Medicare database.

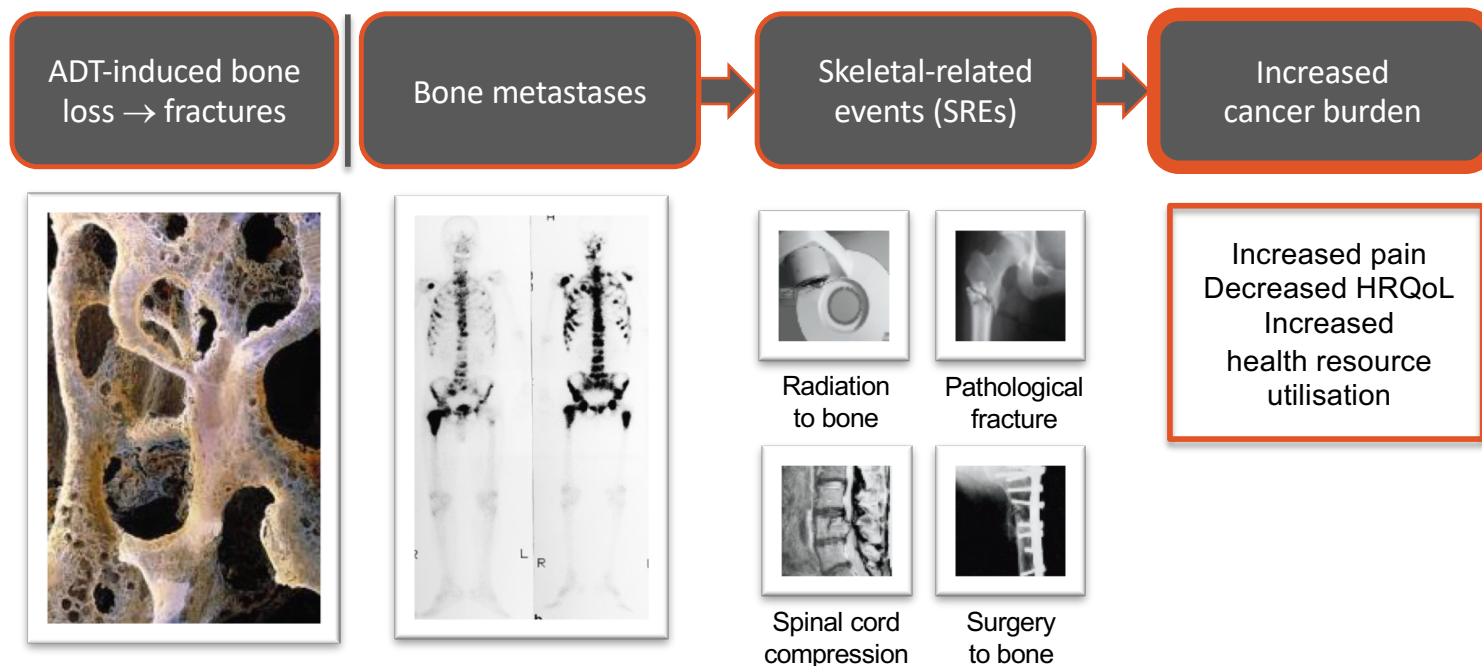
SRE	% of Total Cohort
Radiation therapy	27.3
Fracture	11.9
Spinal cord compression	1.7
Bone surgery	1.0
Total	40.1

Person-time Included	Patients	Incidence rate /100 person-months
All person-time	2,234	3.78 (3,53-4,03)
BTA use		
Person-time before BTA use	1,021	4.16 (3.71-4.65)
Person-time after BTA use	1,539	3.60 (3.32-3.91)

Role of BPA in combination with abiraterone (Sub-analysis of COU-AA-302)

Post-hoc Kaplan-Meier Estimates in Overall Study Population				
	Prior BTT Use Median (95% CI)	No Prior BTT Use, Median (95% CI)	HR (95% CI)	p Value
Primary end points				
rPFS	11.1 (10.8, 13.8)	11.1 (10.8, 13.6)	0.95 (0.81-1.12)	0.565
OS	34.7 (30.2, N/E)	31.2 (28.6, 35.3)	0.92 (0.75-1.12)	0.409
Secondary end points				
Time to opiate use (cancer-related pain)	32.6 (28.3, N/E)	27.2 (22.9, 30.3)	0.81 (0.67-0.99)	0.037
Time to chemotherapy initiation	22.8 (18.9, 29.1)	21.0 (18.7, 22.8)	0.87 (0.73-1.03)	0.108
Time to ECOG PS deterioration	12.9 (11.1, 15.3)	11.1 (10.1, 12.0)	0.79 (0.69-0.91)	0.001

Longer exposure to ADT, as a result of better treatment increases the risk of non-pathological fractures

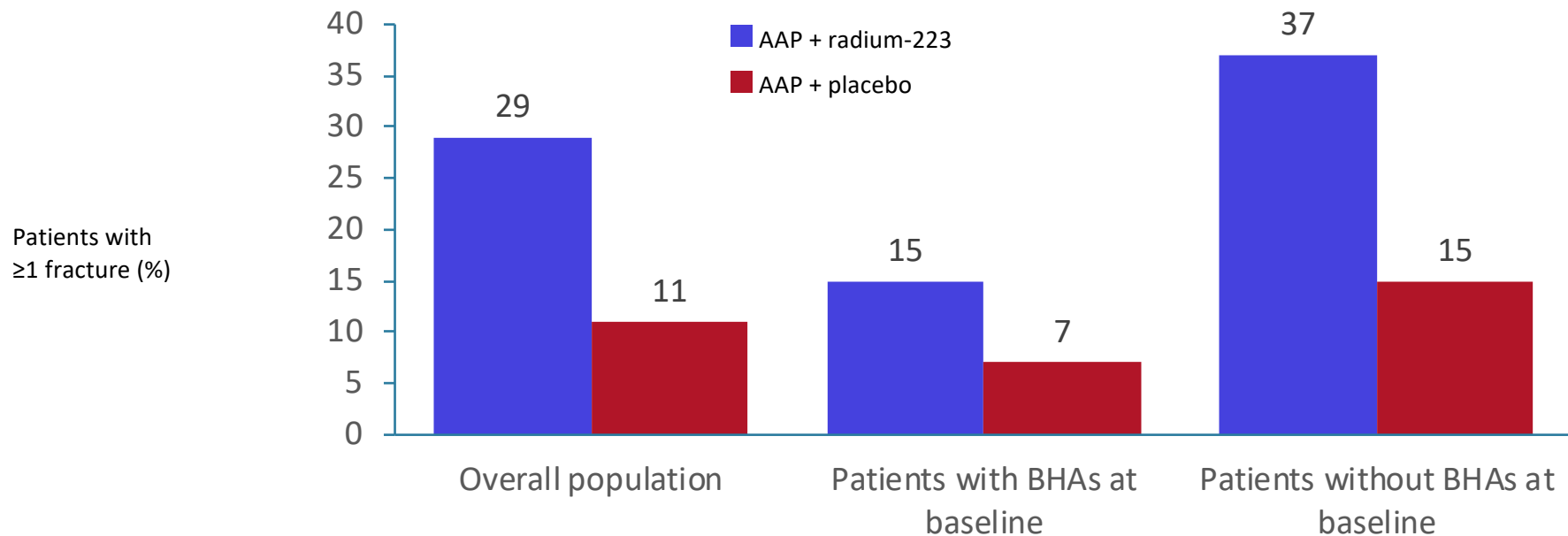


Fractures in ERA 223

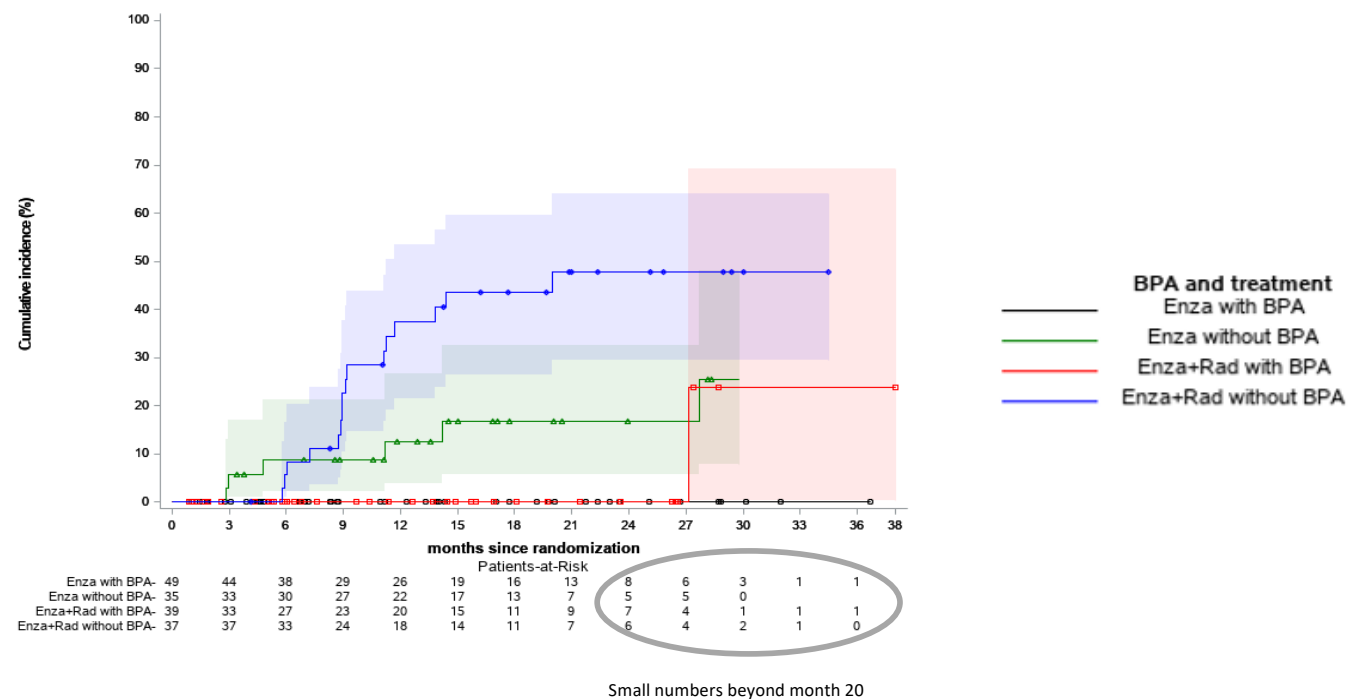
	AAP + Ra223	AAP + placebo
Patients with ≥ 1 fracture, n	29%	11%
No bone metastasis at site of fracture, n	79%	74%
Type of fracture, n		
Pathological	25%	6
Traumatic	36%	13
Osteoporotic	49%	4
Indeterminate	1%	0

- 40% of the patients were receiving bone protecting agent (BPA) at entry.
- In post-hoc analyses, BPA significantly impacted the rate of fracture in both arm (37% vs. 15% in Ra-223/AAP without vs. with BPA)

Post-Hoc Subgroup Analysis of Fractures by Baseline BHA Use in the ERA223 (abiraterone vs. abiraterone + RA223)



Cumulative incidence of fracture in the PEACE III/EORTC GUCG 1333 enzalutamide vs. enzalutamide + Ra223



Safety of long-term BPA therapy:

Cumulative median dmab exposure 12.0 months PCa (n = 942); 295 patients received denosumab for >3 years.

Table 3 Adverse events during the open-label treatment phase

Event, n (%)	Prostate cancer study	
	Denosumab/Denosumab (N = 147) ^a	Zoledronic Acid/ Denosumab (N = 118) ^a
All adverse events	138 (93.9)	105 (89.0)
Serious adverse events	78 (53.1)	63 (53.4)
Most common adverse events		
Nausea	20 (13.6)	16 (13.6)
Anemia	34 (23.1)	26 (22.0)
Fatigue	23 (15.6)	15 (12.7)
Back pain	29 (19.7)	19 (16.1)
Asthenia	29 (19.7)	11 (9.3)
Arthralgia	25 (17.0)	17 (14.4)
Adverse events of infection ^b	58 (39.5)	33 (28.0)
Osteonecrosis of the jaw (ONJ) ^{c, d}	12 (8.2)	7 (5.9)
CTCAE, v 3 grade 3	3 (2.0)	1 (0.8)
CTCAE, v 3 grade 4	0 (0.0)	1 (0.8)
Adverse events of new primary malignancy ^e	1 (0.7) ^h	0 (0.0)
Adverse events of hypocalcemia ⁱ	8 (5.4)	5 (4.2)
Serious	1 (0.7)	1 (0.8)

ONJ: 5-10%

Why most patients should received BPA when mCRPC

- Bone is the most frequent site of metastasis in men with prostate cancer.
- Development of bone metastasis is associated with disease progression, increased mortality, and risk of SREs and SSEs.
- Non pathological fractures are increasingly seem in patients treated for long durations with ARpl
- BPA significantly reduce the incidence of fractures and SRE
- Caveat:
 - We don't know if the registered SRE dosage is required at earlier stage of the disease.