Metastatic castrate-resistant prostate cancer: Toward a chronic disease

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General recommendations in CRPC

- Check serum Testosterone (should be < 0.50 ng/mL)
- Imaging check up (bone scan + CT scan)
- Continue castration
- If ongoing, stop the androgen receptor antagonist (« Withdrawal syndrome »)
- Treat symptoms (bone RXT, TURP, anemia, etc)
- **Discuss a new line of anti-cancer treatment**

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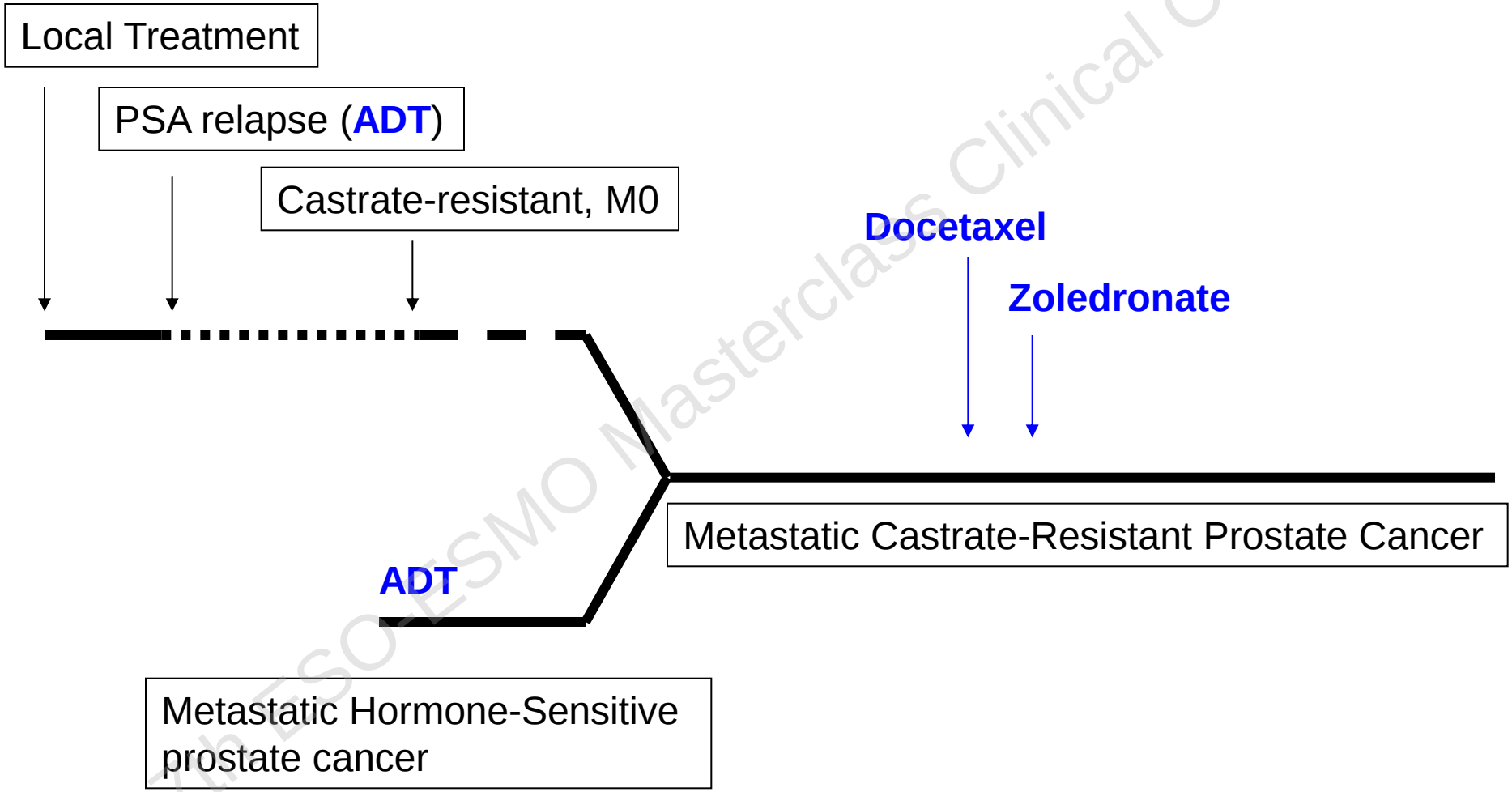
Advanced prostate cancer: Natural history (until 2010)



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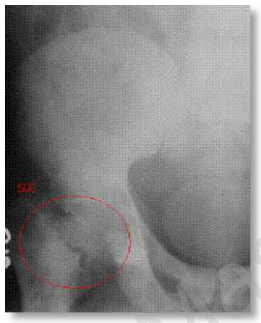
Skeletal Related Events (SRE) in men with bone metastases from prostate cancer

Pain requiring Radiation to Bone

33%



Pathologic Fracture

25%

Spinal Cord Compression

8%

Surgery to Bone

4%

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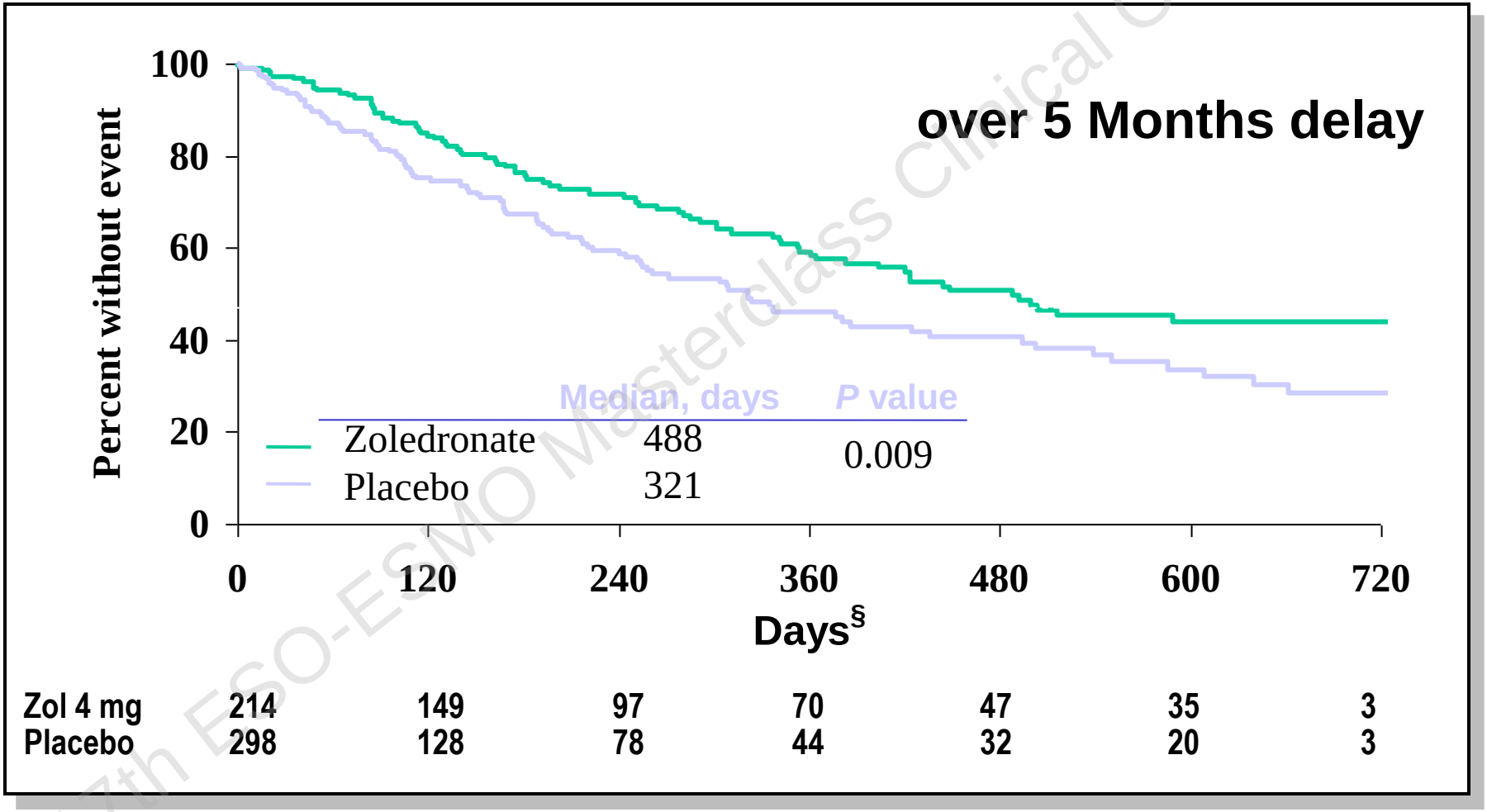
Saad, et al. J Urol 2003;169(Suppl).

Zoledronate: Time to Skeletal Related Event in CRPC



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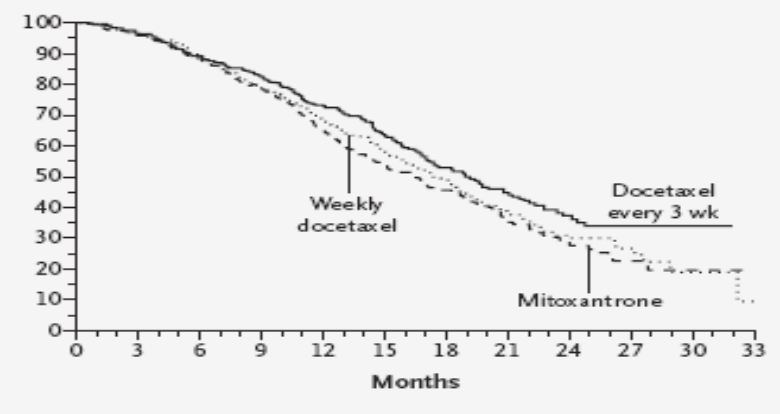
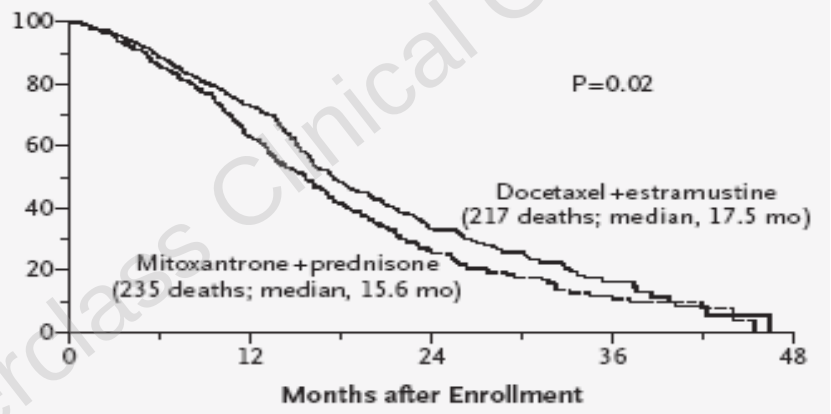
Saad et al. *JNCI 2004; 96:879*

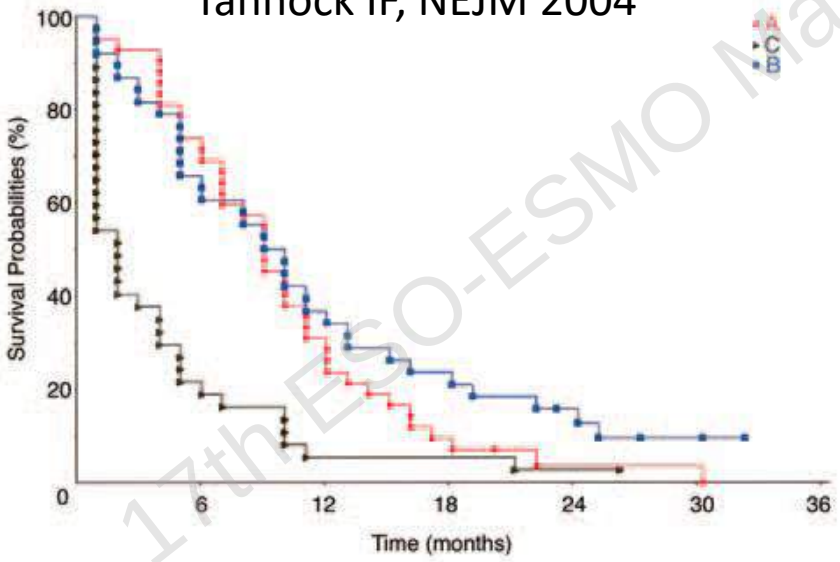
Docetaxel improves OS in metastatic CRPC



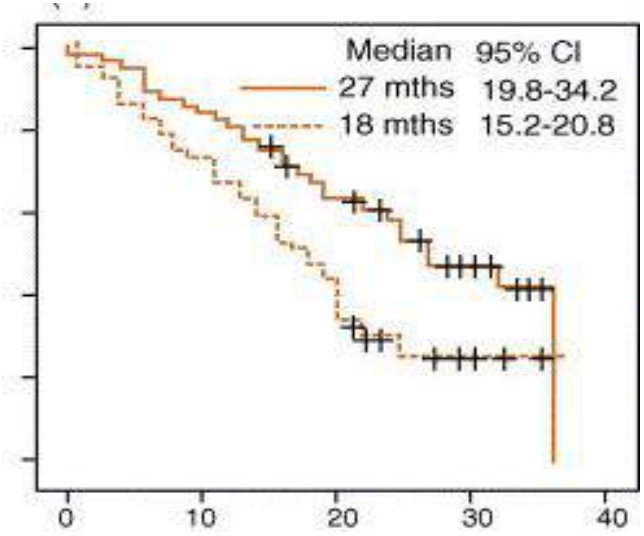
Tannock IF, NEJM 2004



Petrylak DP, NEJM 2004



Oudard S, J Clin Oncol 2005



Fossa S, Eur Urol 2007

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A decade of research in prostate cancer

2004-2009:
No significant result

2010-2014:
- **Sipuleucel-T**
- **Cabazitaxel**
- **Denosumab**
- **Abiraterone**
- **Radium-223**
- **Enzalutamide**

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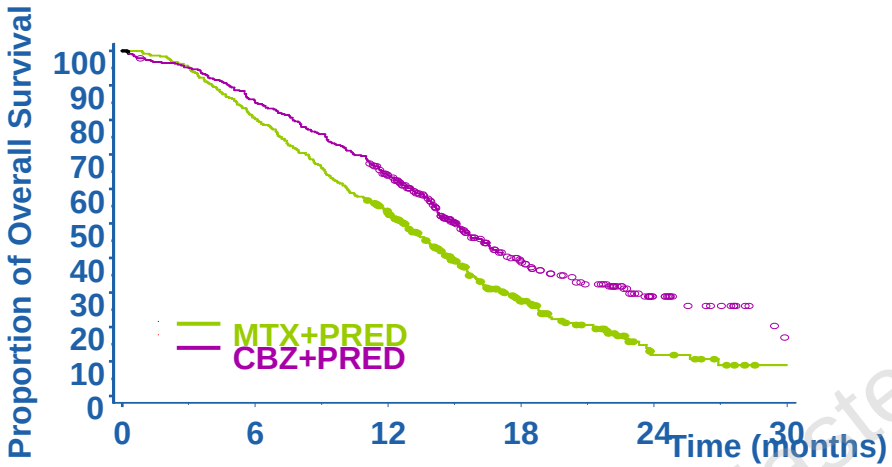
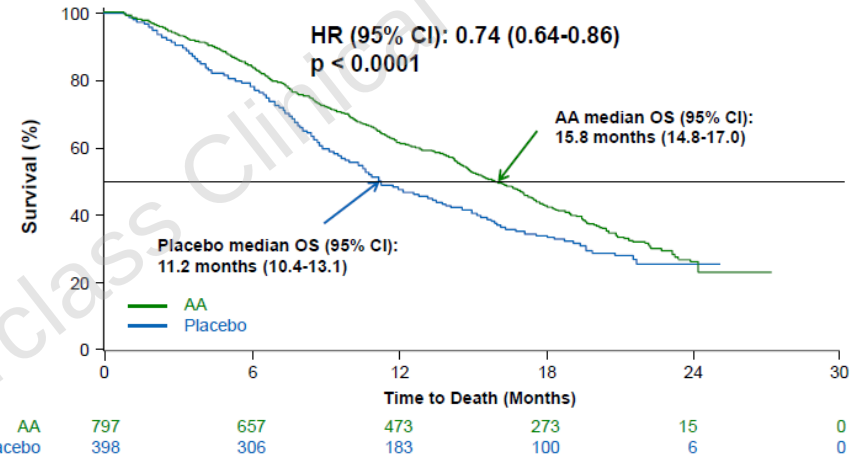
4 new active drugs in 4 years for post-docetaxel CRPC !

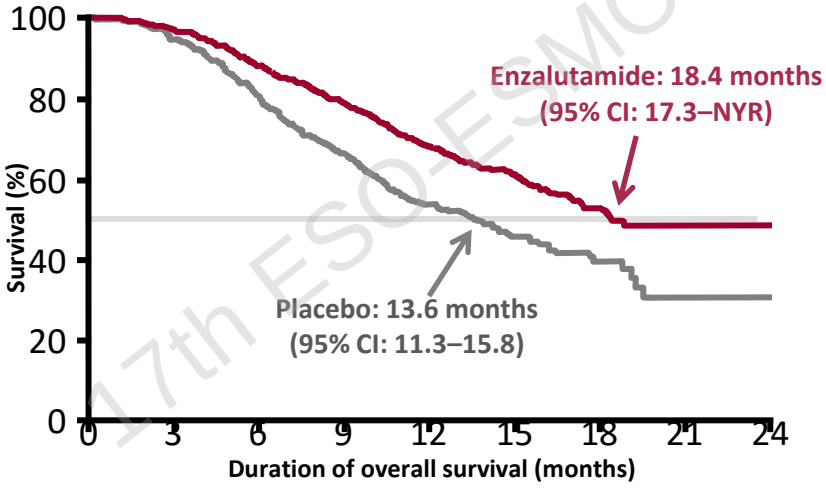
Cabazitaxel, De Bono J, Lancet 2010



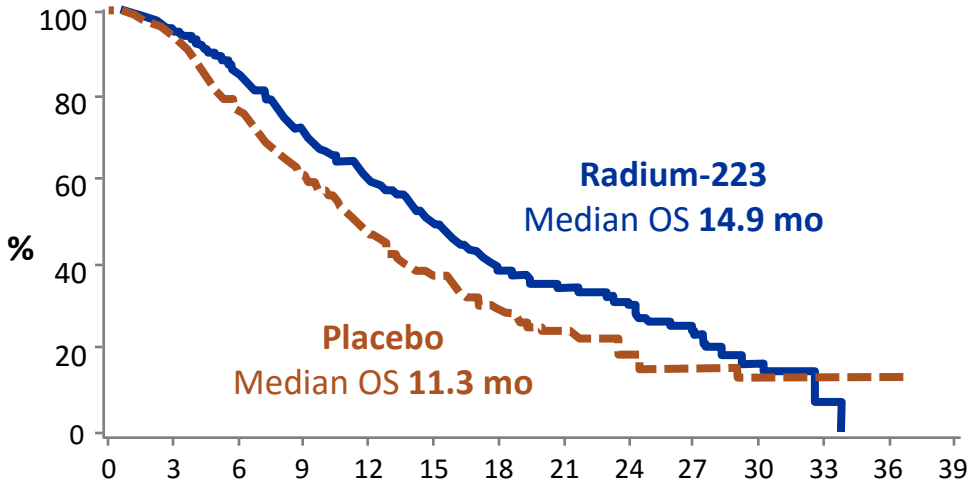
Abiraterone, Fizazi K, Lancet Oncol 2012



Enzalutamide, Scher HI, NEJM 2012



Radium-223, Parker J, NEJM 2013



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Docetaxel and cabazitaxel: toxicity profile

- Docetaxel: more:
  - Peripheral neuropathy
  - Nail changes
  - Alopecia
  - Dysgueusia
- Cabazitaxel: more:
  - Neutropenia
  - Diarrhea

→ G-CSF recommended
Inform patients

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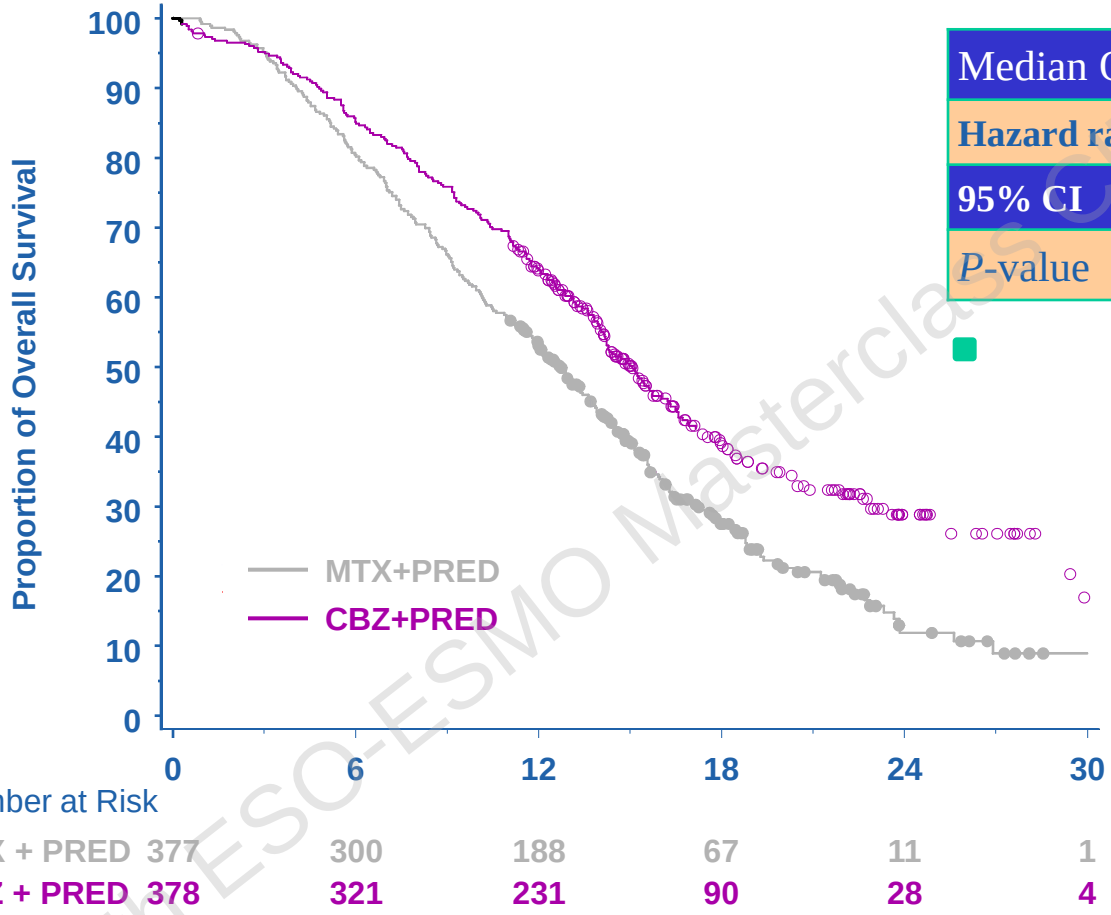
Omlin et al. Clin Genitour Cancer. 2015

Cabazitaxel vs Mitoxantrone in second-line chemotherapy: 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

Median FU: 13.7 mo

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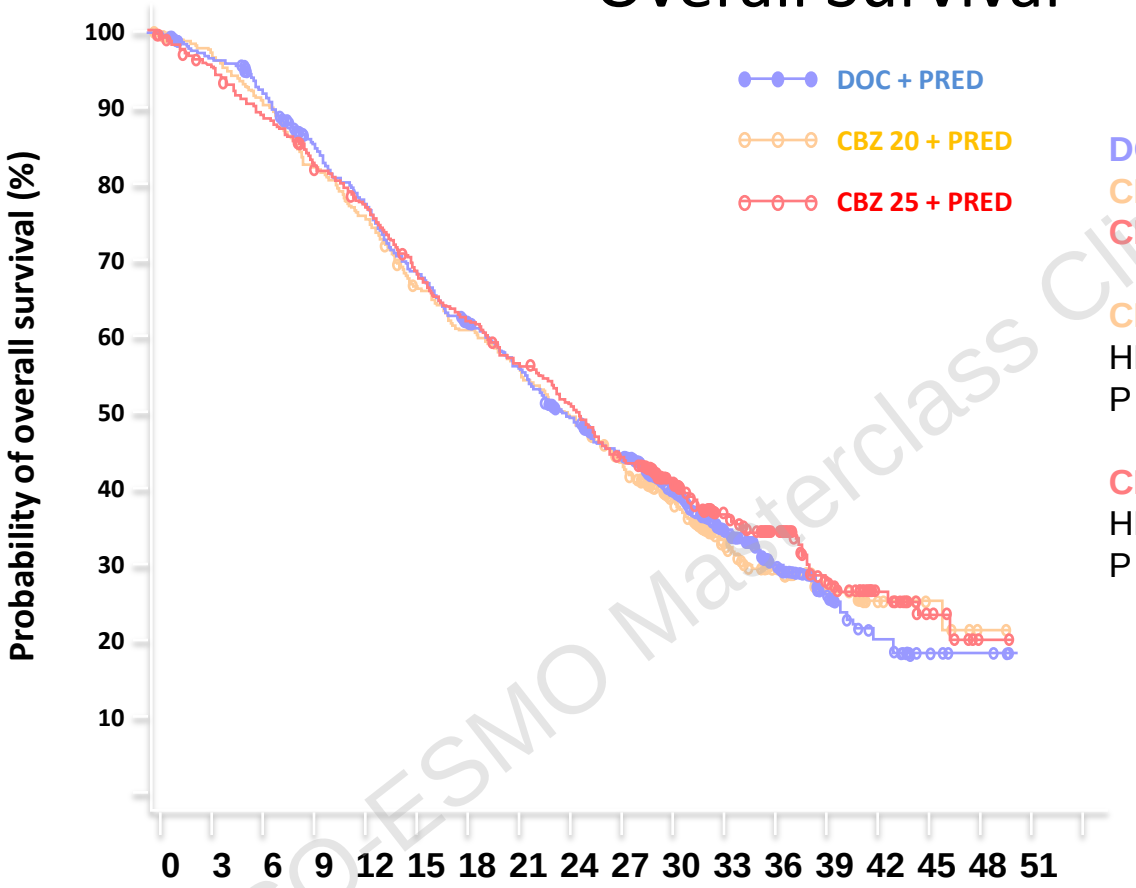
De Bono J, Lancet 2010; 376: 1147-54

Cabazitaxel vs Docetaxel in first-line CRPC (FIRSTANA) Overall Survival



Number at risk									
DOC + PRED	39	36	33	30	24	19	13	57	18	3
	1	6	6	7	3	2	3			
CBZ 20 + PRED	38	35	31	29	23	19	13	49	19	3
	9	6	9	6	4	2	3			
CBZ 25 + PRED	38	34	32	29	23	19	13	70	28	5
	8	5	5	6	9	7	8			

DOC + PRED **24.3** (22.18–27.60
CBZ 20 + PRED **24.5** (21.75–27.20
CBZ 25 + PRED **25.2** (22.90–26.97

CBZ 20 DOC
HR 1.009 (0.85–1.197)
P = 0.9967

CBZ 25 DOC
HR 0.97 (0.819–1.16)
P = 0.7574

Sartor O., ASCO 2016

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FIRSTANA: TEAEs in ≥ 5% of Patients

TEAEs reported in ≥ 5% of patients, n (%)	DOC + PRED N = 387		CBZ 20 + PRED N = 369		CBZ 25 + PRED N = 391	
	All Grades	G 3–4	All Grades	G 3–4	All Grades	G 3–4
Febrile neutropenia	32 (8.3)	32 (8.3)	9 (2.4)	9 (2.4)	47 (12.0)	47 (12.0)
Neutropenic infection	19 (4.9)	16 (4.1)	6 (1.6)	5 (1.4)	24 (6.1)	23 (5.9)
Pyrexia	37 (9.6)	1 (0.3)	23 (6.2)	1 (0.3)	31 (7.9)	0
Abdominal pain	15 (3.9)	1 (0.3)	36 (9.8)	3 (0.8)	32 (8.2)	2 (0.5)
Diarrhea	143 (37.0)	9 (2.3)	120 (32.5)	13 (3.5)	195 (49.9)	22 (5.6)
Vomiting	45 (11.6)	3 (0.8)	44 (11.9)	1 (0.3)	77 (19.7)	6 (1.5)
Dysgeusia	70 (18.1)	0	41 (11.1)	0	59 (15.1)	0
Stomatitis	53 (13.7)	3 (0.8)	18 (4.9)	0	26 (6.6)	1 (0.3)
Constipation	70 (18.1)	4 (1.0)	92 (24.9)	1 (0.3)	78 (19.9)	2 (0.5)
Decreased appetite	65 (16.8)	1 (0.3)	49 (13.3)	2 (0.5)	74 (18.9)	2 (0.5)
Hematuria	14 (3.6)	1 (0.3)	75 (20.3)	13 (3.5)	98 (25.1)	14 (3.6)
Urinary tract infection	9 (2.3)	3 (0.8)	40 (10.8)	12 (3.3)	37 (9.5)	8 (2.0)
Dysuria	9 (2.3)	0	23 (6.2)	0	21 (5.4)	1 (0.3)

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Sartor O, ASCO 2017

FIRSTANA: TEAEs in ≥ 5% of Patients cont.

TEAEs reported in ≥ 5% of patients, n (%)	DOC + PRED N = 387		CBZ 20 + PRED N = 369		CBZ 25 + PRED N = 391	
	All Grades	Grade 3–4	All Grades	Grade 3–4	All Grades	Grade 3–4
Peripheral sensory neuropathy	97 (25.1)	8 (2.1)	43 (11.7)	1 (0.3)	48 (12.3)	0
Paresthesia	24 (6.2)	0	25 (6.8)	0	14 (3.6)	0
Muscle spasms	15 (3.9)	0	28 (7.6)	0	13 (3.3)	1 (0.3)
Arthralgia	31 (8.0)	4 (1.0)	33 (8.9)	2 (0.5)	43 (11.0)	1 (0.3)
Bone pain	25 (6.5)	6 (1.6)	31 (8.4)	8 (2.2)	30 (7.7)	4 (1.0)
Edema peripheral	79 (20.4)	6 (1.6)	36 (9.8)	0	30 (7.7)	1 (0.3)
Weight decreased	19 (4.9)	1 (0.3)	17 (4.6)	0	40 (10.2)	3 (0.8)
Alopecia	151 (39.0)	0	33 (8.9)	0	51 (13.0)	0
Nail disorder	35 (9.0)	1 (0.3)	1 (0.3)	0	3 (0.8)	0

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FIRSTANA: Deaths

	DOC + PRED N = 387	CBZ 20 + PRED N = 369	CBZ 25 + PRED N = 391
Deaths within 30 days from last dose, n (%)	**12 (3.1)**	**10 (2.7)**	**16 (4.1)**
Disease progression	4 (1.0)	5 (1.4)	2 (0.5)
Adverse event	8 (2.1)	3 (0.8)	11 (2.8)
Other	0	2 (0.5)	3 (0.8)
Any death during treatment or post-treatment phase, n (%)	259 (66.9)	254 (68.8)	249 (63.7)
Disease progression	225 (58.1)	227 (61.5)	203 (51.9)
Adverse event	8 (2.1)	4 (1.1)	12 (3.1)
Other	26 (6.7)	23 (6.2)	34 (8.7)

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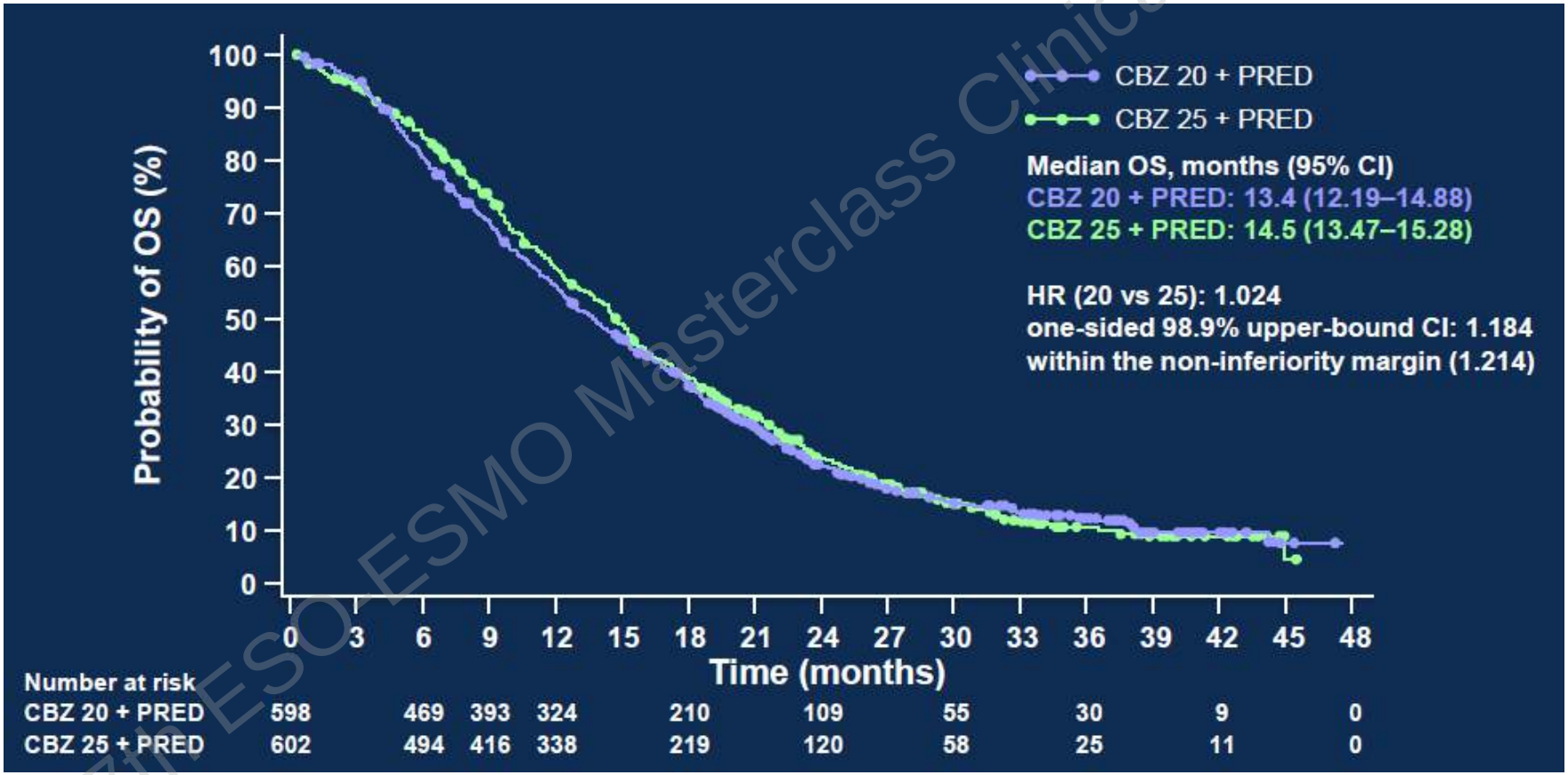
Cabazitaxel 20 vs 25 in second-line CRPC (Proselica): OS



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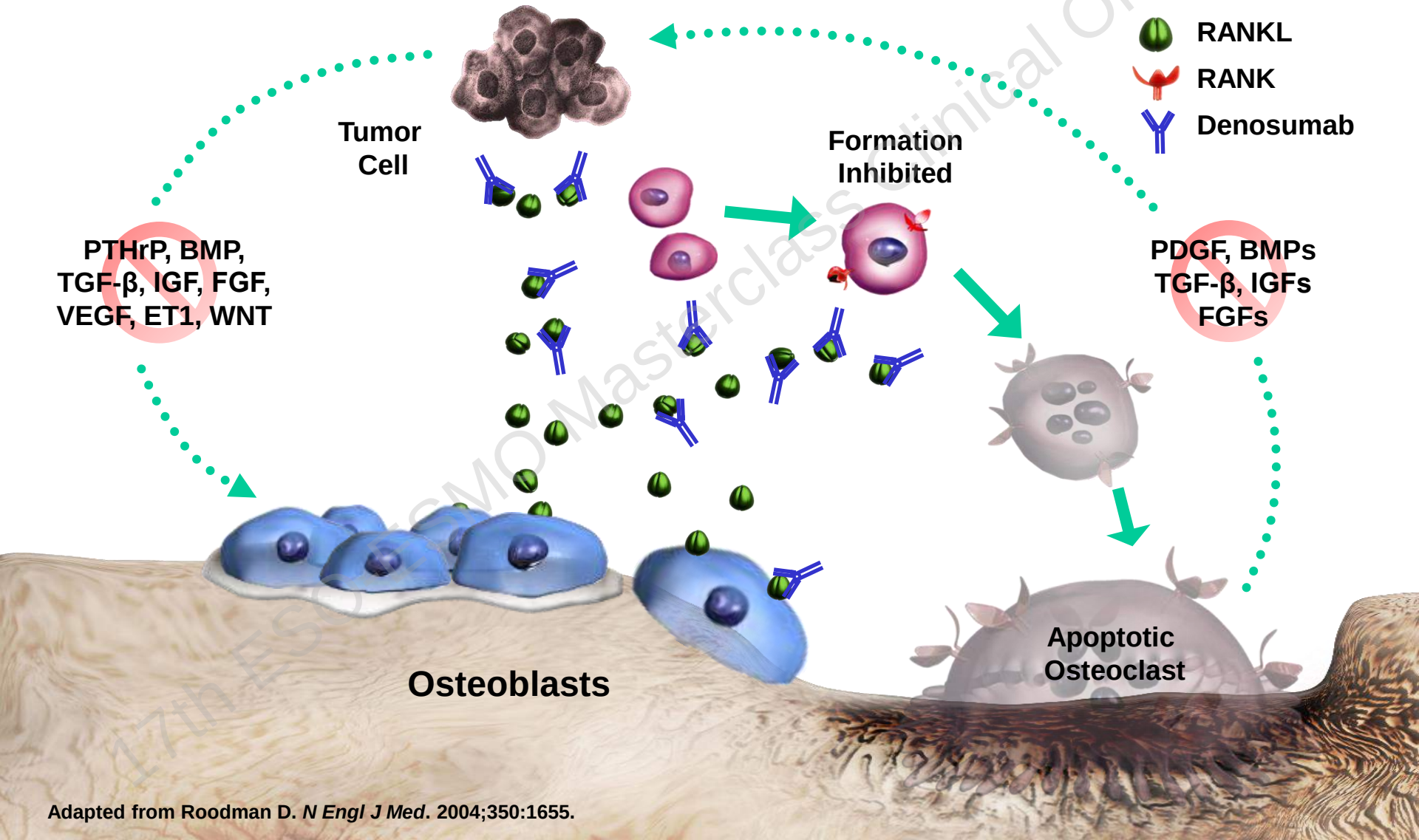
De Bono J, ASCO 2016

Denosumab may interrupt the "vicious cycle" of bone metastases



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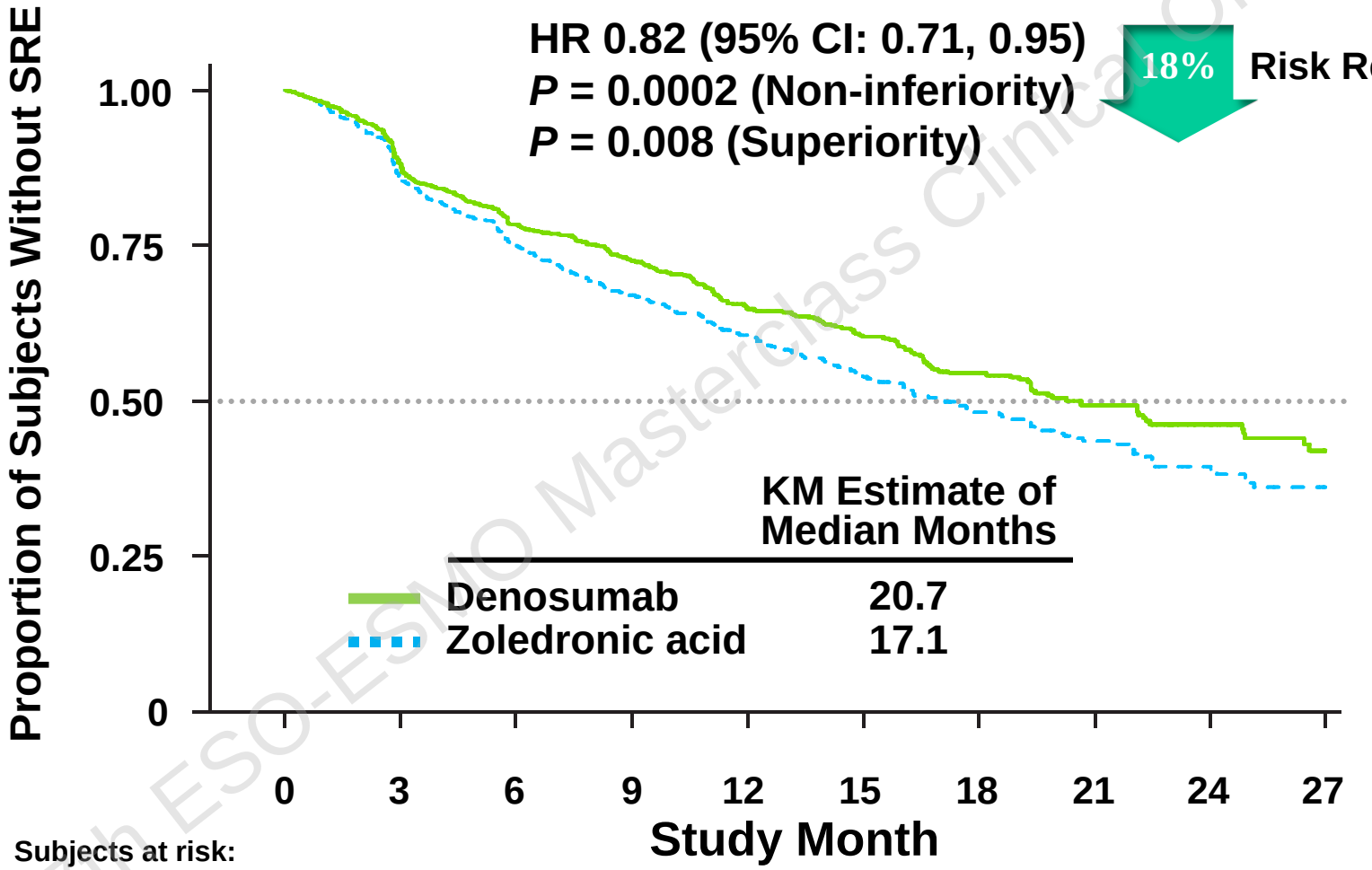
Adapted from Roodman D. *N Engl J Med*. 2004;350:1655.

Denosumab: Time to First SRE in patients with established bone metastases



Subjects at risk:

Zoledronic Acid	951	733	544	407	299	207	140	93	64	47
Denosumab	950	758	582	472	361	259	168	115	70	39

Fizazi et al. Lancet 2011; 377: 811-822

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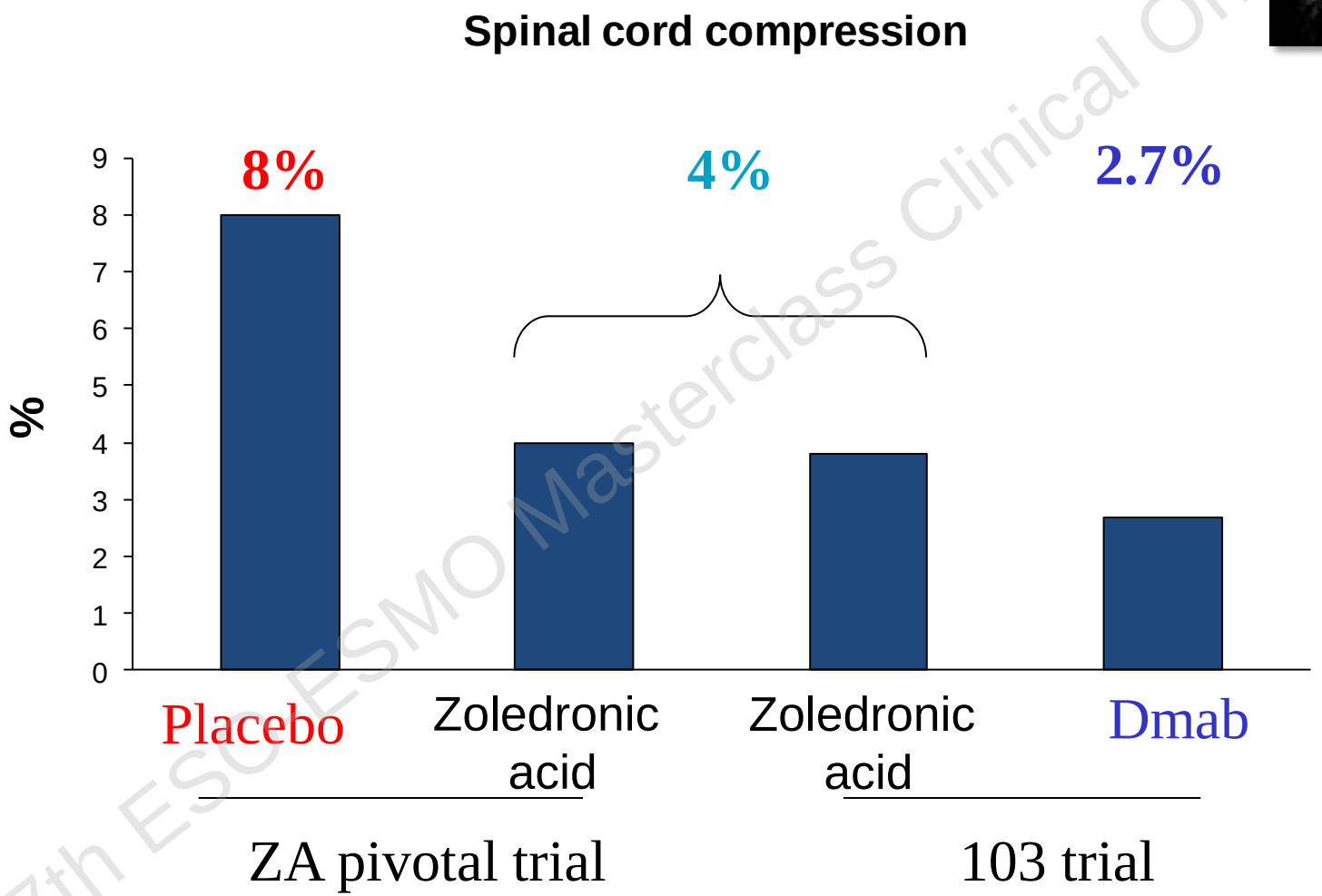
Preventing the onset of the worst enemy:



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Saad, et al. J Natl Cancer Inst 2004;96:879–82;
Fizazi et al. Lancet 2011; 377: 811-822

Bone-targeted agents: Are they worth using?

- Morbidity reduced
- Prevention vs treatment
- Overall good tolerance
- Cheaper than most new cancer drugs

- No demonstrated role on survival
- ONJ (1-2%), hypocalcemia

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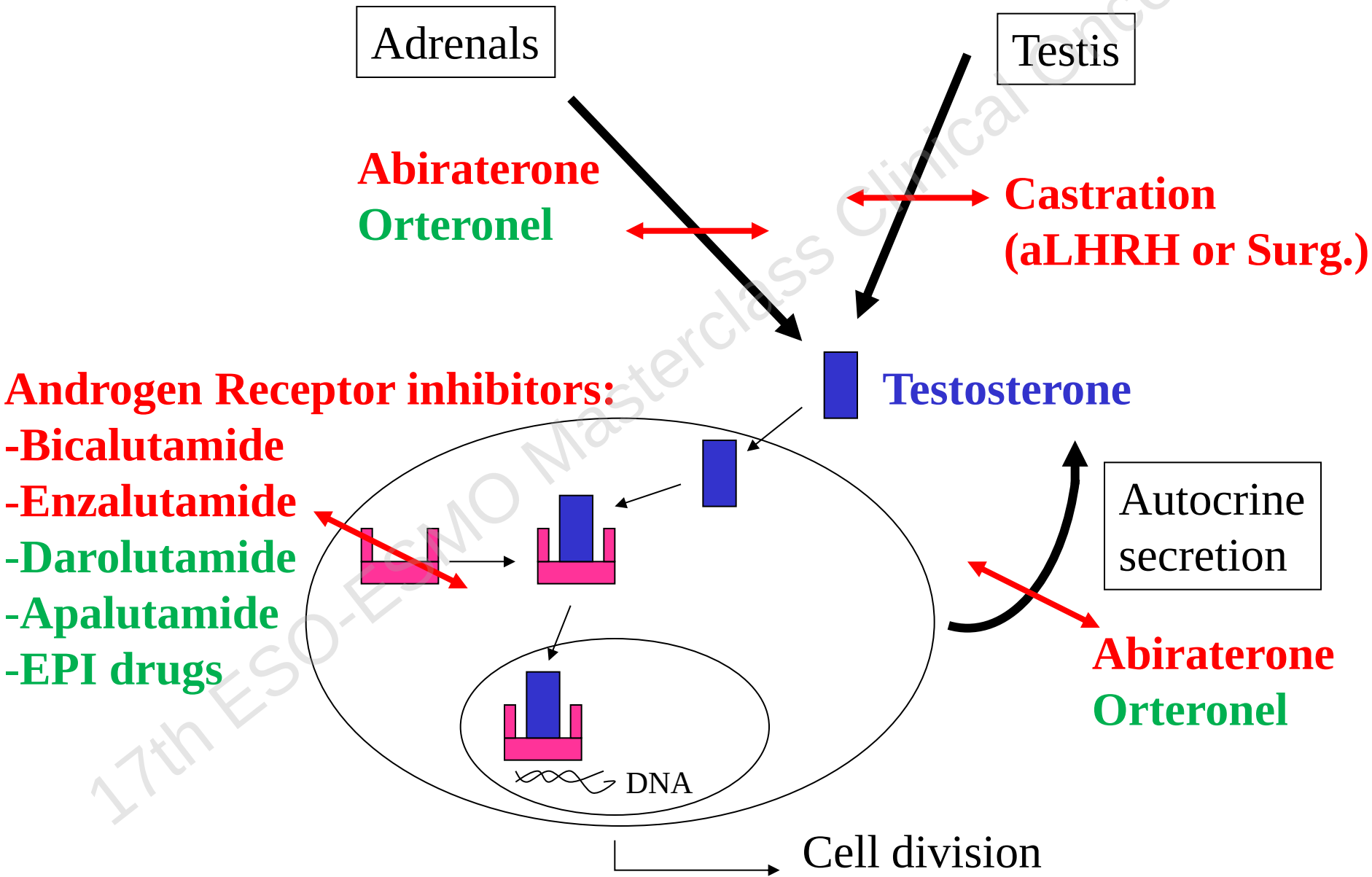
Targeting the AR pathway



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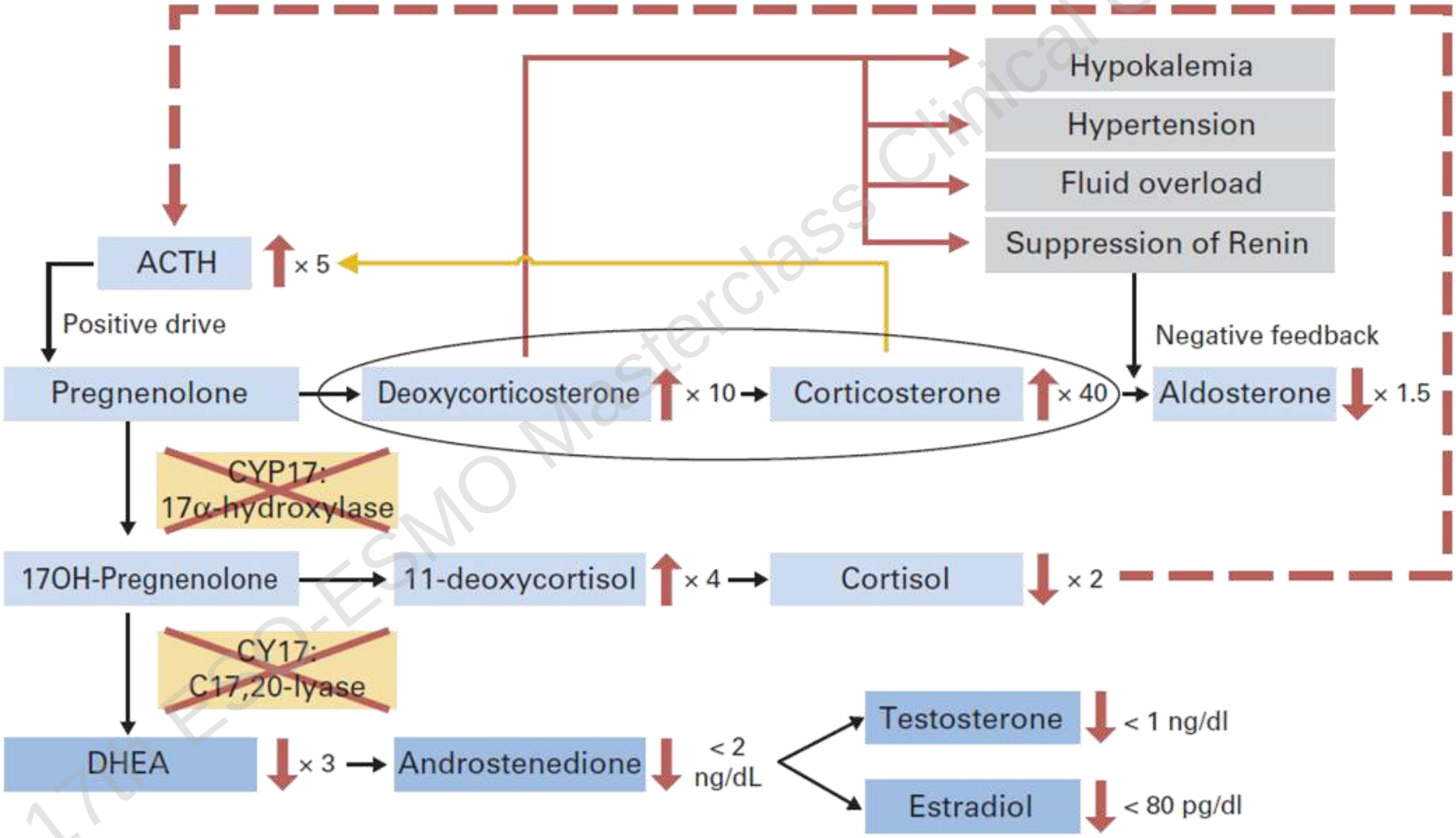
CYP17 blockade inhibits androgen synthesis



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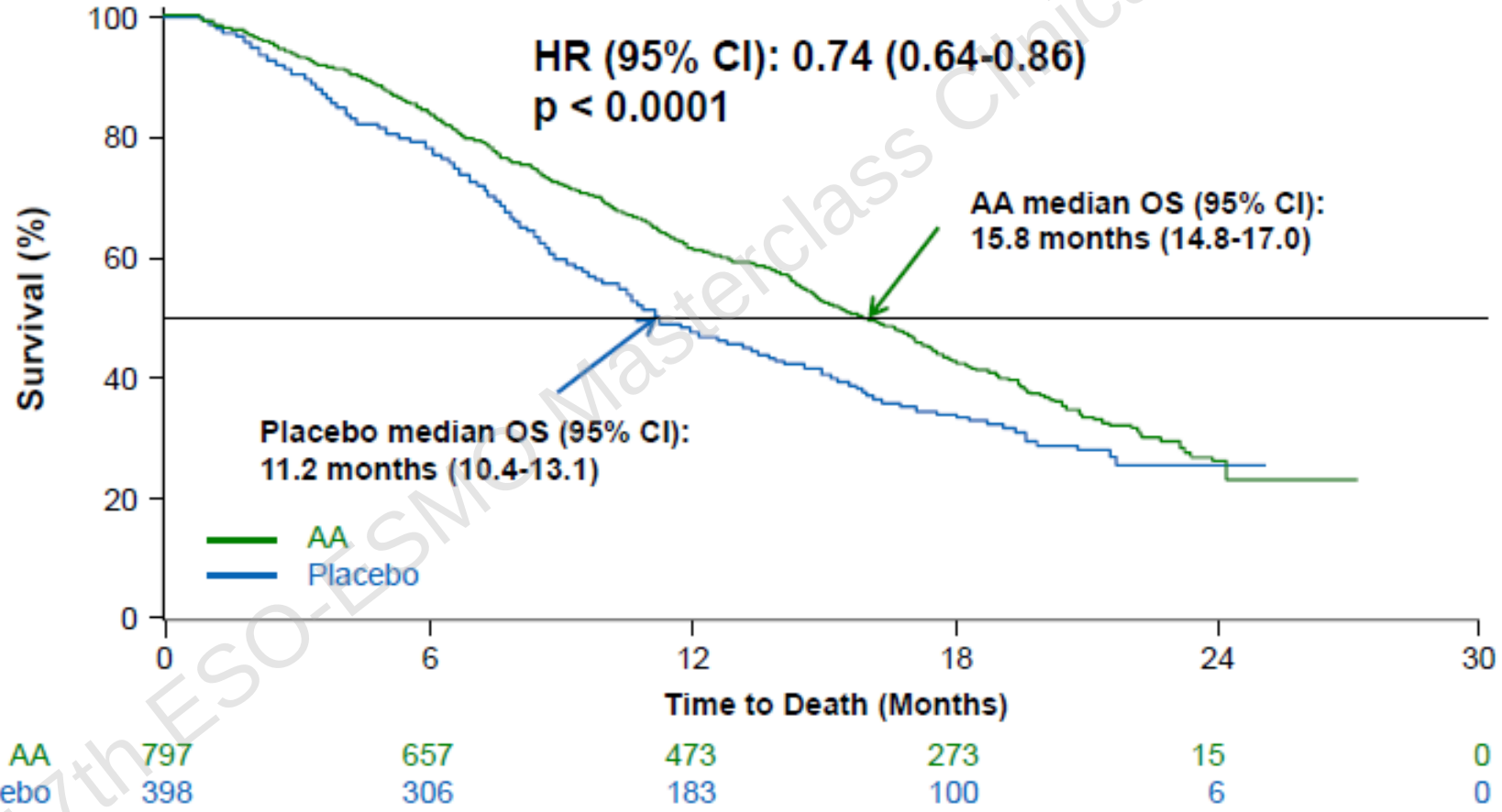
COU-301: Abiraterone prolongs survival in post-docetaxel mCRPC patients



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Fizazi K. Lancet Oncol 2012; 13: 983–992
De Bono J. N Engl J Med 2011; 346: 1995-2005

Abiraterone-Prednisone: Adverse events of special interest

	AA (n=791)		Placebo (n=394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	31%	2%	22%	1%
Hypokalemia	17%	3%	8%	1%
Hypertension	10%	1%	8%	<1%
Cardiac disorders[a]	13%	3%	11%	2%
LFT abnormalities	10%	3%	8%	3%

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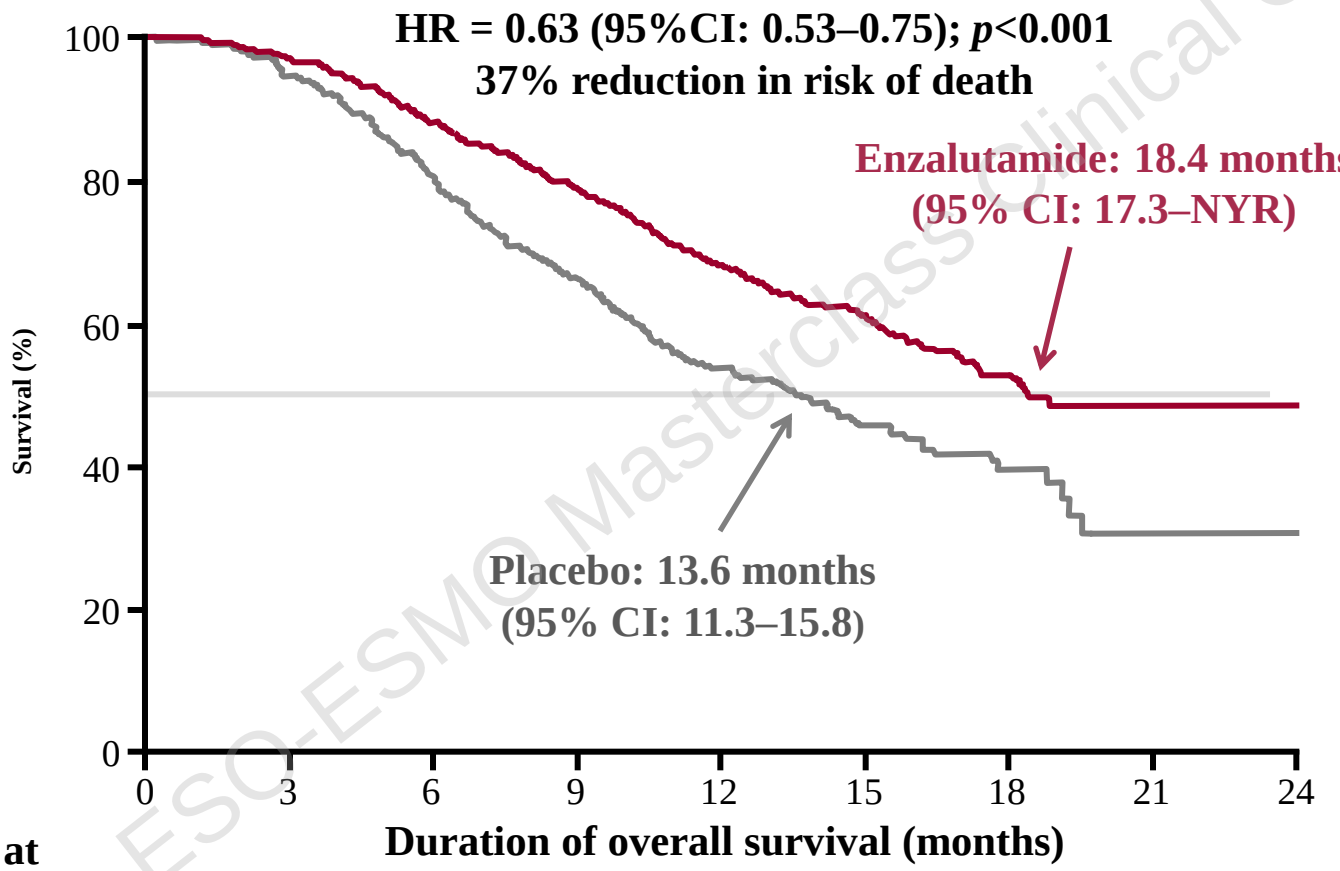
Fizazi K, et al. Lancet Oncol.2012;13:983–992
de Bono et al. N Engl J Med 2011; 346: 1995-2005

Enzalutamide: AFFIRM trial
Overall survival (Post-docetaxel)



4.8 month difference in median overall survival

Nº at risk:									
Enzalutamide, n =	800	775	701	627	400	211	72	7	0
Placebo, n =	399	376	317	263	167	81	33	3	0

Scher HI *et al*. *N Engl J Med* 2012; 367(13): 1187–1197.

CI, confidence interval;
HR, hazard ratio;
NYR, not yet reached

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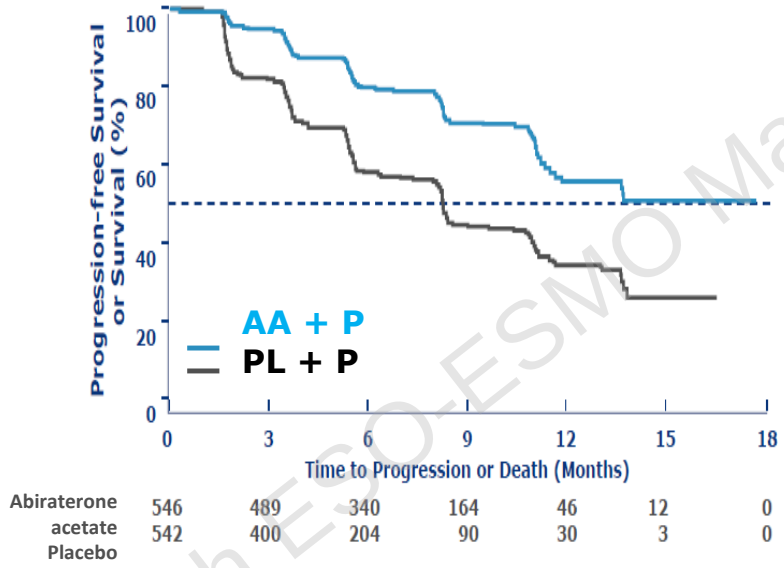
COU-302: Abiraterone in docetaxel-naïve CRPC patients

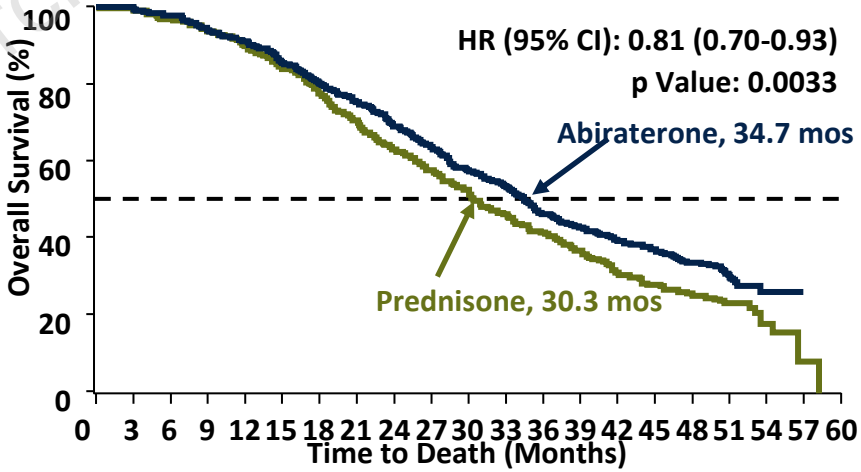
Radiographic progression-free survival (rPFS)

HR 0.43 (95% CI: 0.35–0.52; *P* < 0.0001)



Ryan C, *et al. N Engl J Med 2013*

Overall survival (Final analysis)



Ryan C *et al.*, *Lancet Oncol 2015*

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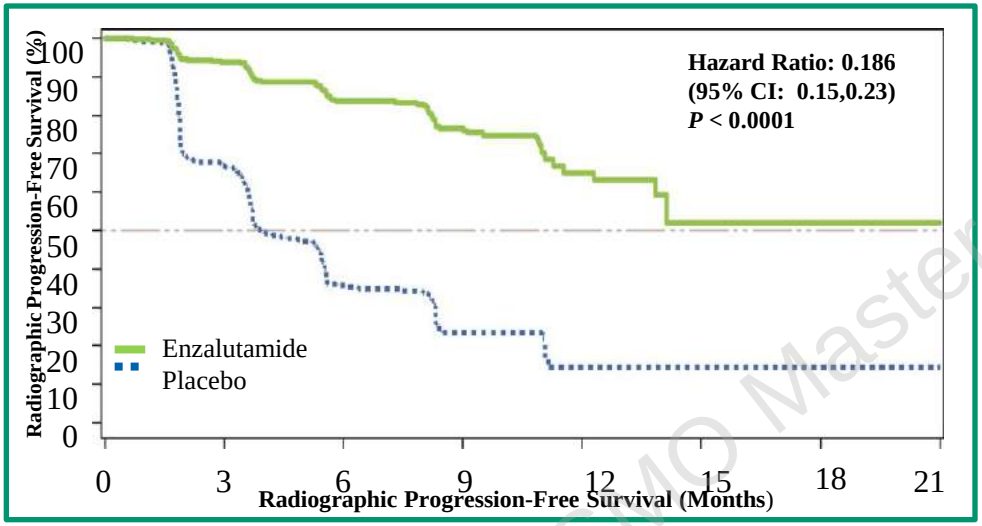
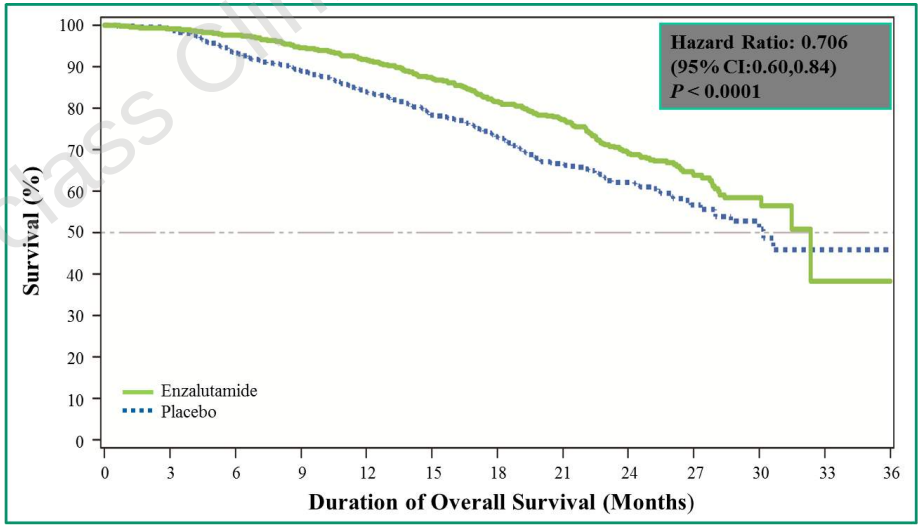
Prevail: Enzalutamide in docetaxel-naïve mCRPC patients

rPFS



OS



Beer T, N Engl J Med 2014

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Prevail: safety of Enzalutamide pre-docetaxel

	All Grades (%)		Grade ≥3 events (%)	
	Enzalutamide (n=871)	Placebo (n=844)	Enzalutamide (n=871)	Placebo (n=844)
Fatigue	35.6	25.8	1.8	1.9
Back pain	27.0	22.2	2.5	3.0
Constipation	22.2	17.2	0.5	0.4
Arthralgia	20.3	16.0	1.4	1.1
Cardiac AEs	10.1	7.8	2.8	2.1
Hypertension	13.4	4.1	6.8	2.3
ALT increased	0.9	0.6	0.2	0.1
Seizure	0.0†	0.1	0.0†	0.0

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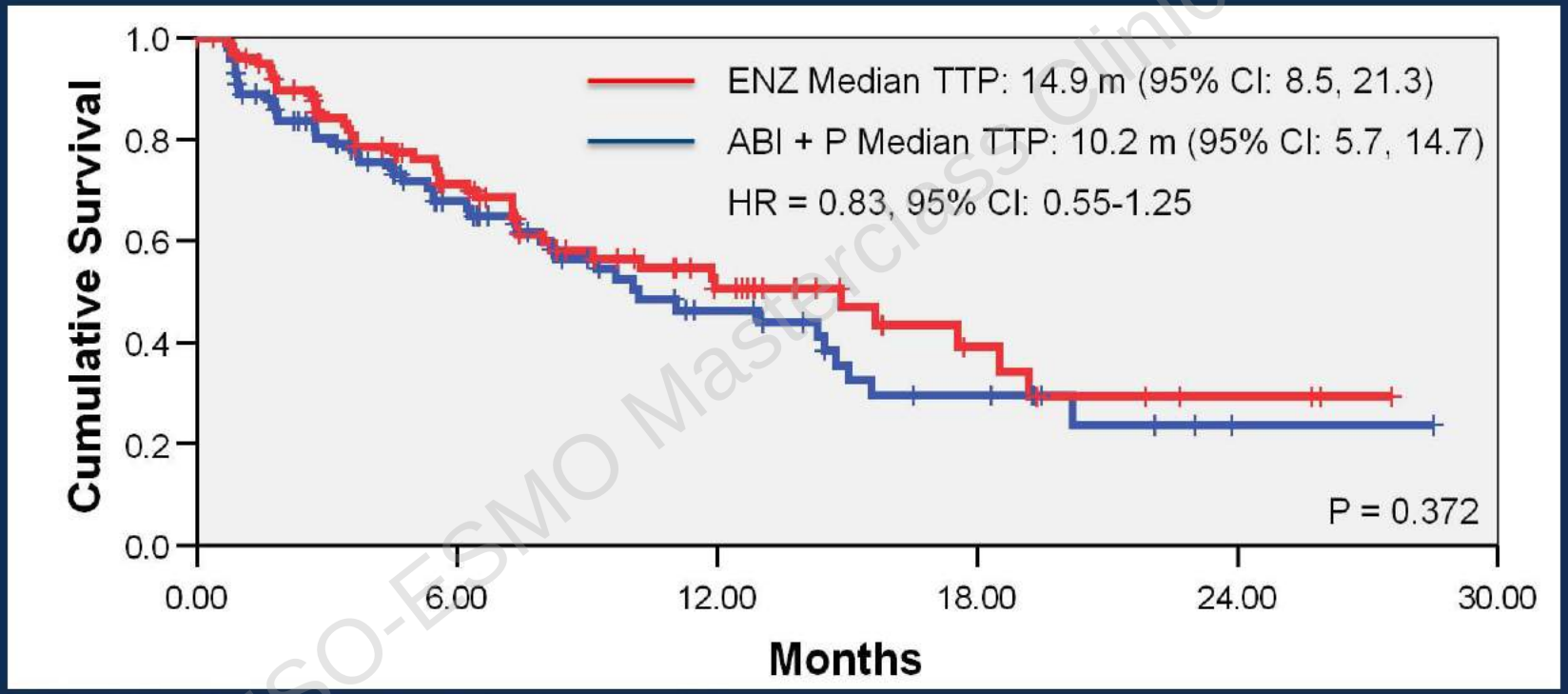
Abiraterone or Enzalutamide?

Time to PSA Progression (Confirmed)



*PCWG3: ≥ 25% and ≥ 2 ng/mL above nadir/baseline

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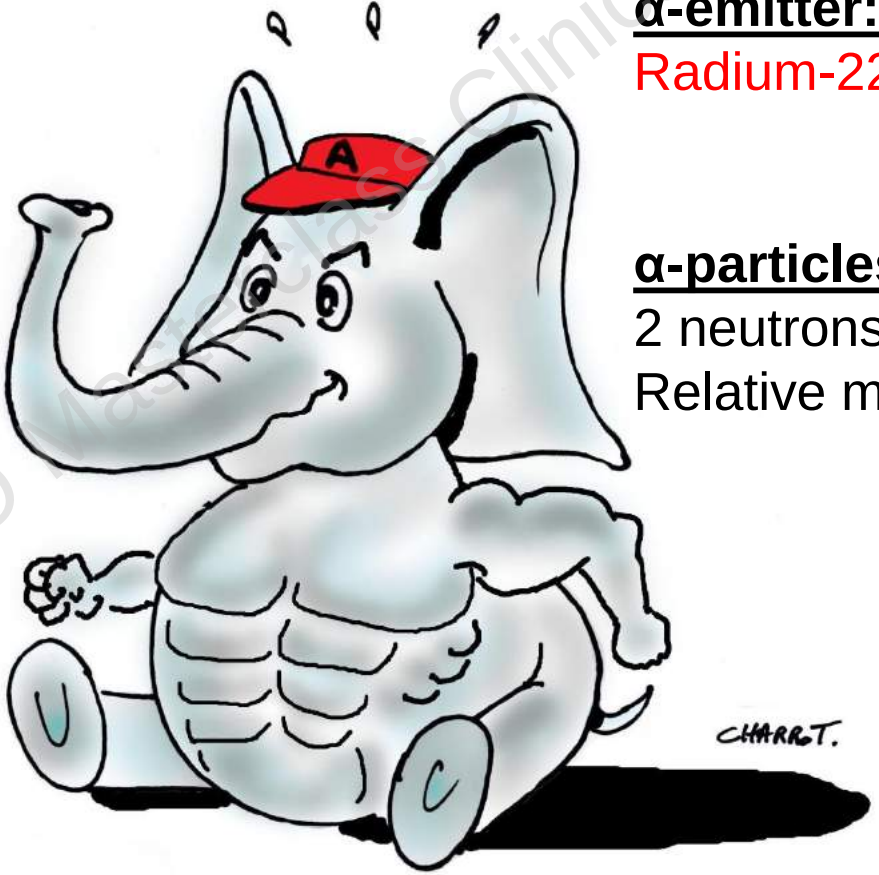
Presented By Kim Chi at 2017 ASCO Annual Meeting

Radiopharmaceuticals: α versus β-emitters

β-emitters:
Strontium-89
Samarium-153

β-particles:
1 electron
Relative mass: 1



α-emitter:
Radium-223

α-particles:
2 neutrons + 2 protons
Relative mass: 7000

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Cell killing and marrow penetration: Two advantages of α-emitters

Large molecule
+
High Linear Energy Transfer

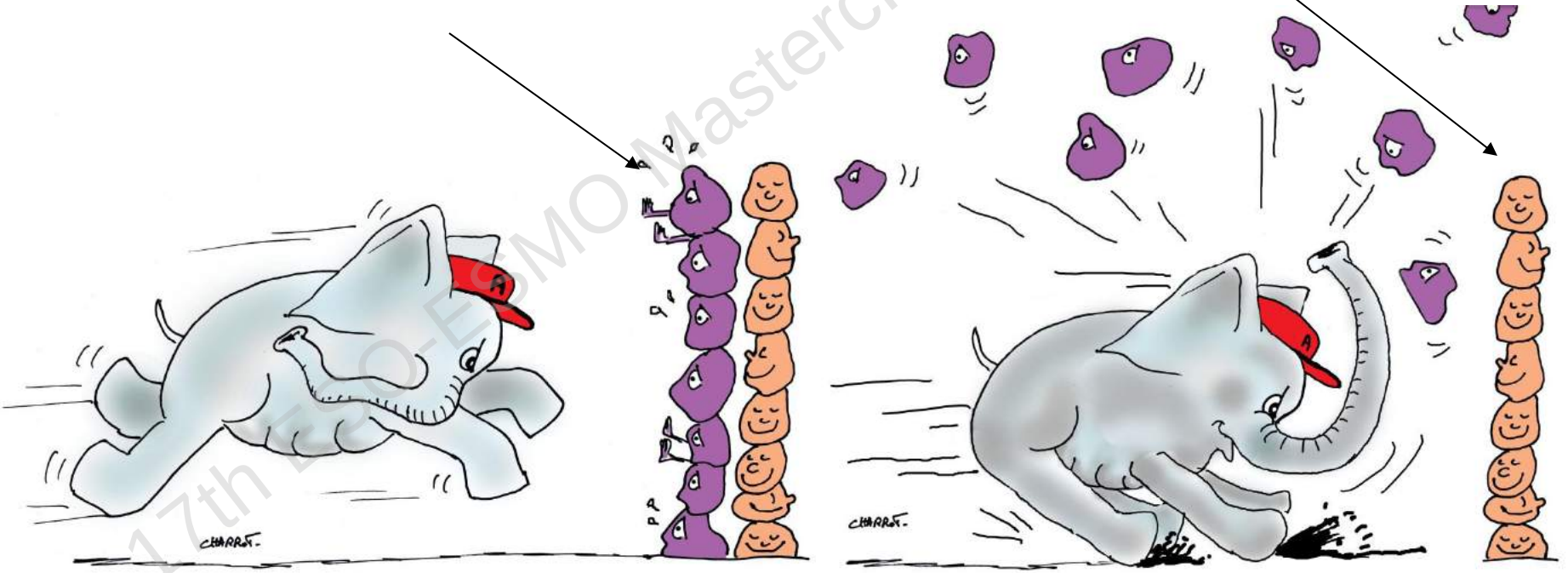
▼

More DNA double-strand breaks
In (cancer) cells

Low marrow penetration (≤100 µm)

⬇

Limited hematological toxicity



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Radium-223 phase III in mCRPC

- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

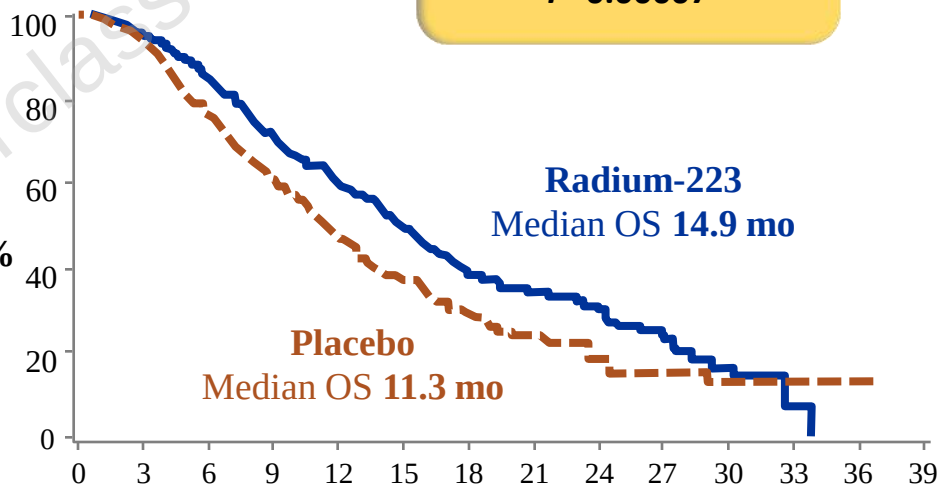
RANDOMISED 2:1

Radium-223 (50 kBq/kg)

Placebo (saline)

n=921

Hazard ratio 0.695
95% CI [0.581-0.832]
***P*=0.00007**



Parker C, N Engl J Med 2013

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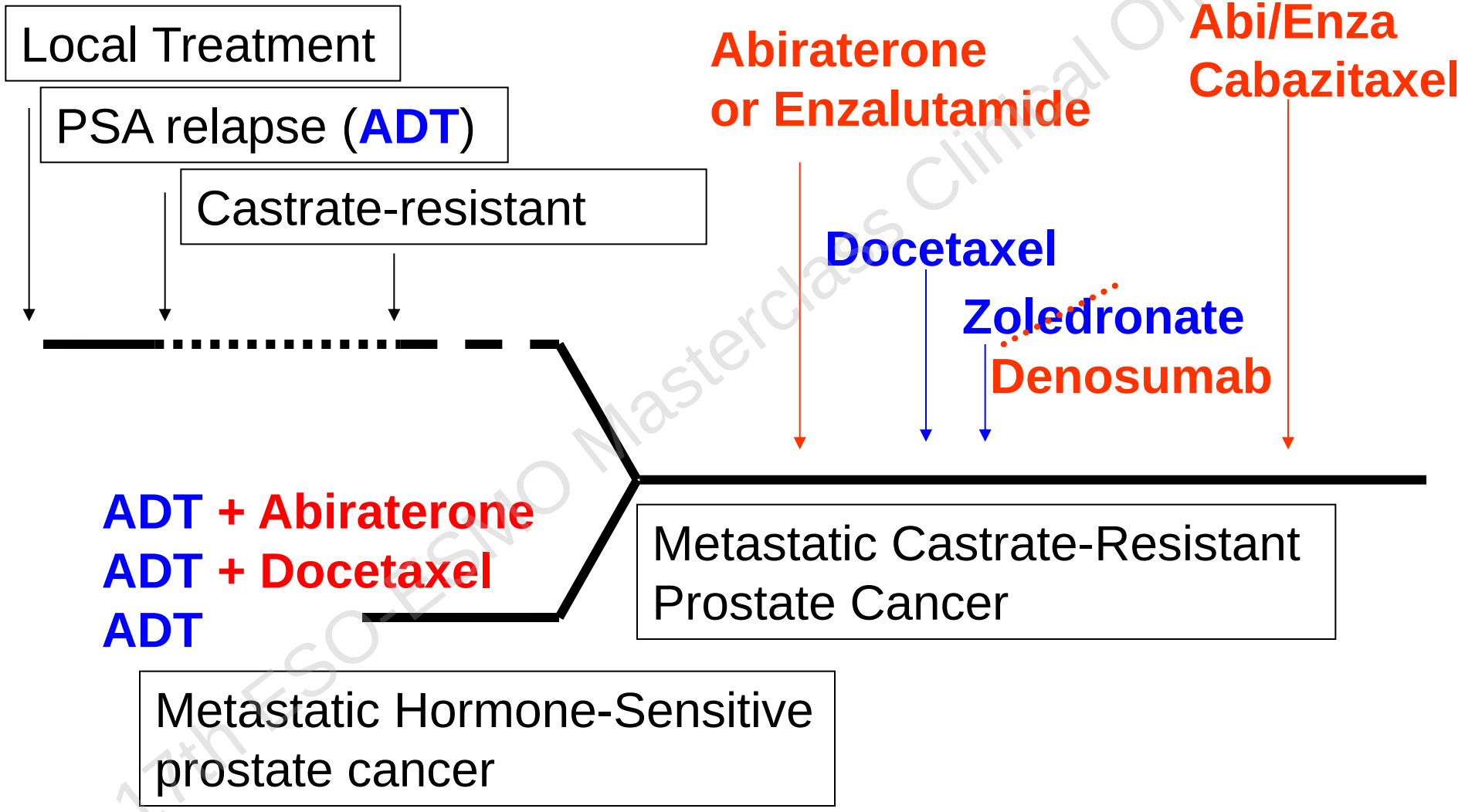
Systemic treatment for CRPC in 2018



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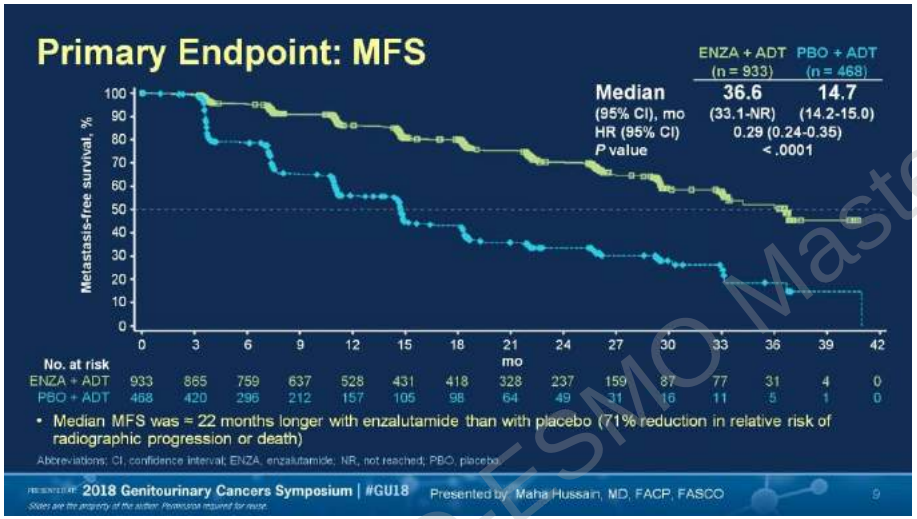
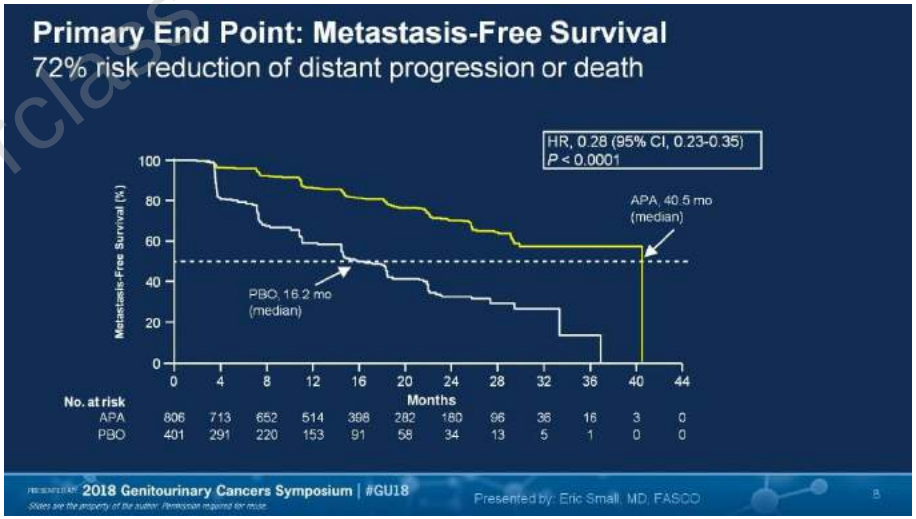
Non-metastatic CRPC: Metastases-Free Survival (MFS)

Enzalutamide (PROSPER)



Apalutamide (SPARTAN)



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Hussain M, ASCO GU 2018
Small E, ASCO GU 2018

CRPC pre-treated by abiraterone or enzalutamide:

How to treat?

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Cross-resistance between abiraterone and enzalutamide

Author	Year published	N pts	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
ENZ →ABI					
Loriot et al.	2013	38	3 mo	8%	2.7 mo
Noonan et al.	2013	30	13 wks	3%	3.6 mo
ABI → ENZ					
Schrader et al.	2013	35	4.9 mo	29%	-
Badrising et al.	2014	61	3 mo	21%	-
Bianchini et al.	2014	39	2.9 mo	23%	-
Schmid et al.	2014	35	2.8 mo	10%	-
Brasso et al.	2014	137	3.2 mo	18%	-

Zhang T et al. Expert Opin Pharmacotherap 2014;16:1-9

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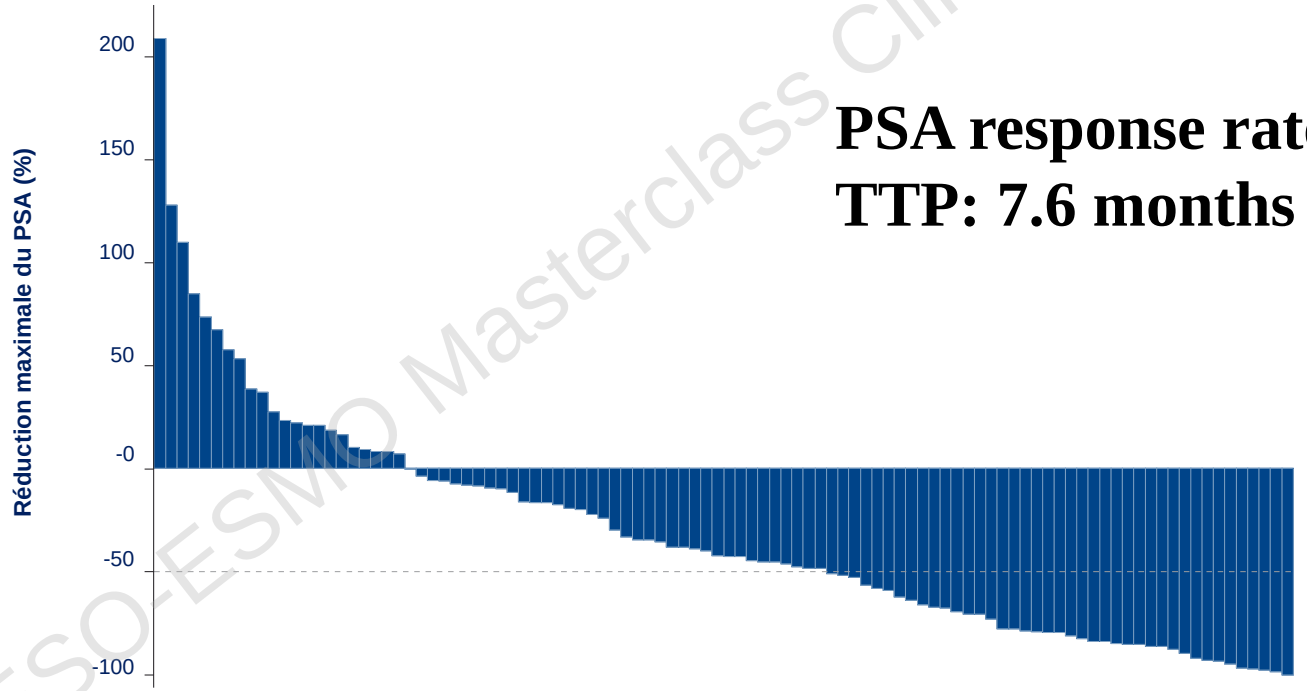
Docetaxel post-Abiraterone (COU-302)



PSA response rate=47%
TTP: 7.6 months

Flaig T, ASCO GU 2016
De Bono J, Eur Urol 2016

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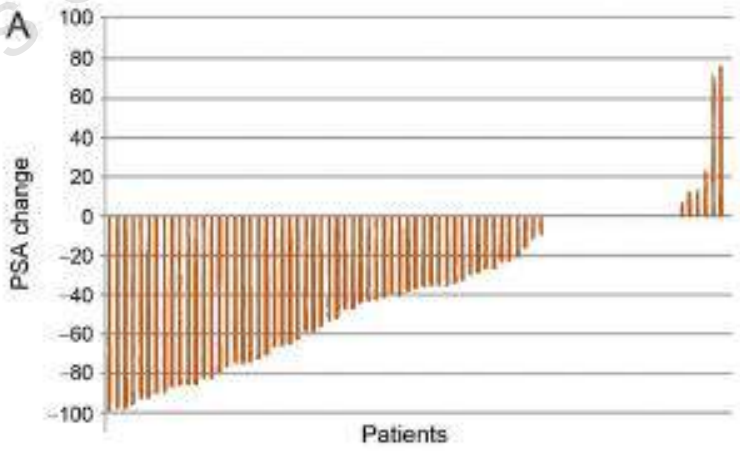
Cabazitaxel post-Abiraterone (and post-docetaxel)

- n=79 pts
- PSA response>30%: **62%**
- PSA response>50%: **35%**
- PFS: 4.4 mo
- OS: 11 mo
- *In vitro*: Caba active against both enza-S and enza-R cells

PSA response



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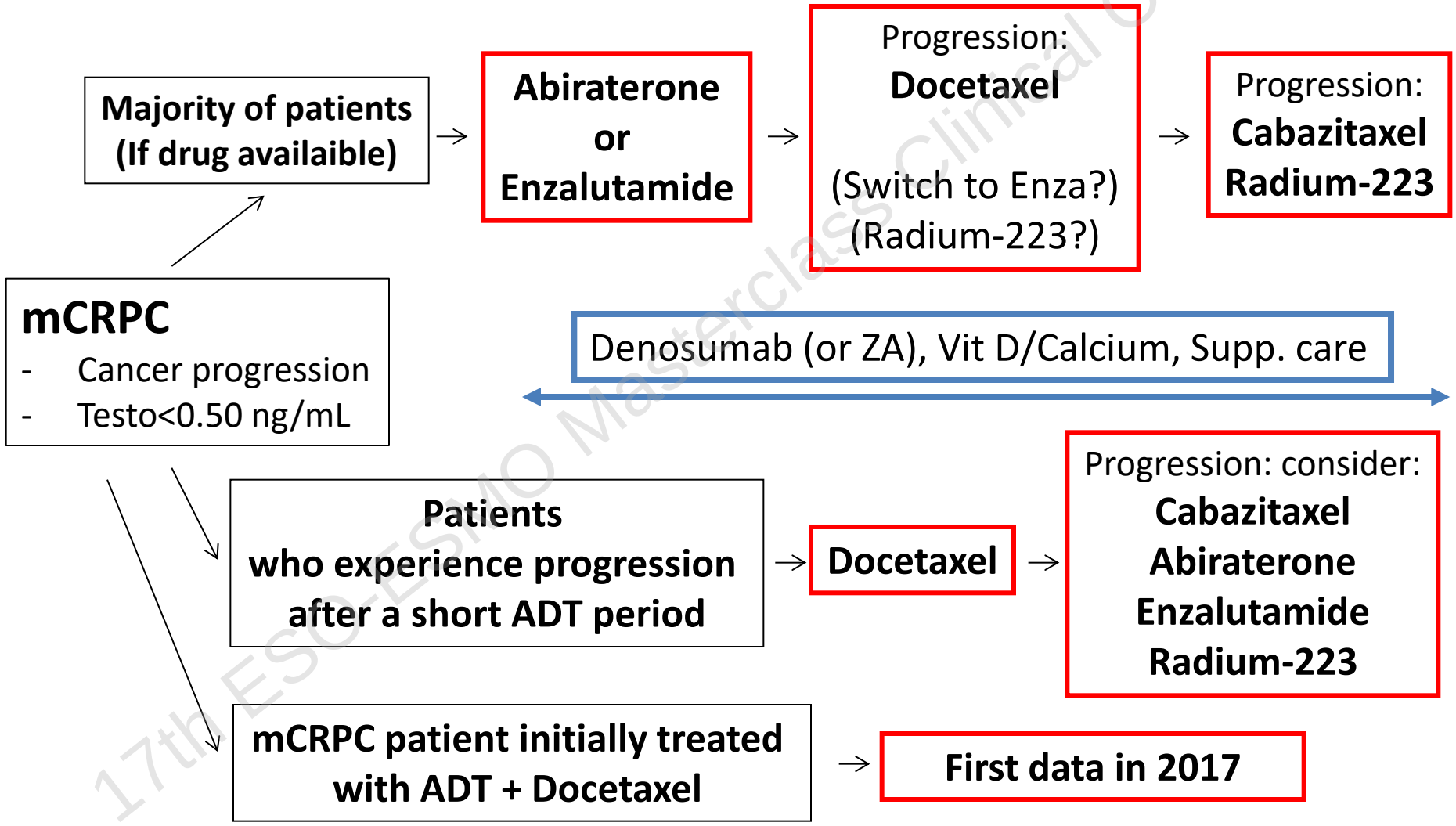
Al Nakouzi N, Eur Urol 2015; 68: 228-35

A proposed decision tree for metastatic CRPC (2018)



Fizazi K, Eur J Cancer 2016; 66: 125-130

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CRPC in a patient treated upfront with chemo-hormonal therapy for M1 disease:

How to treat?

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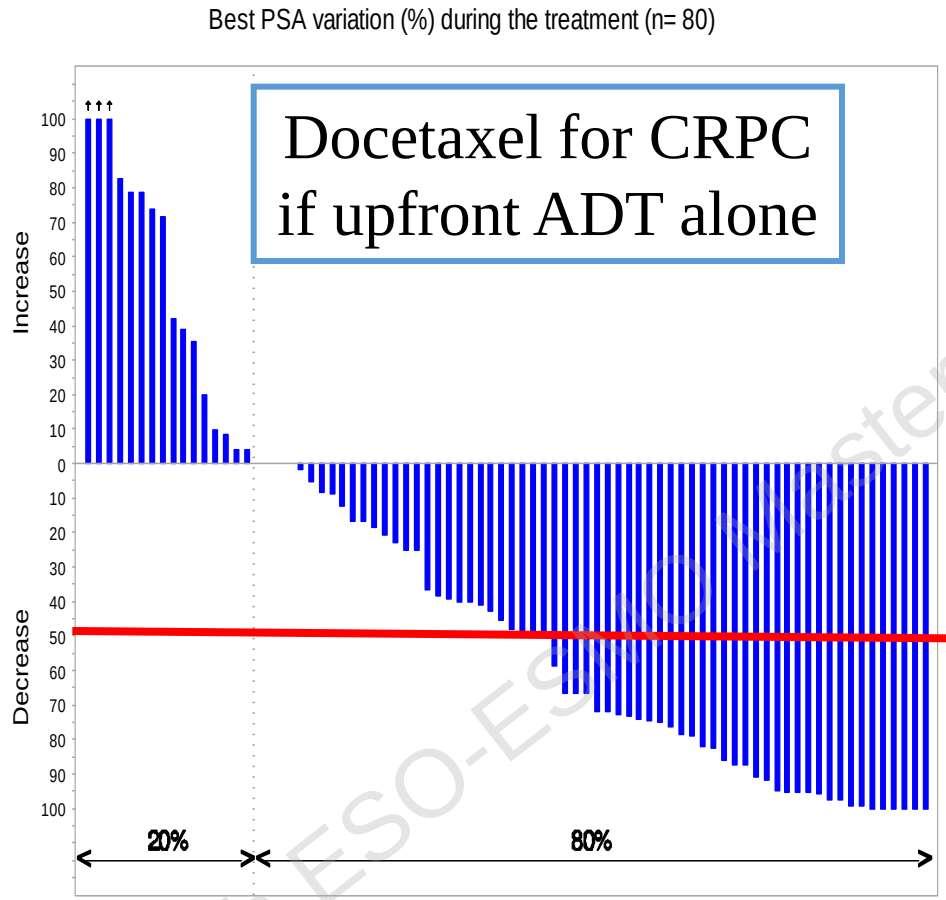
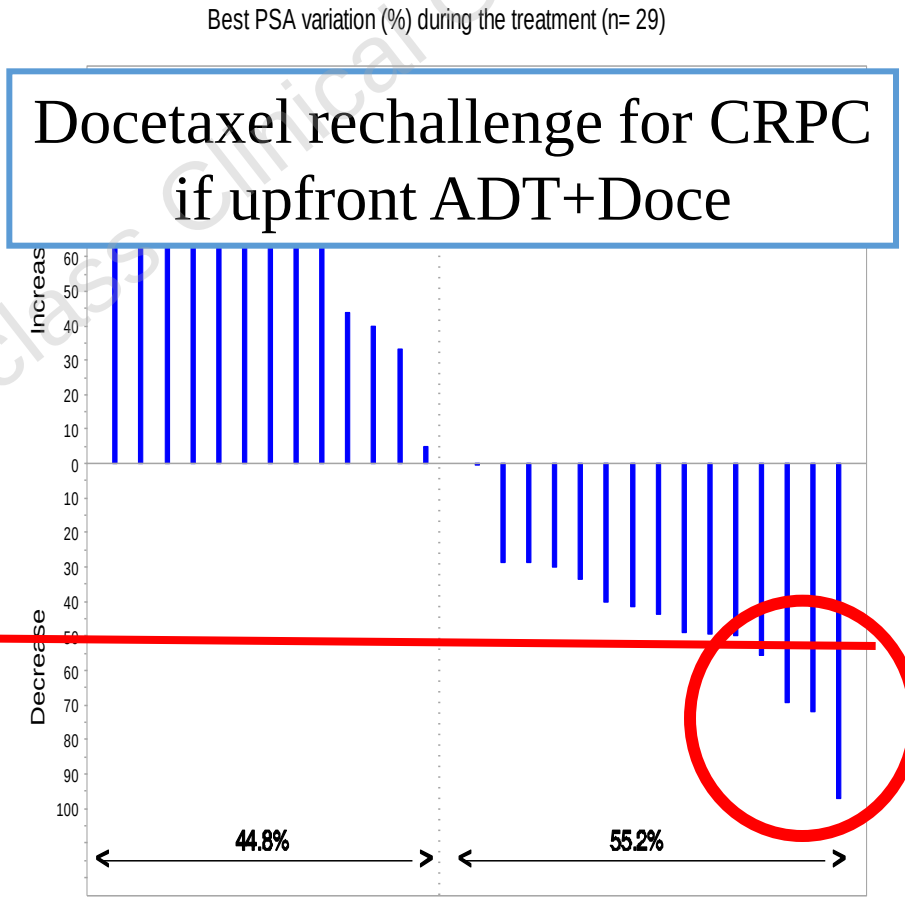
GETUG 15: PSA response for CRPC pts treated with docetaxel according to primary treatment for M1





Lavaud P, Eur Urol 2017

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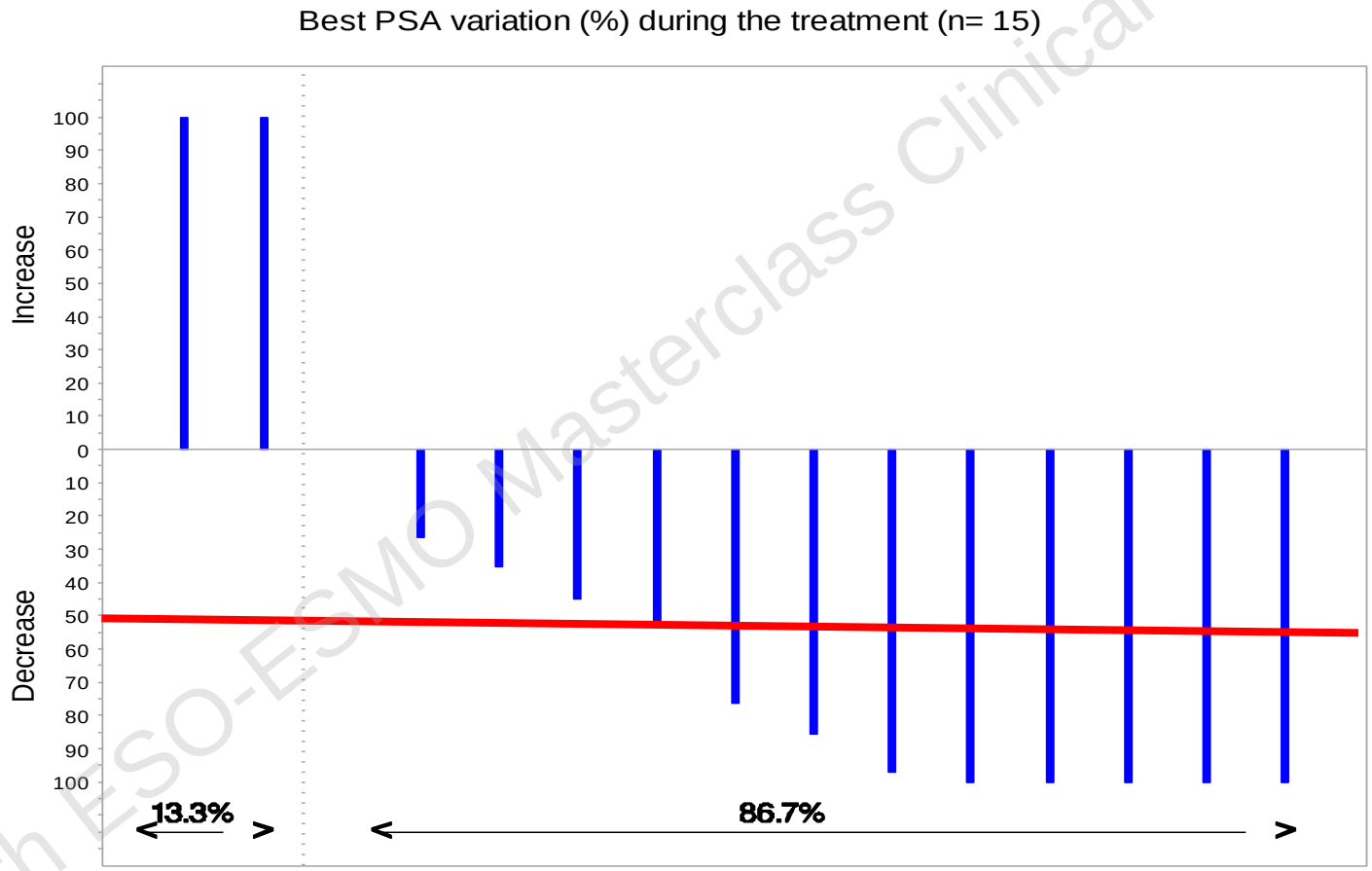
GETUG 15: PSA response for CRPC pts treated with abiraterone/enzalutamide when treated upfront with ADT+Docetaxel for M1



Lavaud P, Eur Urol 2017

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Should We Keep Using "Old" Hormonal Manipulations Before Using Next-generation AR-Targeting Drugs?

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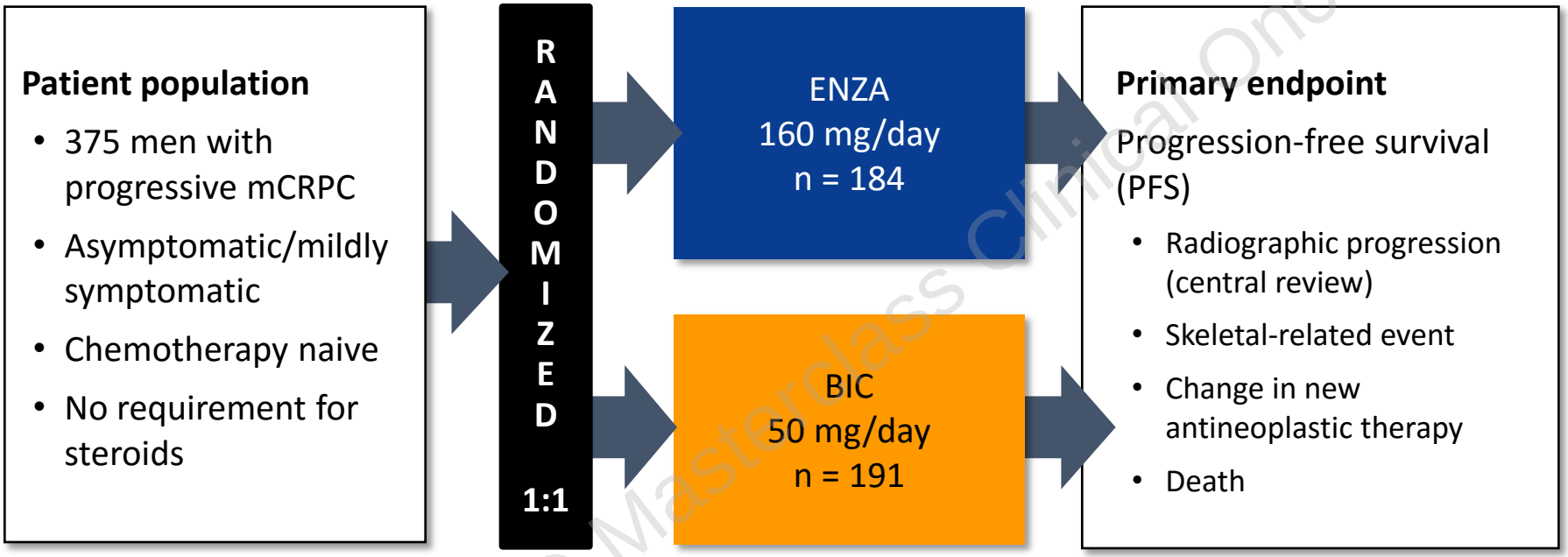
TERRAIN Study Design



TERRAIN trial: NCT01288911

Statistical design

- The final analysis was planned at ≥220 progression events with 85% power to detect a target hazard ratio of 0.67 (assuming a median PFS of 9 months vs 6 months[1])
- The data cutoff date was 19 October 2014, with 240 events for the primary efficacy endpoint

Secondary endpoints

- PSA response
- Time to PSA progression

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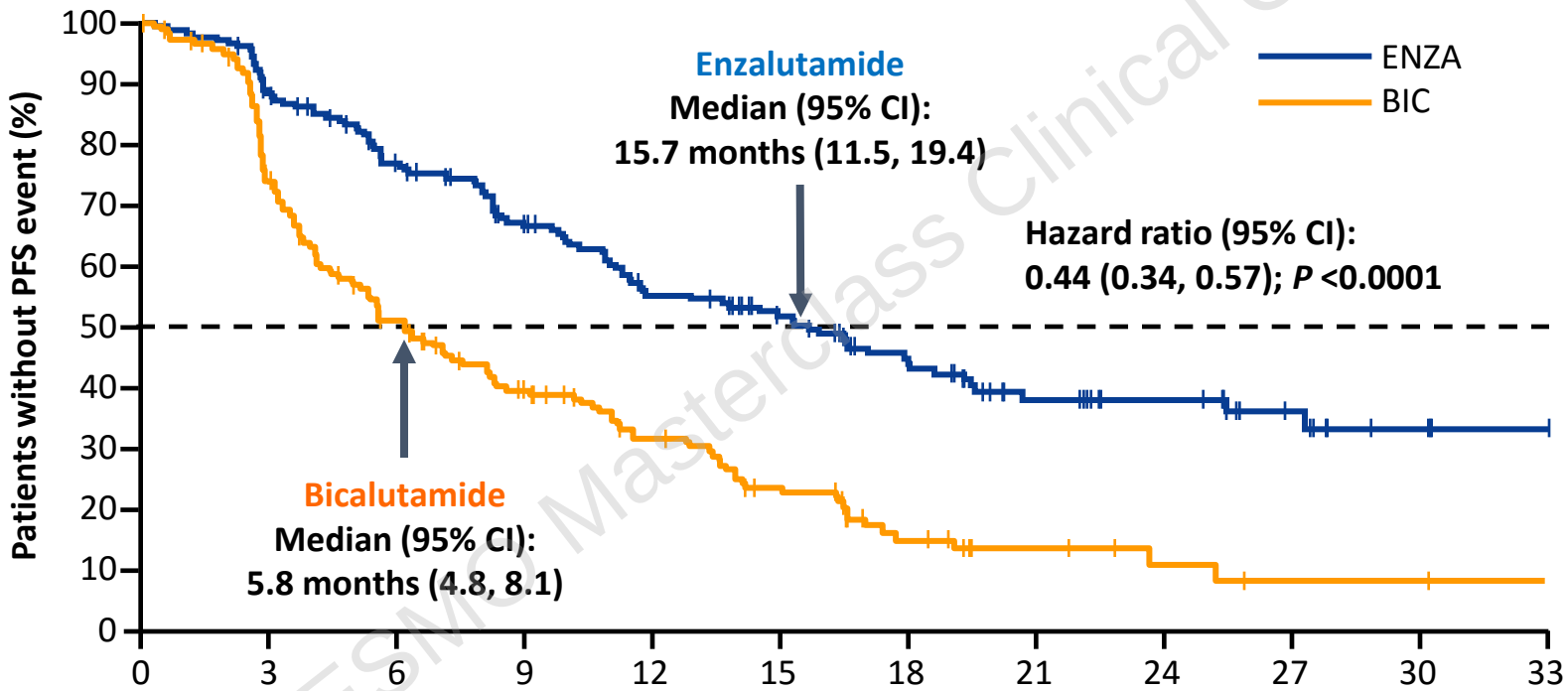
1. Kucuk O, et al. *Urology*. 2001;58:53-58.
Heidenreich A. EAU 2015. Abstract 234.

Progression-Free Survival in TERRAIN



ENZA												
Patients at risk	184	159	131	107	86	71	52	33	21	13	8	5
BIC												
Patients at risk	191	133	85	61	44	30	13	7	4	2	2	1

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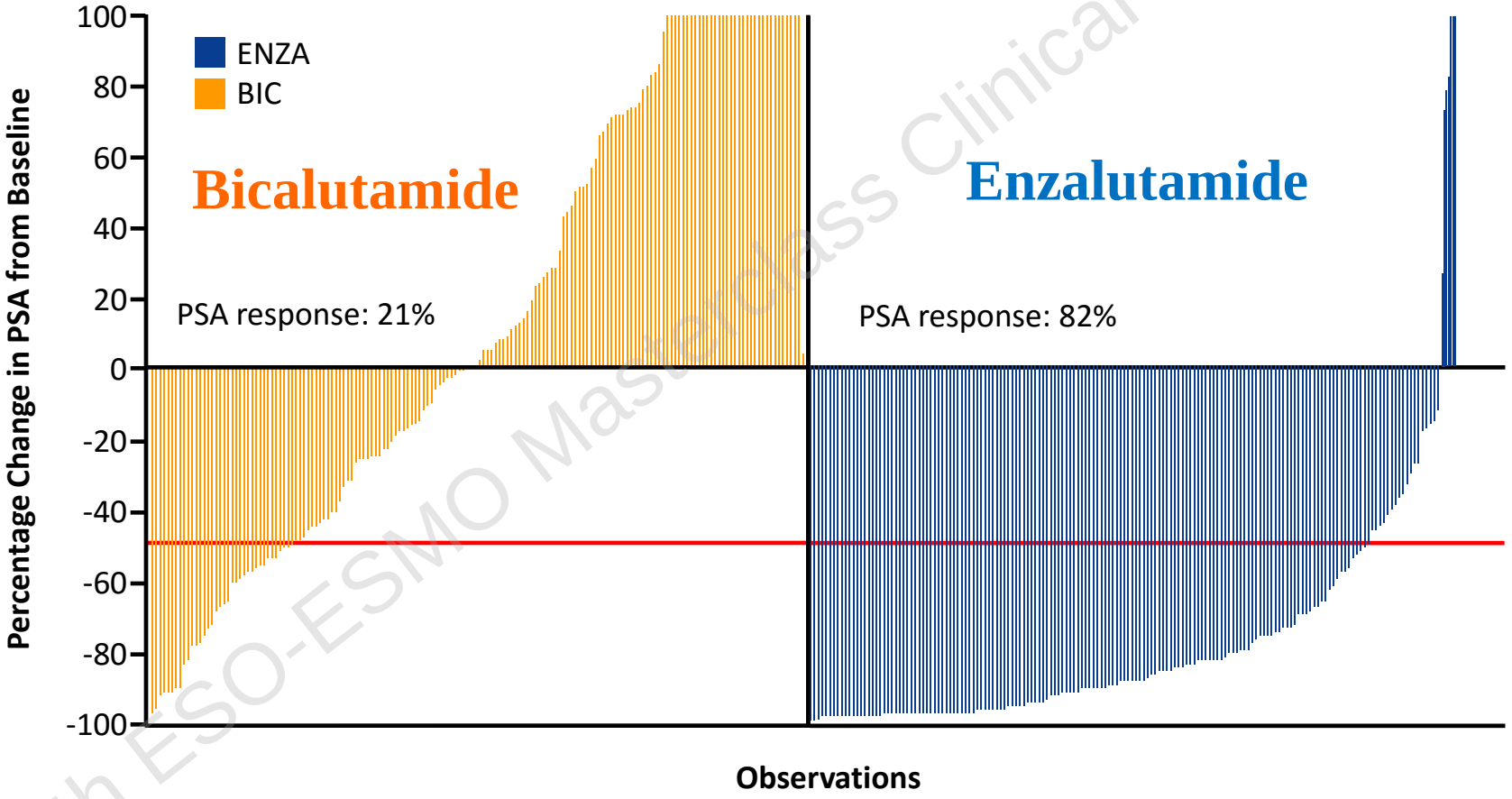
Shore N, Lancet Oncol 2016; 17: 153-163

PSA Response by Week 13 with ENZA or BIC



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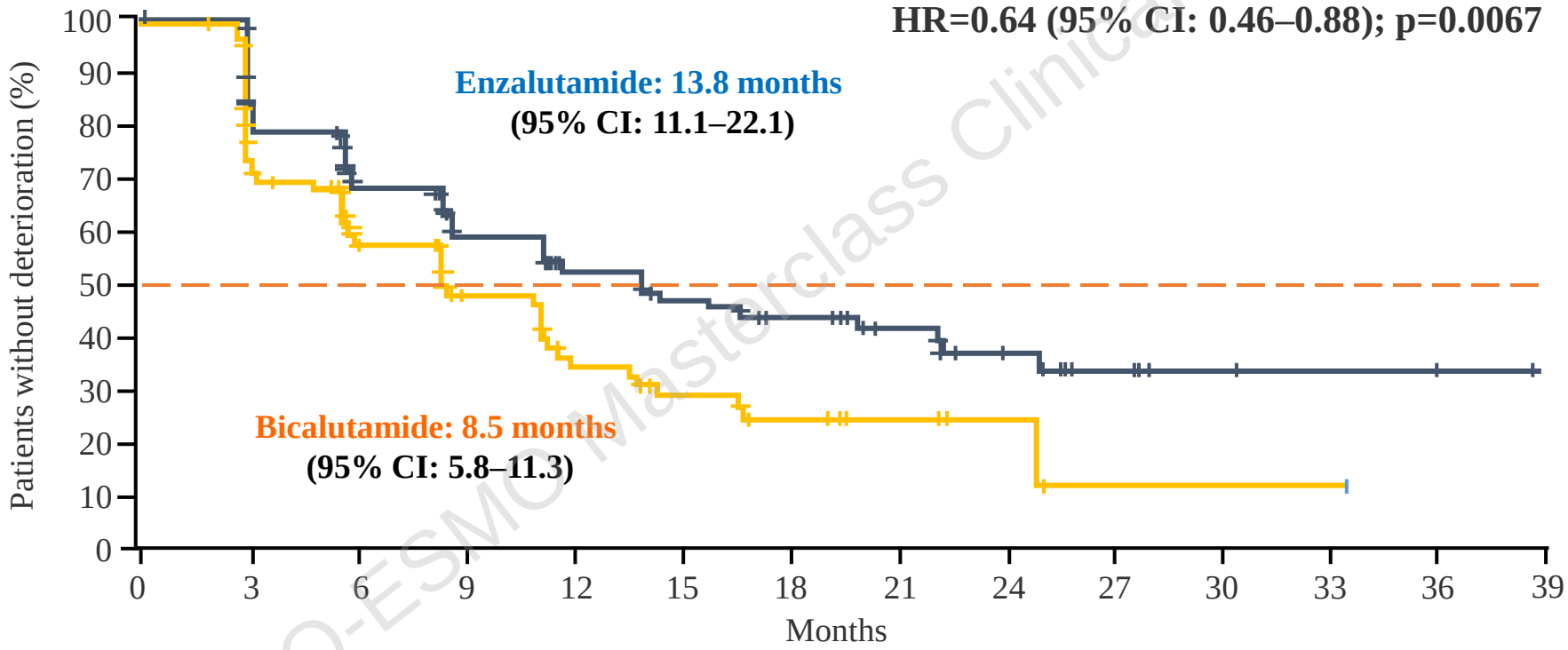
Shore ND, Lancet Oncol 2016: 17: 153-63

Enzalutamide or bicalutamide? TERRAIN: Quality of life (Time to FACT-P deterioration)



Enzalutamide, n	184	121	91	71	55	45	33	19	12	6	3	2	1	0
Bicalutamide, n	191	88	50	30	20	15	10	6	4	1	1	1	0	0

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CI=confidence interval; HR=hazard ratio; FACT-P=Functional Assessment of Cancer Therapy – Prostate.

Shore N, *et al.* AUA 2015; Oral presentation PII-LBA4.

New drugs to come for CRPC?

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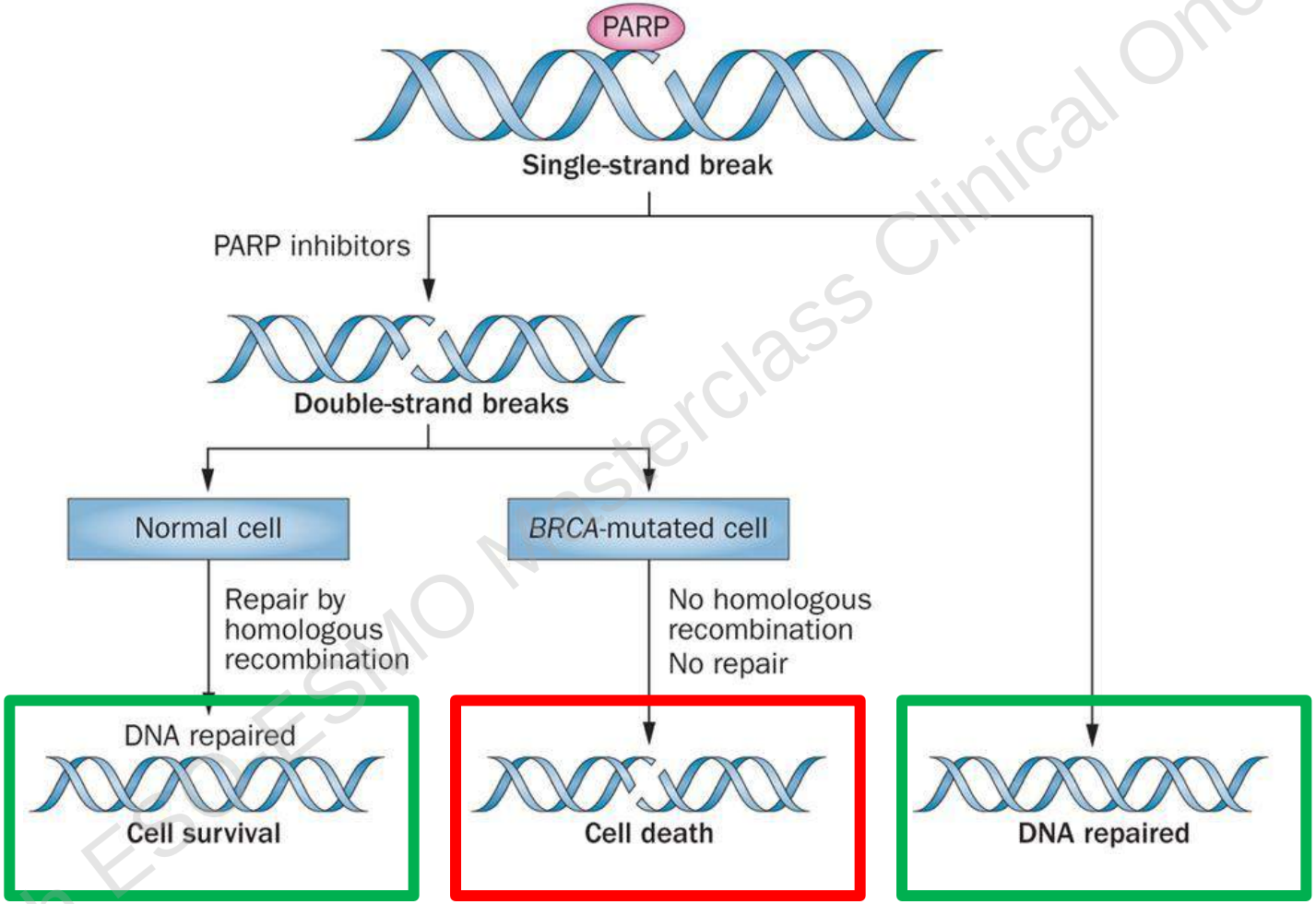
BRCA-related synthetic lethality with PARP inhibition



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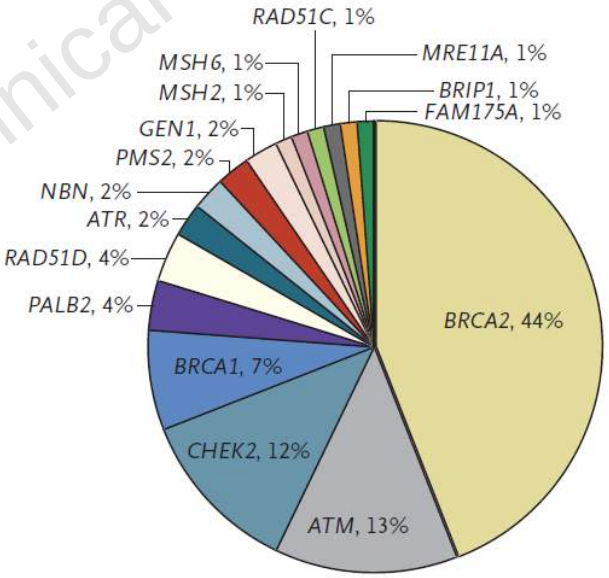
Sonnenblick et al. Nature Reviews Clinical Oncology 2015; 12: 27–41

DNA repair and prostate cancer

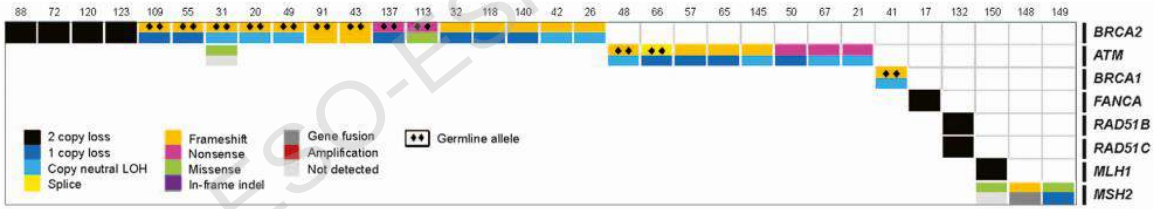
<u>Germline</u> DNA repair mutations:

- **12%** in men with M1 prostate cancer
- 5% in men with localized CaP
- 3% general population



<u>Somatic</u> DNA repair mutations:

- **10%** in men with mCRPC?



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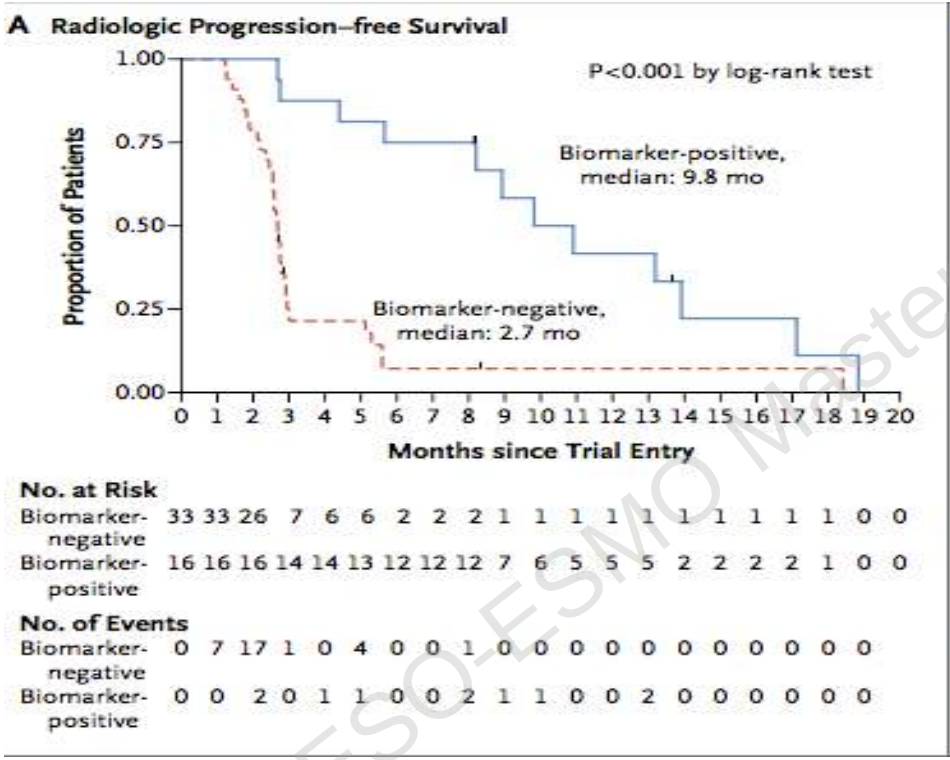
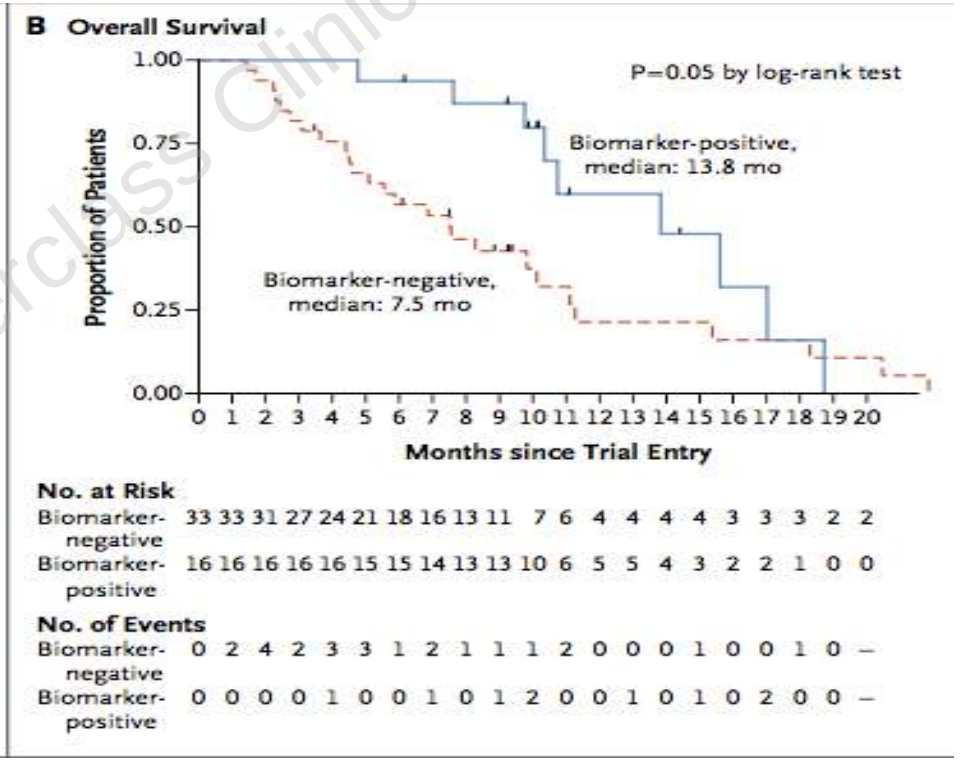
Pritchard CC, NEJM 2016: 375: 443-53
Robinson D, Cell 2015; 162: 454

Olaparib: activity is predicted by DRD gene mutations





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Mateo, N Engl J Med 2015;373:1697-708.

PARP inhibitors in CRPC

- 4 compounds currently in trials (P2-3):
  - Olaparib
  - Niraparib
  - Rucaparib
  - Talazoparib
- Patient selection:
  - Tumor sample vs ctDNA?
  - Monoallelic vs Biallelic?
  - Are all gene mutations the same?
  - Germline vs somatic mutations?

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Prostate specific membrane antigen (PSMA)

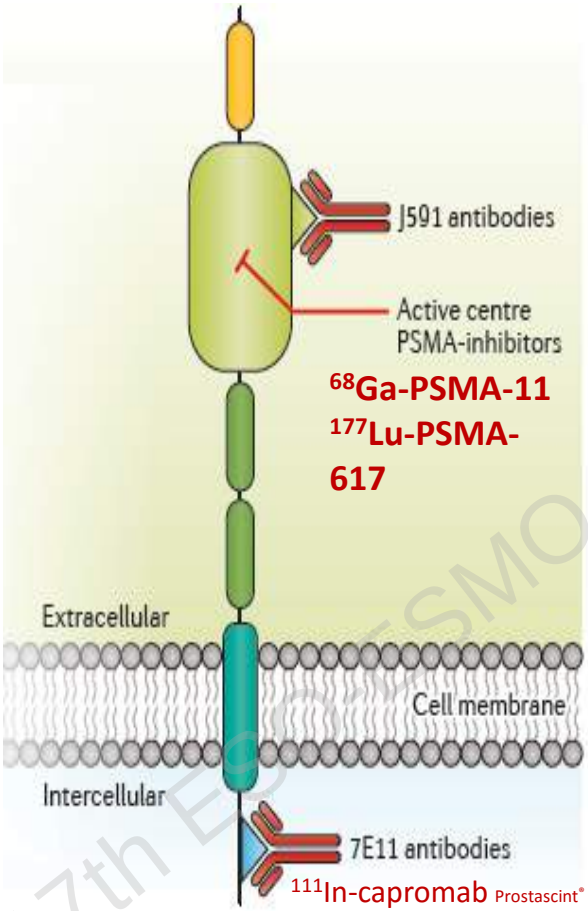
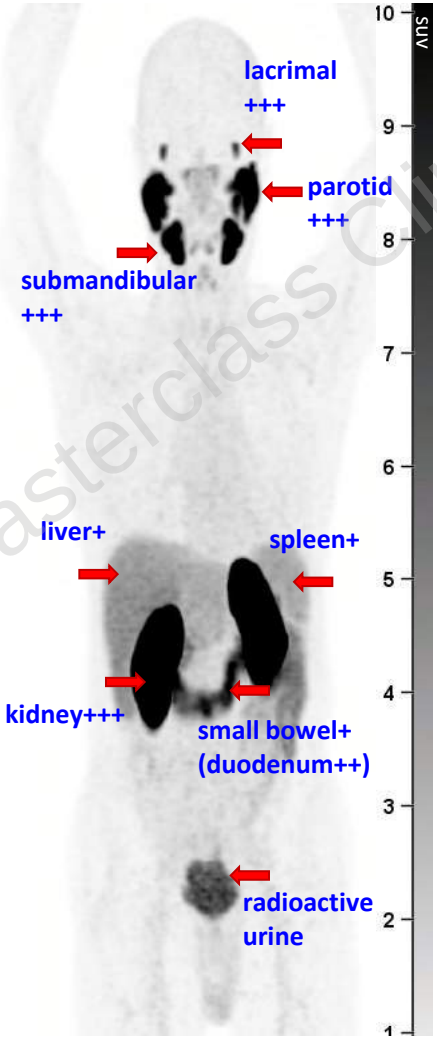


Image from Maurer T et al. Nat Rev Urol, 2016 Apr;13(4):226-35



PSMA PET
normal biodistribution

- Type II transmembrane glycoprotein (FOLH1)
- Highly over-expressed in prostate cancer
- ↑↑ castrate-resistant metastatic disease

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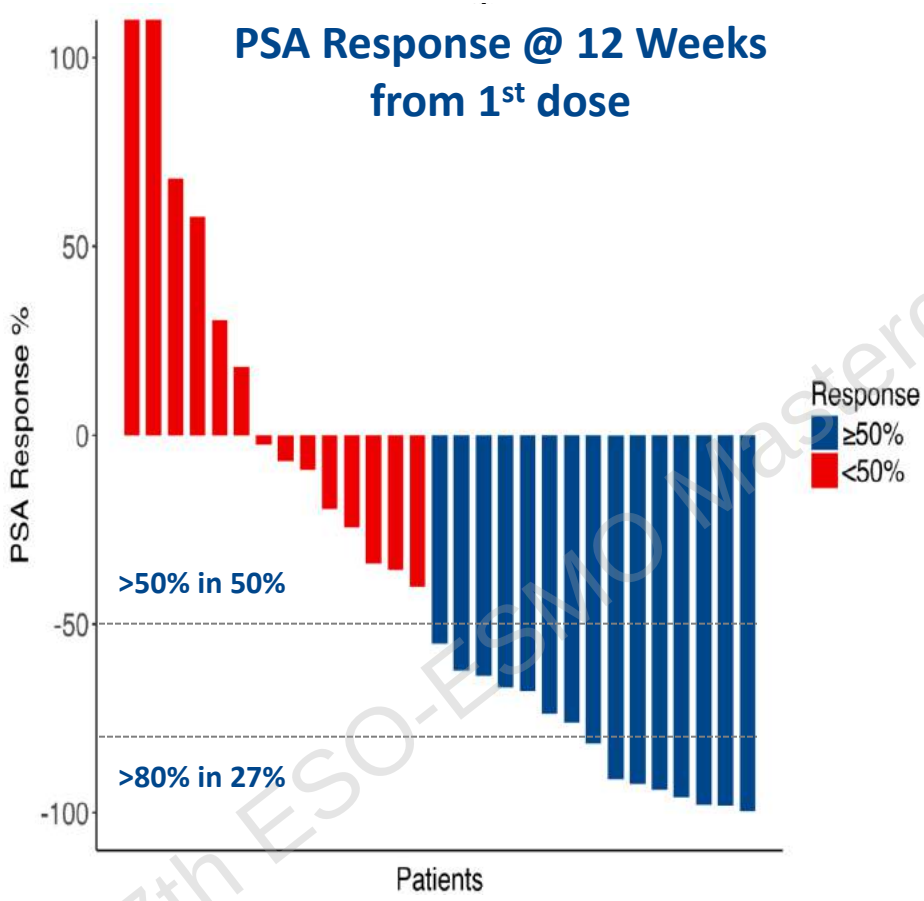
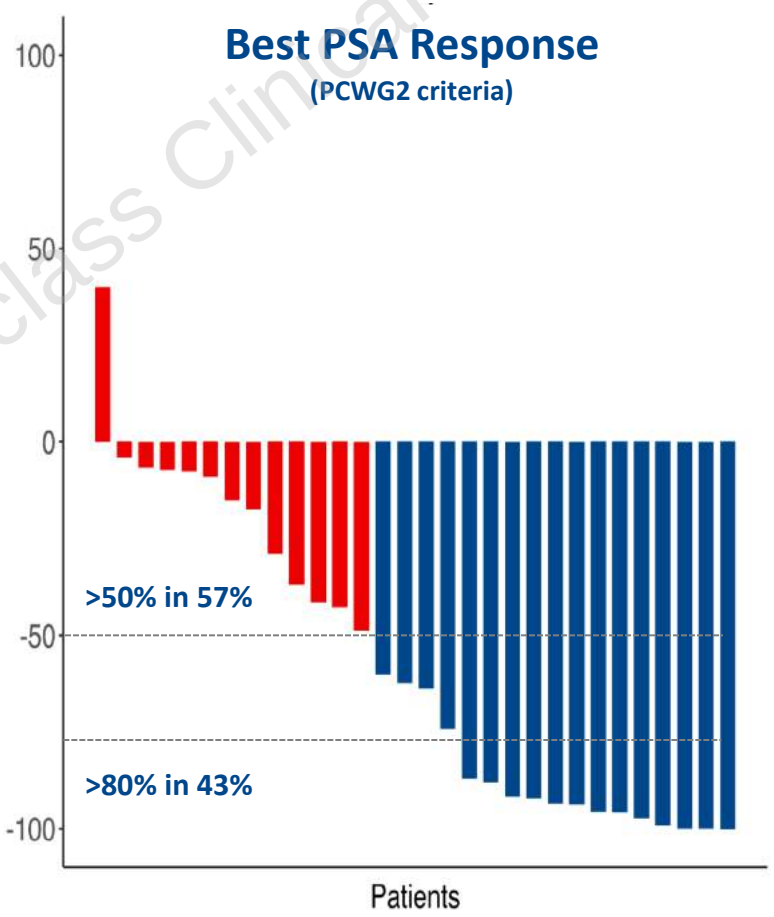
^{177}LU-PSMA-617: 1º ENDPOINT: PSA RESPONSE





Hofman MS, ESMO 2017

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Pembrolizumab + continuous Enzalutamide in Enzalutamide-progressing CRPC

Responder	Cycle 1	PSA (ng/ml) every 3-weeks and nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI
1	April 2015	**70.65** → 11.11 → 1.18 → 0.11 → **0.08**	Yes (lymph)	PR	present
2	October 2015	**46.09** → 41.22 → 12.99 → 9.89 → **0.02**	No	n/a	n/a
3	January 2016	**2502.75** → 1.26 → 0.07 →0.01 → **<0.01**	Yes (liver)	PR	absent
4	March 2016	**82.43** → 17.34 → 0.3 → **0.01**	No	n/a	n/a
5	June 2016	**250** → 88.69 → 5.1 → 0.43 → **0.18***	Yes (liver)	PR	pending

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Graff JN, ESMO 2016

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Conclusion

- Sequential treatment still routinely used in 2017 for CRPC; Combination experimental
- Cross-resistance between Abiraterone and Enzalutamide (20% responders)
- Taxanes still active after abi/enza
- Biomarkers clearly emerging (AR-V7, DRD, PTEN loss)
- Immunotherapy works: let's prove it!

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Thank you !

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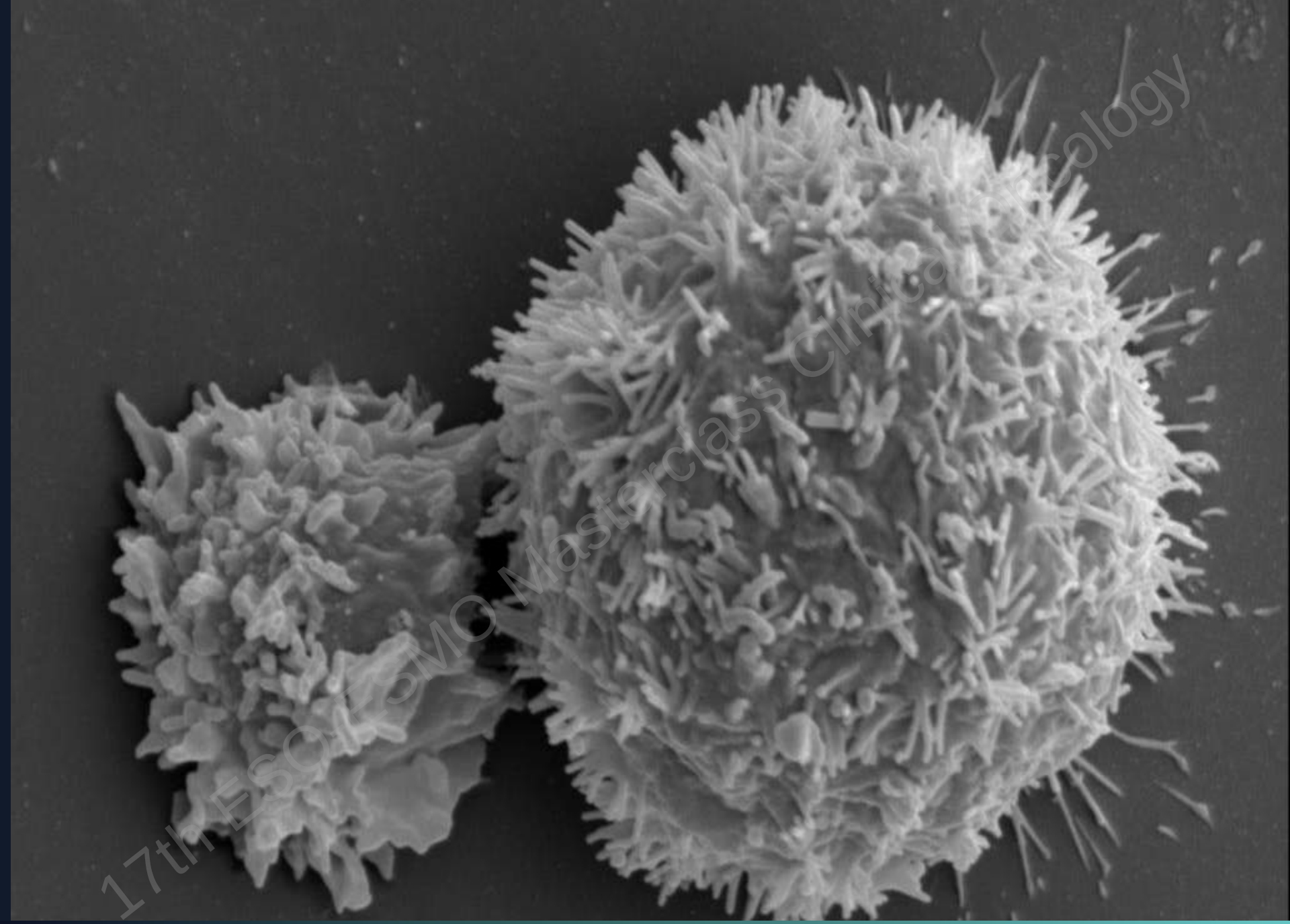
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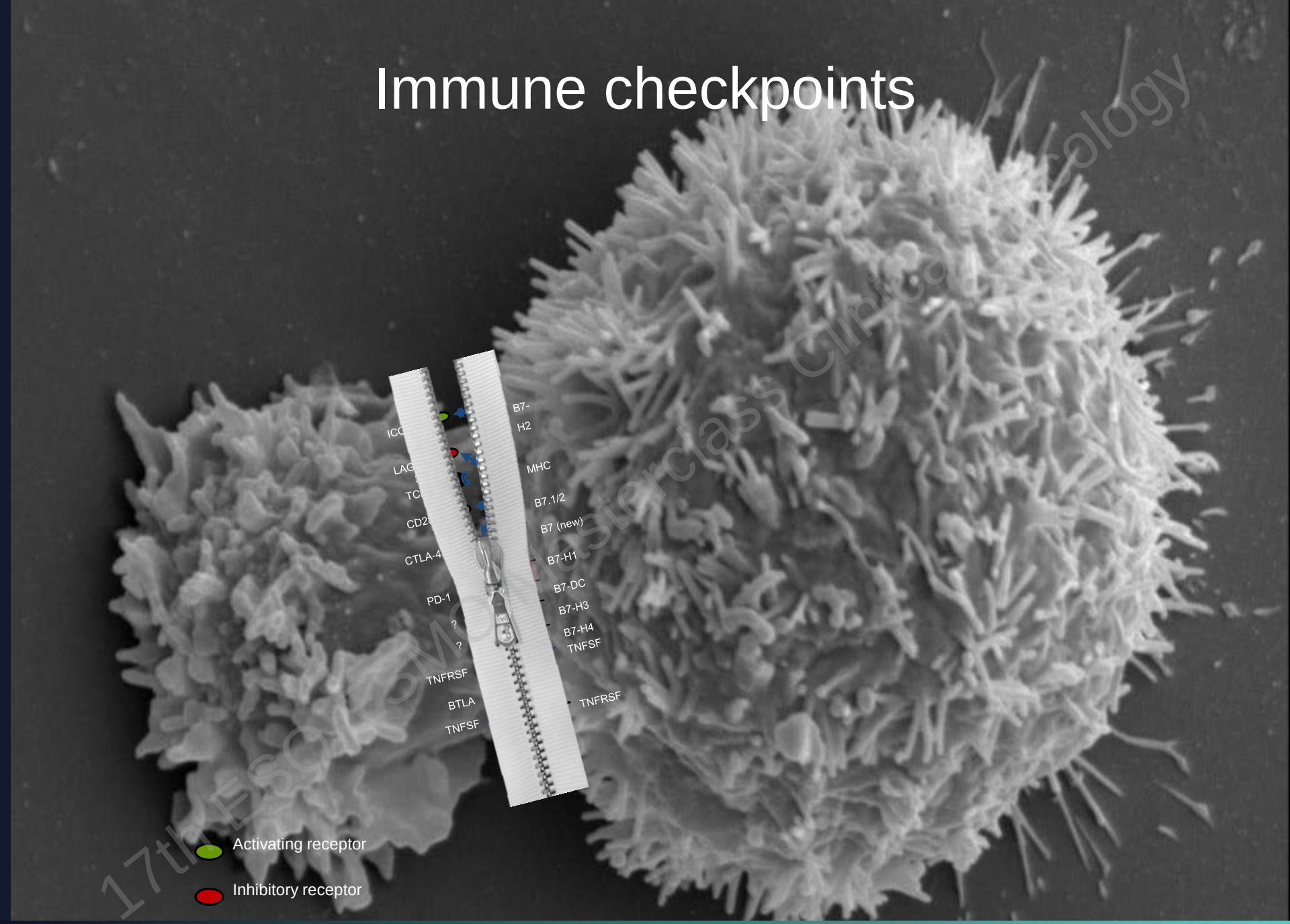
Immune checkpoints



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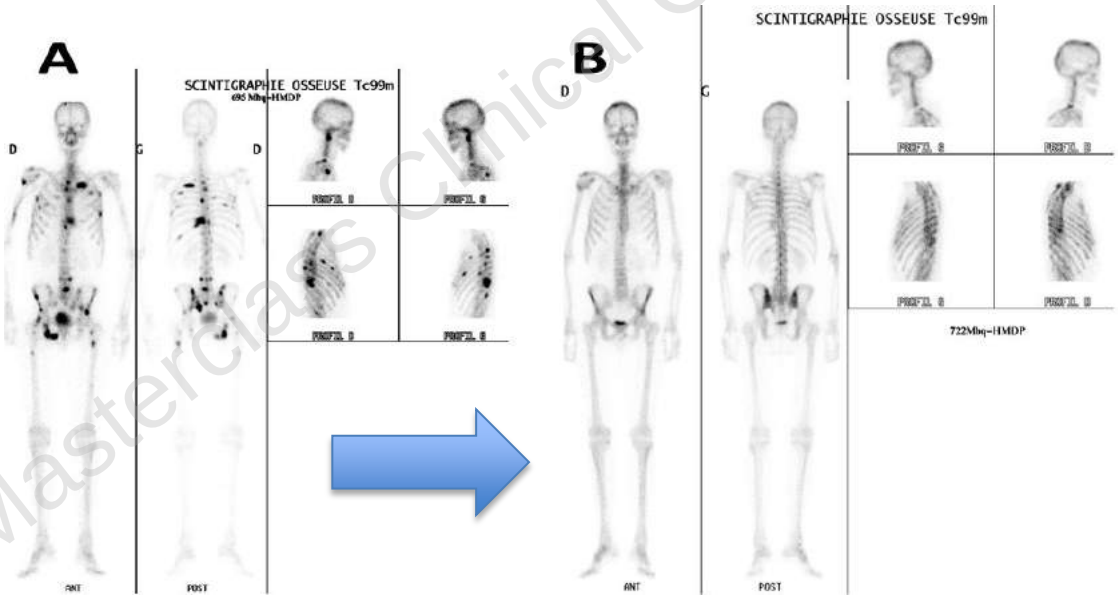
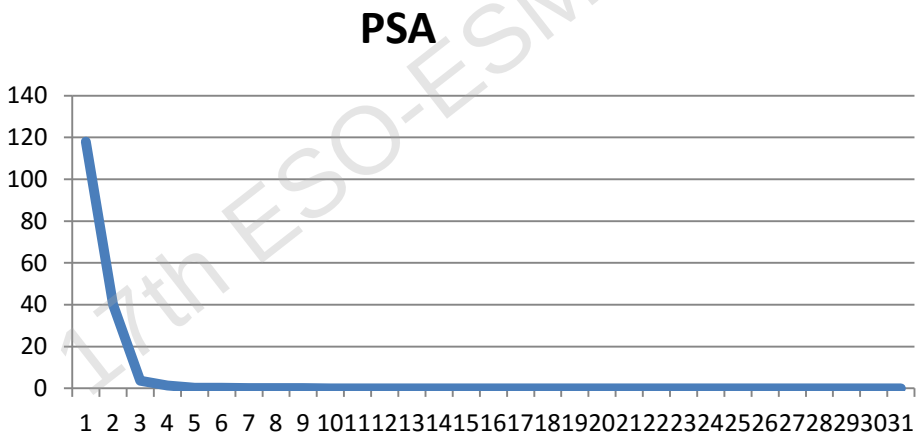
Long-lasting complete response after Ipilimumab in CRPC

2011:
mCRPC progressing post-docetaxel
Pain requiring opioids
Ipilimumab + RXT to 1 bone

2016:
No detectable disease at 5 years+





Cabel L, J Immunother Cancer 2017; 5: 31

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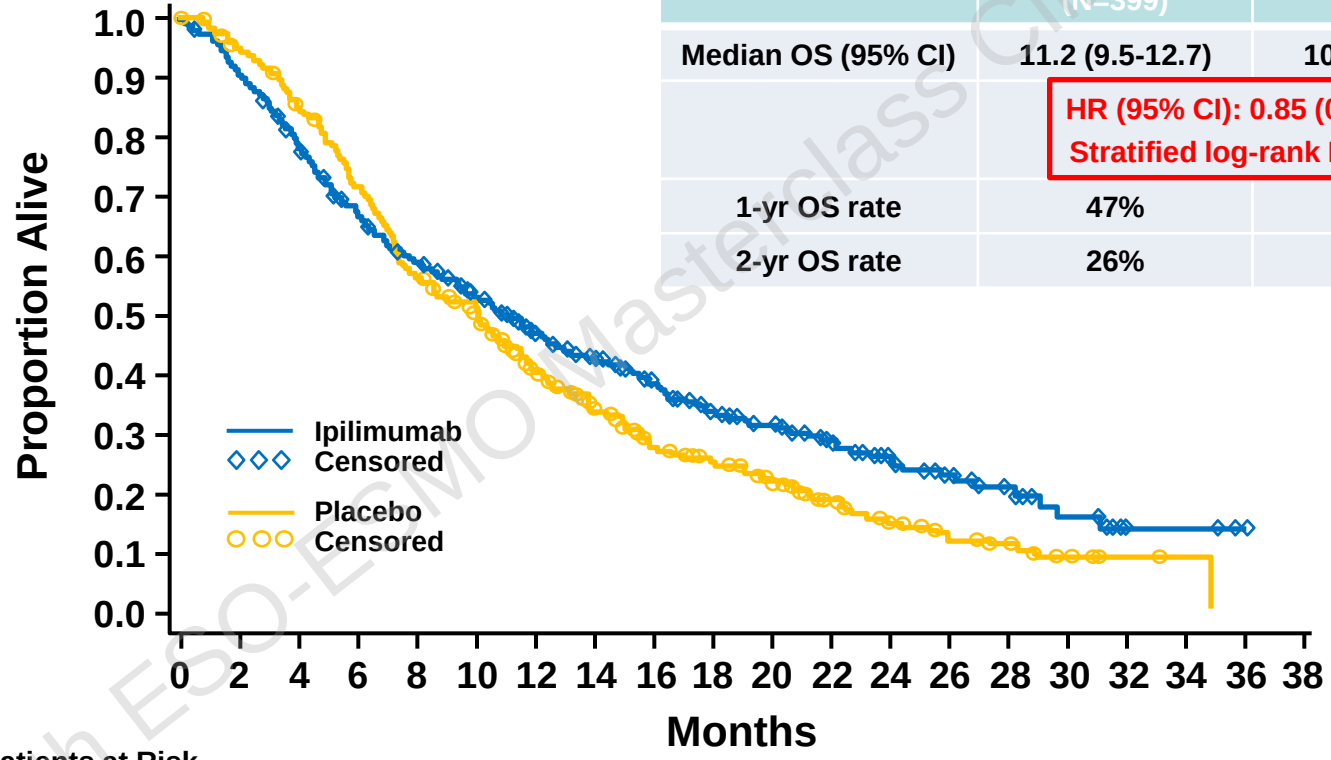
Ipilimumab vs Placebo in post-docetaxel CRPC: Overall Survival

	Ipilimumab (N=399)	Placebo (N=400)
Median OS (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank P=0.0530	
1-yr OS rate	47%	40%
2-yr OS rate	26%	15%



Patients at Risk

Ipilimumab	399	362	306	260	228	195	155	131	106	85	69	52	37	24	15	9	4	3	1	0
Placebo	400	376	332	281	222	184	138	106	77	65	47	36	26	16	12	6	2	1	0	0

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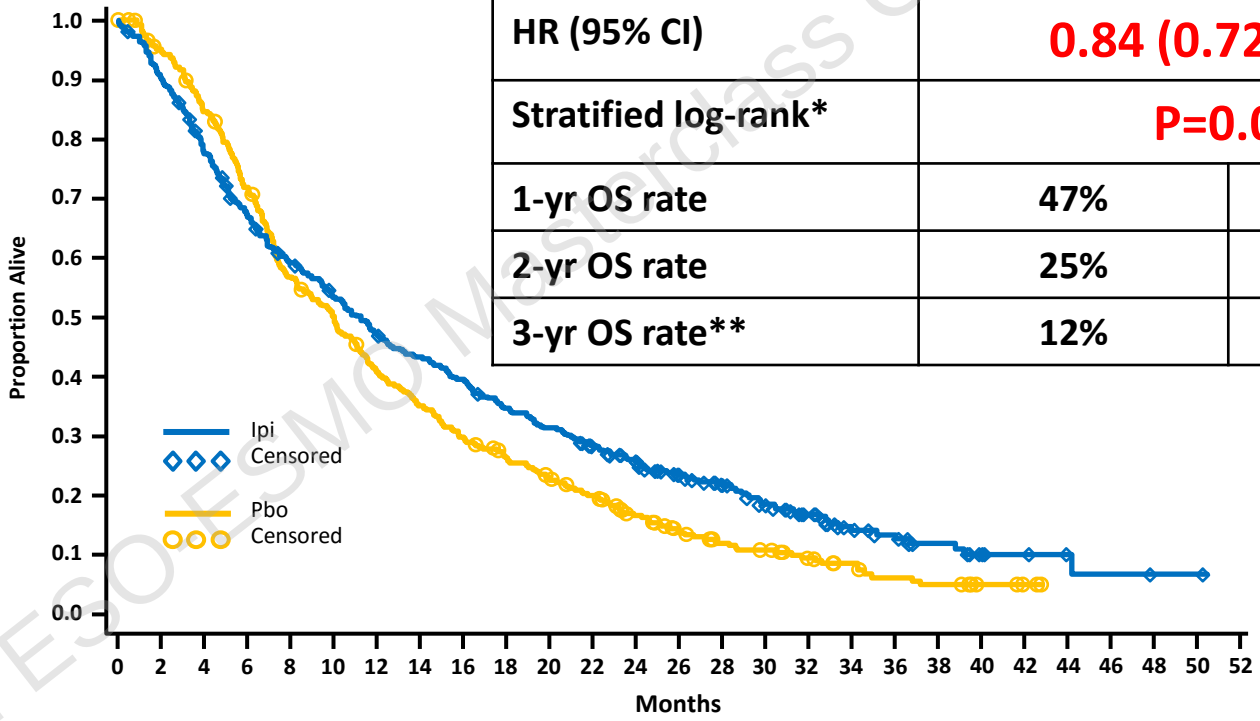
Kwon E, Lancet Oncol 2014; 15: 700-12

Ipilimumab post-docetaxel phase III trial

Results: Updated OS

- n=799
- Primary endpoint= OS

	Ipi (n=399)	Pbo (n=400)
Median OS, mo (95% CI)	11.2 (9.6–12.6)	10.0 (8.4–11.2)
HR (95% CI)	0.84 (0.72–0.98)	
Stratified log-rank*	P=0.03	
1-yr OS rate	47%	41%
2-yr OS rate	25%	17%
3-yr OS rate**	12%	6%



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