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Farmaci e nuovi farmaci nel carcinoma della prostata: meccanismi di azione, integrazione nel trattamento ed effetti collaterali

Dott. Luca Triggiani

Spedali Civili di Brescia

Università degli Studi di Brescia

Società Italiana di Radiobiologia

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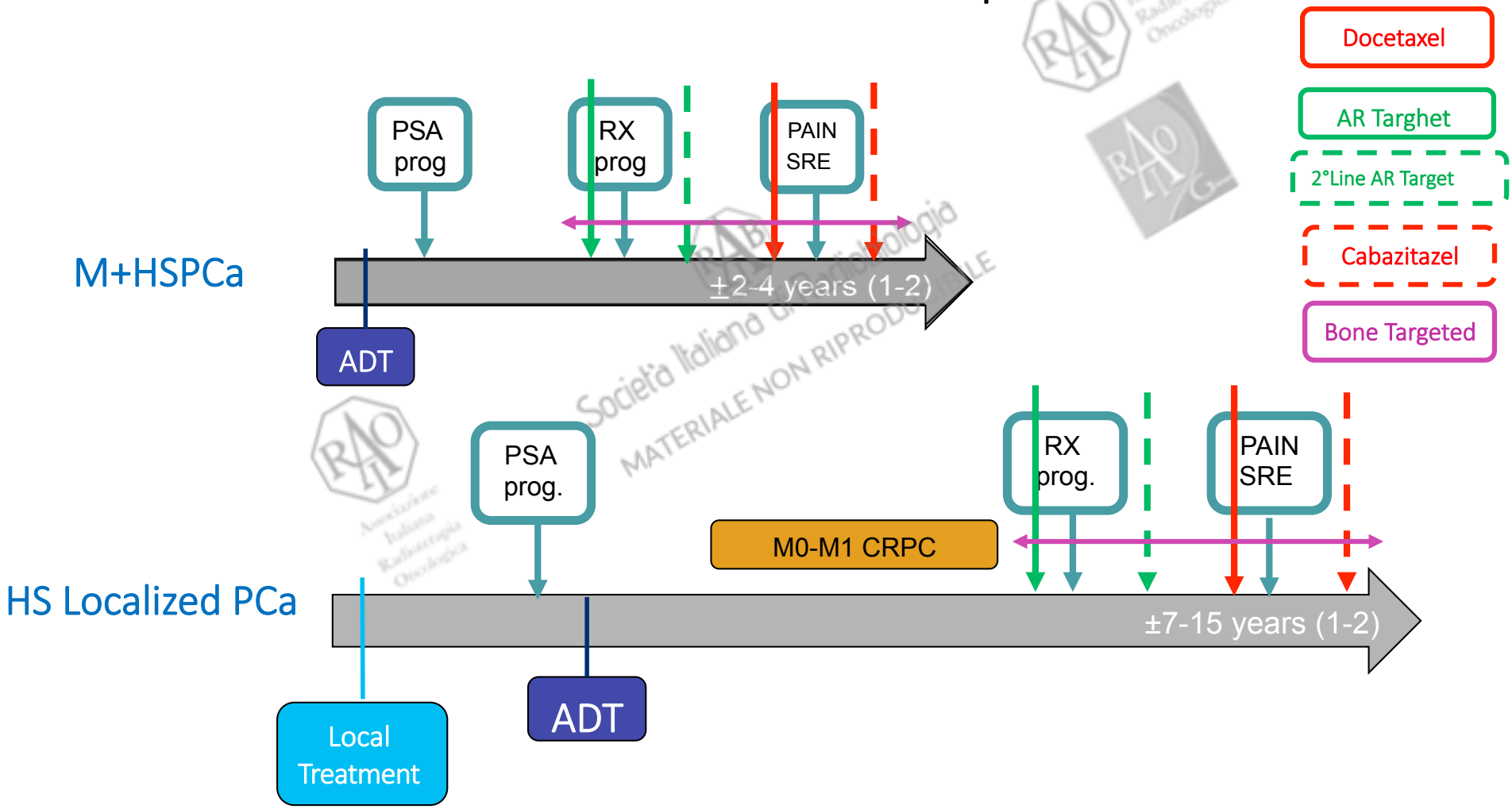
DICHIARAZIONE

Relatore: LUCA TRIGGIANI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

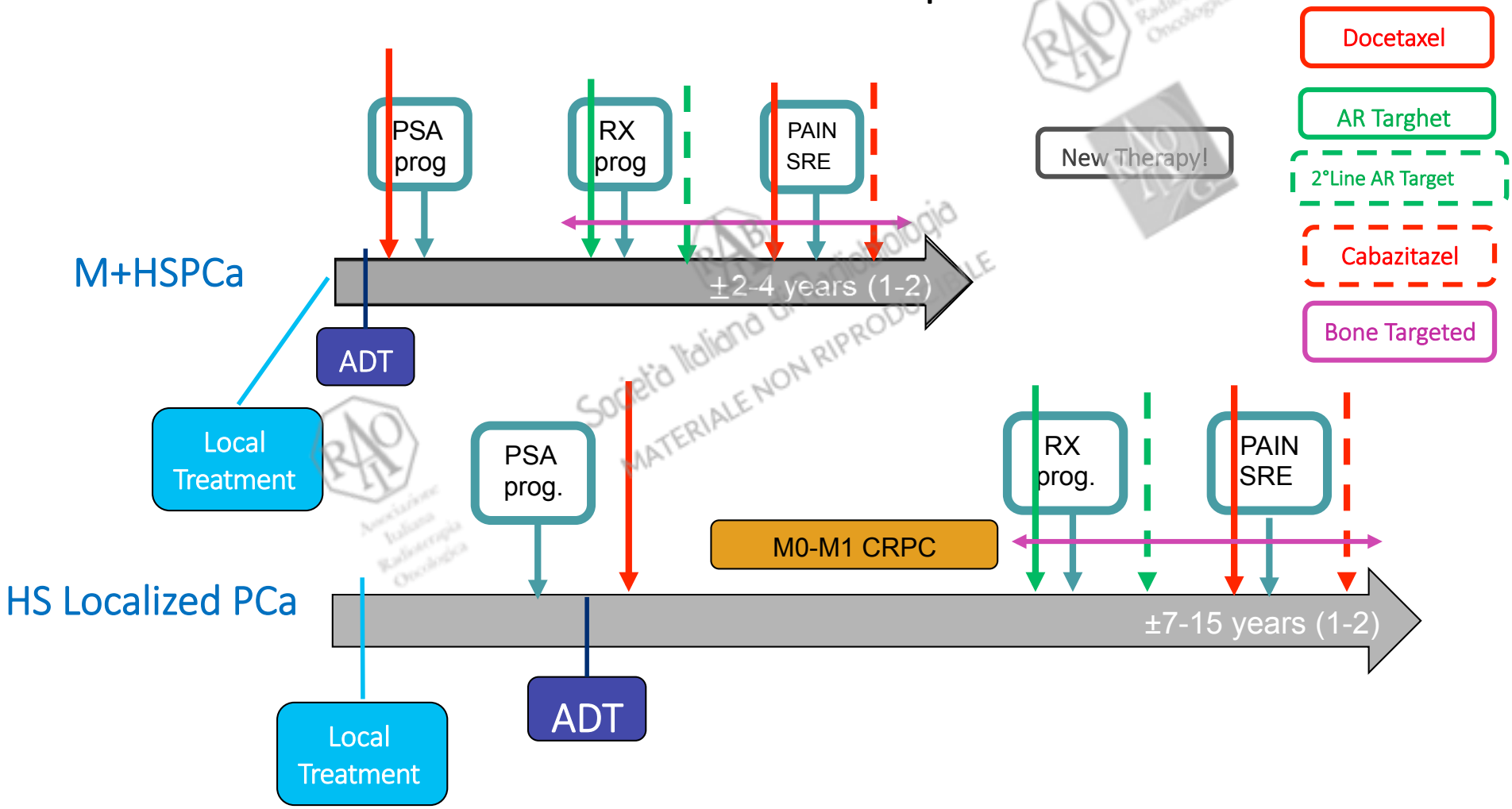
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**

The advance PCa Landscape in 2016



HN PC: hormone naïve PCa; CRPC: Castration-Resistant Prostate Cancer; M0, non-metastatic; RX progression: radiological progression; SRE skeletal related events. 1. Gravis G, et al. Lancet Oncol 2013;14(2):149-58; 2. James ND, Eur Urol. 2014 Oct 6. pii: S0302-2838(14)00969-5; 3. Joniau S for EmPACT, Eur Urol. 2014 Jan 25. *epub*; 4. Widmark A, SPCG-7, Lancet. 2009 373(9660):301-8; Warde P, SPCG-7, Lancet. 2011 378(9809):2104-11.

The advance PCa Landscape in…future…



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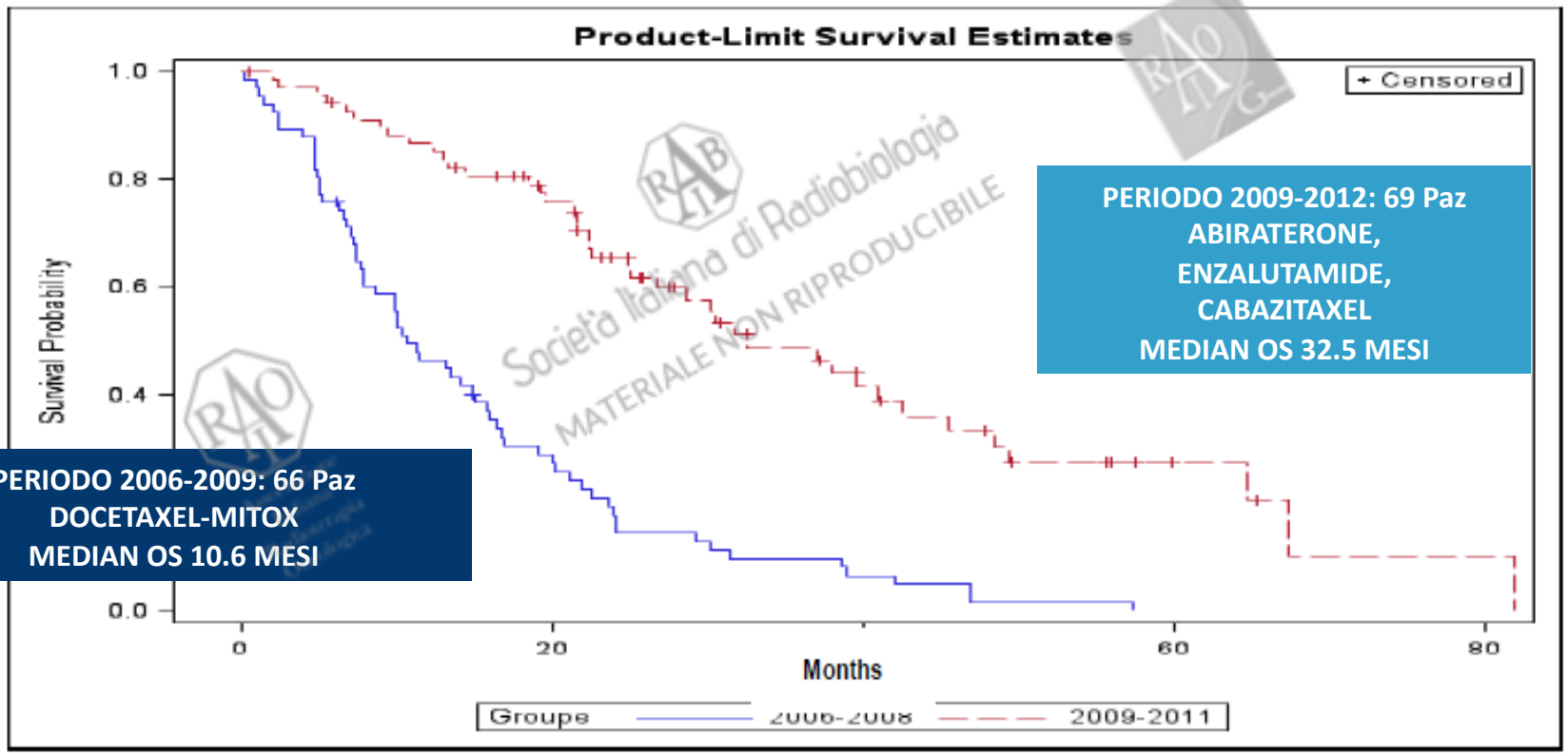
Impact of new drugs in the median OS of pts with mCRPC

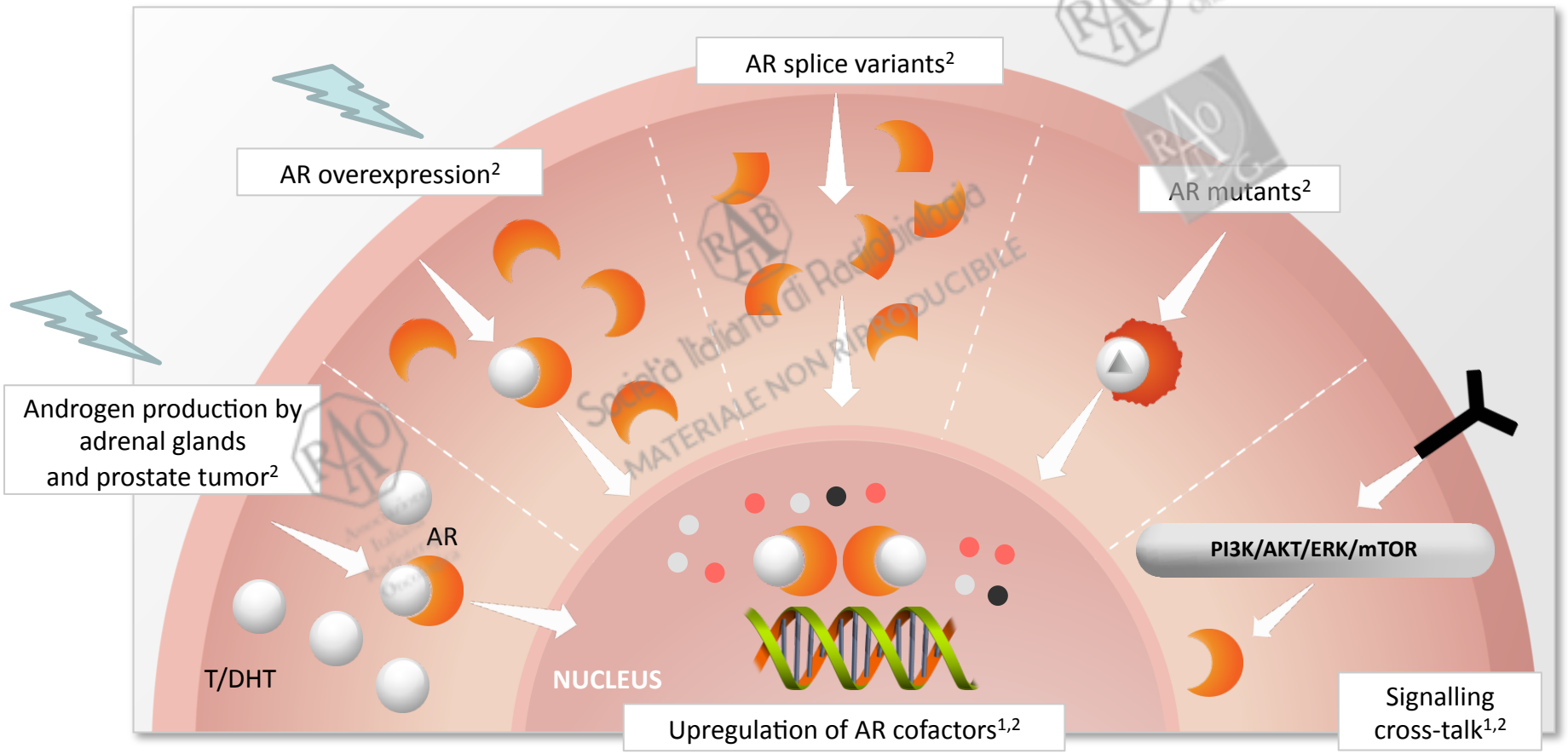


PERIODO 2006-2009: 66 Paz
DOCETAXEL-MITOX
MEDIAN OS 10.6 MESI

PERIODO 2009-2012: 69 Paz
ABIRATERONE,
ENZALUTAMIDE,
CABAZITAXEL
MEDIAN OS 32.5 MESI

Hall, Poster 417 ECCO 2013

CRPC: AR remains a driver

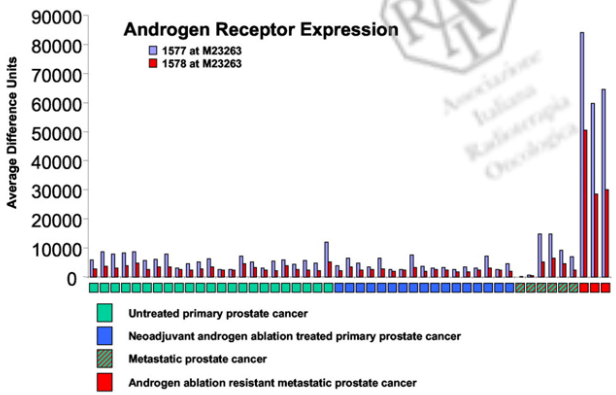


1. Heinlein CA & Chang C. Endocr Rev, 2004; 25: 276-308;
2. Hu R et al. Expert Rev Endocrinol Metab, 2010; 5: 753-64
DHT: dihydrotestosterone; ERK: extracellular signal-regulated kinase;
mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-3 kinase; T: testosterone

AR Amplification/Overexpression

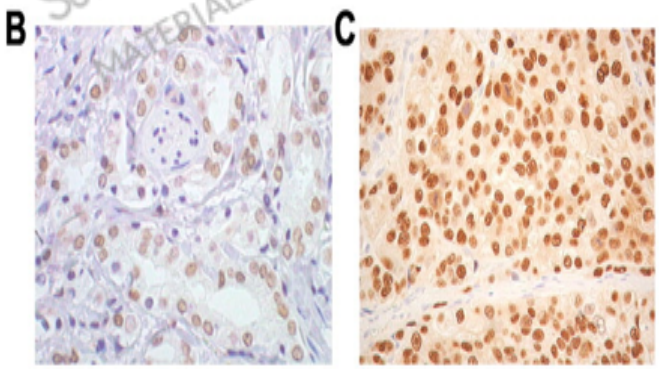
A number of reports have shown increased expression of AR in human mCRPC tissues based on:

gene expression



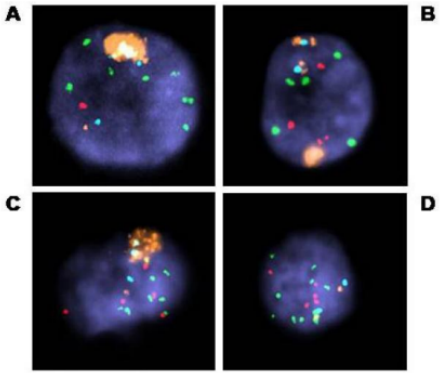
Cancer Cell 2010, 18, 11–22

Immunohistochemistriy



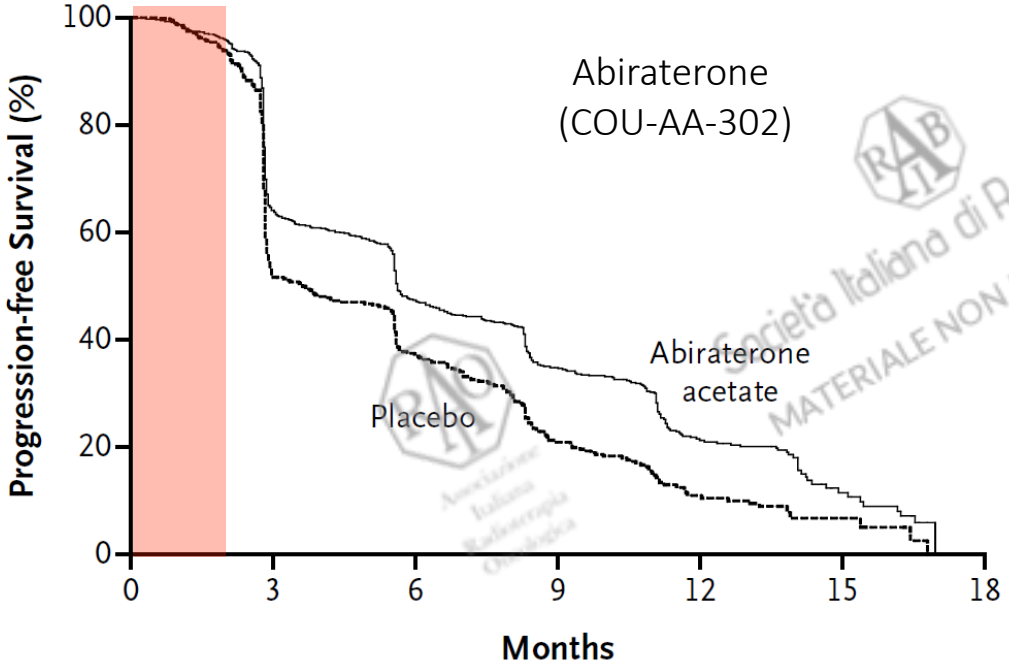
The American Journal of Pathology 2004 164, 217-227.

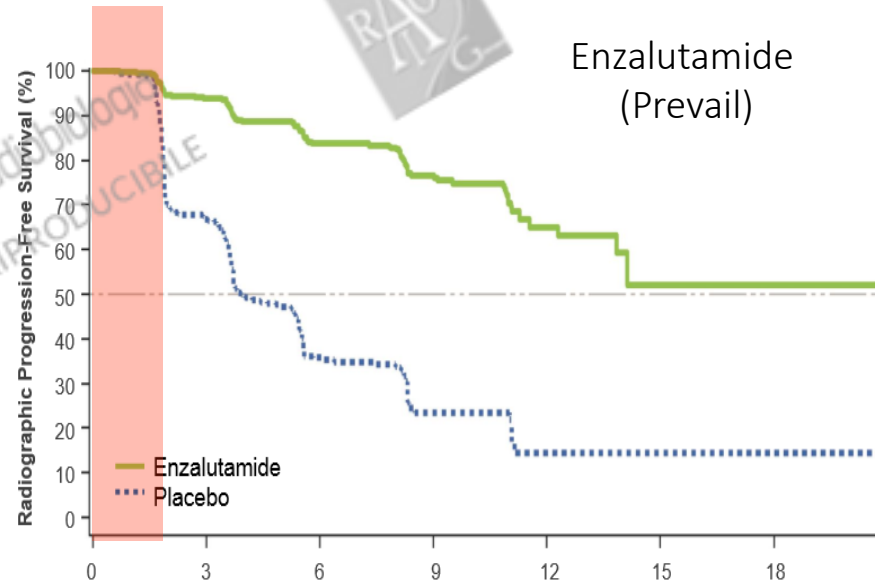
circulating tumor cell



Clin. Cancer Res. 2009, 15, 2091–2097.

Not All the Patients Respond to New Hormonal Agent (Abiraterone, Enzalutamide)





35% of patients had PD as best response a 3 mos with Abiraterone.

25% of patients had PD as best response a 3 mos with Enzalutamide.

1. De Bono JS, et al. N Engl J Med. 2011; 364(21): 1995–2005

2. Scher HI, et al. N Engl J Med 2012;367:1187-97

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QUESTIONS

- SEQUENCING CURRENT THERAPIES IN THE TREATMENT OF METASTATIC PROSTATE CANCER: Should all mCRPC patients receive all available treatments ?

- DOCETAXEL + ADT UPFRONT IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER

- NEWS

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QUESTIONS

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- DOCETAXEL + ADT UPFRONT IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER

- NEWS

How to choose the treatment for mCRPC currently? What is the best sequence?

- No head-to-head studies
- No prospective sequencing trials
- No predictive markers
- Difficult response assessment for bone mets
- Likely cross-resistance among drugs

✦ **Let's be honest**

→ CLINICAL TRIALS RESULTS

1°line mCRPC

Radiological/clinical progression

Biomarkers

Toxicity

Docetaxel: TAX 327

	Docetaxel Q 3 week	Docetaxel weekly	Mitoxantrone
Randomized	335	334	337
Ineligible*(%)	12	12	12
Median age (range)	68 (42-92)	69 (36-92)	68 (43-86)
≥ 80 Karnofsky PS (%)	88	87	86
Pain level ≥ PPI 2 or AS ≥ 10 (%)	45	45	46
Prior treatment (%)			
Prostatectomy	19	24	21
Radiotherapy	52	44	51
Estramustine	19	18	21
Hormonal Manipulations (%)			
1	9	8	6
2	68	72	69
> 2	23	21	25
Median PSA (ng/ml)	114	108	123
Gleason Score (%)			
≤ 7	42	40	42
8-10	31	31	28
Not available	26	29	30
Extent of Disease (%)			
Bone Metastases	90	91	92
Visceral Disease	22	24	22

Tannock et al, N Engl J Med 2004; 351: 1502-1512

Comparison between 302 & PREVAIL

	COU-AA-302	PREVAIL
Number of pts	1088	1717
Conditions	- Progressive chemo-naïve mCRPC - Asymptomatic/ mildly symptom - No visceral mets	- Progressive chemo-naïve mCRPC - Asymptomatic/ mildly symptom - Visceral mets
Treatment	- AA+Prednisone - Prednisone	- Enzalutamide (steroid is allowed) - Placebo (steroid is allowed)
Primary endpoint	- rPFS - OS	- rPFS - OS
Secondary endpoint	- Time to opiate use Time to initiation of chemotherapy - Time to ECOG-PS deterioration - TTPP	- Time to initiation of chemotherapy - -Time to 1st SRE
Design	Multicentre, randomized, double-blind, placebo controlled	Multicentre, randomized, double-blind, placebo controlled
Locations	151 sites in 12 countries (USA, EU, Australia, Canada)	207 sites in 22 countries (USA, EU, Australia, Canada, Asia)

1°line mCRPC

- Docetaxel
- AR therapy

Radiological/clinical progression

Visceral MTS +
Visceral MTS –
Symptomatic
Asymptomatic/ mildly symptomatic

Biomarkers

Toxicity

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Comparison between 302 & PREVAIL

	Improvement in OS months median	HR (95% CI; P-value
Abiraterone/P vs. placebo/P (COU-AA-302)	4.4	0.81 (0.70-0.93; P < 001)
Enzalutamide vs. placebo (PREVAIL)	4	0.77 (0.67- 0.8; P = 0.0002)

	Abiraterone n (%)	Prednisone n (%)
No. with subsequent therapy for mCRPC	365 (67)	435 (80)
Abiraterone	69 (13)	238 (44)[a]
Cabazitaxel	100 (18)	105 (19)
Docetaxel	311 (57)	331 (61)
Enzalutamide	87 (16)	54 (10)
Ketoconazole	42 (8)	68 (13)
Radium-223	20 (4)	7 (1)
Sipuleucel-T	45 (8)	32 (6)

	Enzalutamide N (%)	Placebo N (%)
No. with subsequent therapy for mCRPC	457 (52.4)	685 (81.1)
Docetaxel	358 (41.1)	504 (59.6)
Abiraterone acetate	256 (29.4)	417 (49.3)
Cabazitaxel	79 (9.1)	149 (17.6)
Enzalutamide*	21 (2.4)	249 (29.5)
Sipuleucel-T	17 (1.9)	11 (1.3)
Radium-223	16 (1.8)	22 (2.6)

Ryan et al. Lancet Oncol. 2015 Feb;16(2):152-60;
Beer TM, NEJM. 2014 Jul 31;371(5):424-33;

Comparison between 302 & PREVAIL: Secondary Endpoint

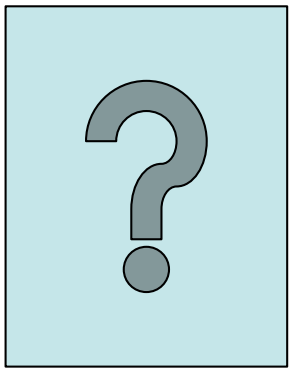
	Abi/Pred	Pred.	Δ	p
Time to chemotherapy	25.2	16.8	17.2	< 0.001
Time to PSA progression (months)	11.1	5.6	8.4	< 0.001
Time to SRE				< 0.001
Time to time to opiate use	NR	23.3		
Median time to progression of mean pain intensity[1]	26.7	18.4		0.049
Time to HRQoL degradation (months)[2]	12.7	8.3		0.03
PSA response > 50% (%)	62	24		
Objective response (%	36	16		< 0.001

Ryan CJ, et al. N Engl J Med 2013;368:138–48. Basch E, et al. Lancet Oncol. 2013 Nov;14(12):1193-9.

COU-AA-302

	Enzalutamide	Pred.	Δ	p
Time to chemotherapy	28.0	10.8	17.2	< 0.001
Time to PSA progression (months)	11.2	2.8	8.4	< 0.001
Time to SRE	31.1	31.3		< 0.001
Time to pain (months) [1]	NR yet			
Time to HRQoL degradation (months)[2]	11.3	5.6	5.7	<0.0001
PSA response > 50% (%)	78	3.5		< 0.001
Objective response (%	58.8	5		< 0.001

Beer TM, NEJM. 2014 Jul 31;371(5):424-33;



PREVAIL

Different side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomised controlled trials

Meta-analysis

- Inclusion of 4 RCTs reporting side effects in mCRPC pts treated with ABI or ENZA

Study	Treatment arm	Pts for analysis (N)
PREVAIL (Beer, NEJM 2014)	ENZA	871
	Pbo	844
AFFIRM (Scher, NEJM 2012)	ENZA	800
	Pbo	399
COU-AA-301 (de Bono, NEJM 2011)	ABI + P	797
	Pbo + P	398
COU-AA-302 (Ryan, NEJM 2013)	ABI + P	546
	Pbo + P	542

ASCO 2016: Moreira RB. J Clin Oncol 2016;34(Suppl 2S):19(abs.73)

Different side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomised controlled trials

Conclusion: In this meta-analysis, ABI was associated with an cardiac events, while ENZA was associated with fatigue.

Side effects	Treatment (events)	Comparator (events)	Relative risk	95% CI	*P*
Fatigue	**ABI + P**	**Pbo + P**			
Any	558	354	1.07	0.97-1.19	0.2
Grade ≥3	66	39	0.85	0.58-1.23	0.4
	ENZA	**Pbo**			
Any	579	334	**1.29**	**1.15-1.44**	**<0.001**
Grade ≥3	66	45	0.89	0.62-1.29	0.5
Cardiac events	**ABI + P**	**Pbo + P**			
Any	239	144	**1.28**	**1.06-1.35**	**0.01**
Grade ≥3	64	27	**1.76**	**1.12-2.75**	**0.01**
	ENZA	**Pbo**			
Any	137	96	1.06	0.67-1.65	0.8
Grade ≥3	31	26	0.81	0.28-2.33	0.7

ASCO 2016: Moreira RB. J Clin Oncol 2016;34(Suppl 2S):19(abs.73)

Abiraterone real world data post Docetaxel

Table 2 Comorbidities.

Comorbidity	No. of patients (%)
Hypertension	147 (55)
No comorbidities	52 (20)
Diabetes	46 (17)
Cardiac ischaemia	33 (11)
Arrhythmia	29 (10)
Chronic obstructive pulmonary disease	15 (5)
Peripheral vascular disease	13 (4)
Arthropathies	13 (4)
Cerebrovascular disease	9 (2)
Gastroduodenal ulcer	7 (2)
Chronic renal failure	5 (1)

Caffo et al., BJU Int 2014.

Abiraterone real world data post Docetaxel

Results

We assessed 265 patients with mCRPC treated with AA post chemo. **The most frequent (>1%) grade 3–4 toxicities were anaemia (4.2%), fatigue (4.2%), and bone pain (1.5%).** The median progression-free survival was 7 months; median overall survival was 17 months after starting AA, and 35 months after the first docetaxel administration. Our study reproduced the clinical outcomes reported in the AA pivotal trial, including those relating to special populations such as the elderly, patients with a poor performance status, symptomatic patients, and patients with visceral metastases.

Conclusions

Our data show the safety and activity of AA when administered outside clinical trials, and confirm the findings of the post-docetaxel pivotal trial in the patients as a whole population and in special populations of specific interest.

Caffo et al., BJU Int 2014.

1°line mCRPC

- Docetaxel
- AR therapy

Radiological/clinical progression

Visceral MTS +
Visceral MTS –
Symptomatic
Asymptomatic/ mildly symptomatic

Biomarkers

Toxicity

Fatigue (Enza)
Cardiac Event (Abi)

Androgen Receptor Splice variant

- Numerous ARVs have been identified in several prostate cancer cell lines and xenograft tumors at the level of mRNA, and some of them have been confirmed in clinical specimens.
- Loss of the LBD as a common feature of this splice variant

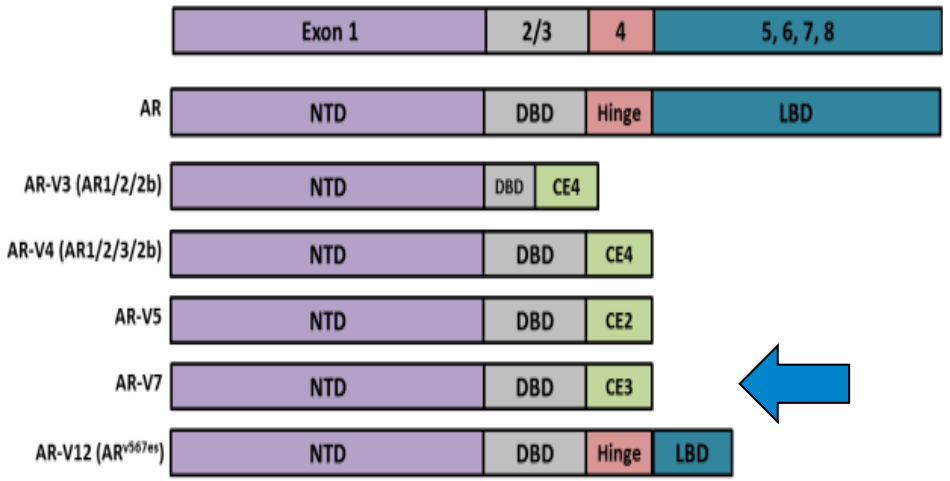
Int. J. Mol. Sci. **2013**, *14*, 14833-14859; doi:10.3390/ijms140714833

OPEN ACCESS
International Journal o
Molecular Science
ISSN 1422-006
www.mdpi.com/journal/ijm

Review

Posttranslational Modification of the Androgen Receptor in Prostate Cancer

Travis van der Steen [1], Donald J. Tindall [1,2] and Haojie Huang [2,*]



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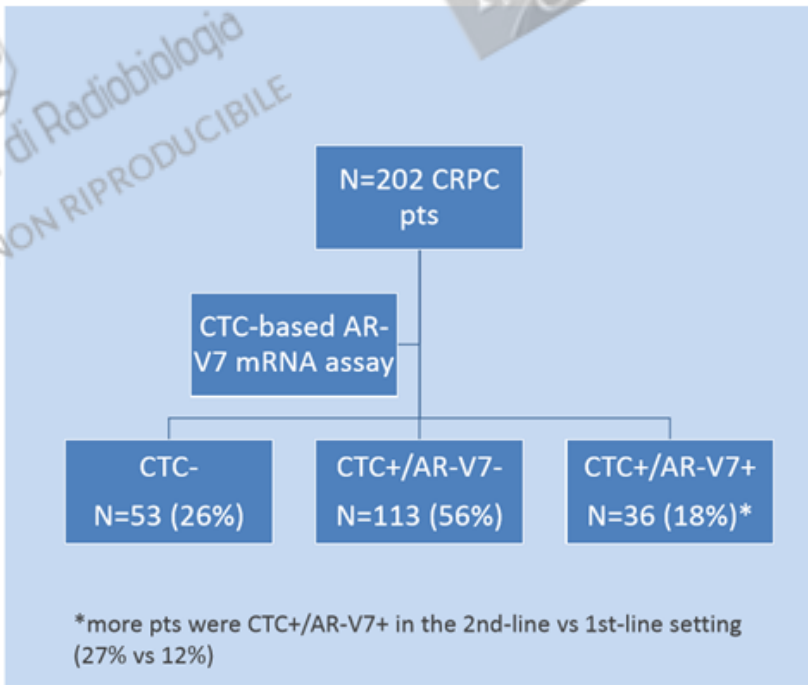
AR-V7 and efficacy of abiraterone and enzalutamide in castration-resistant prostate cancer: expanded analysis of the Johns Hopkins cohort

Prospective biomarker study

- N=202 pts with CRPC starting treatment with ABI or ENZA
  - 1st-line setting: N=124
  - 2nd-line setting: N=78
- Median FU: 13 mo



ASCO 2016: Antonarakis ES. J Clin Oncol 2016;34(15S):269s(abs.5012)

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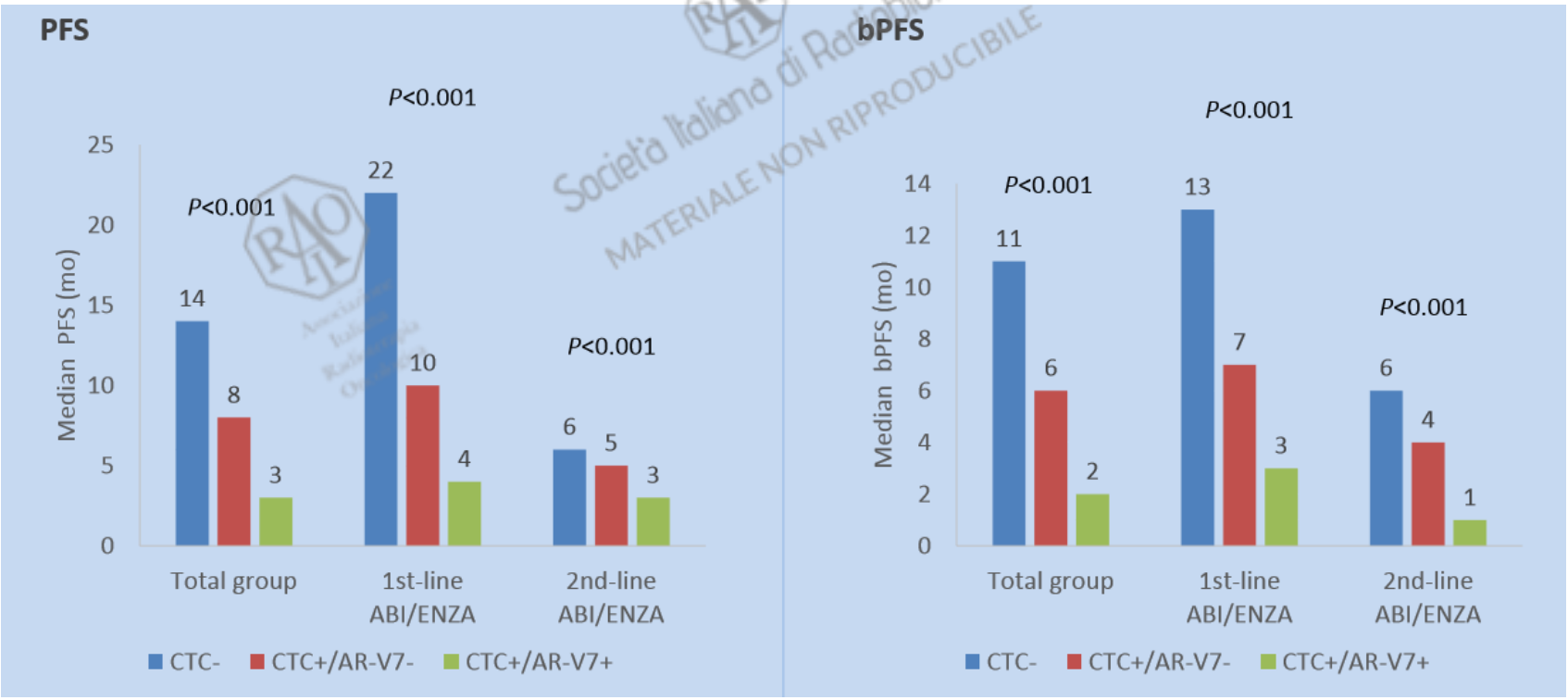
AR-V7 and efficacy of abiraterone and enzalutamide in castration-resistant prostate cancer: expanded analysis of the Johns Hopkins cohort

Detection of AR-V7 in CTCs in the blood of men with CRPC implies a lower response rates to ABI / ENZA and worse prognosis



ASCO 2016: Antonarakis ES. J Clin Oncol 2016;34(15S):269s(abs.5012)

1°line mCRPC

- Docetaxel
- AR therapy

Radiological/clinical progression

Visceral MTS +
Visceral MTS –
Symptomatic
Asymptomatic/ mildly symptomatic

Biomarkers

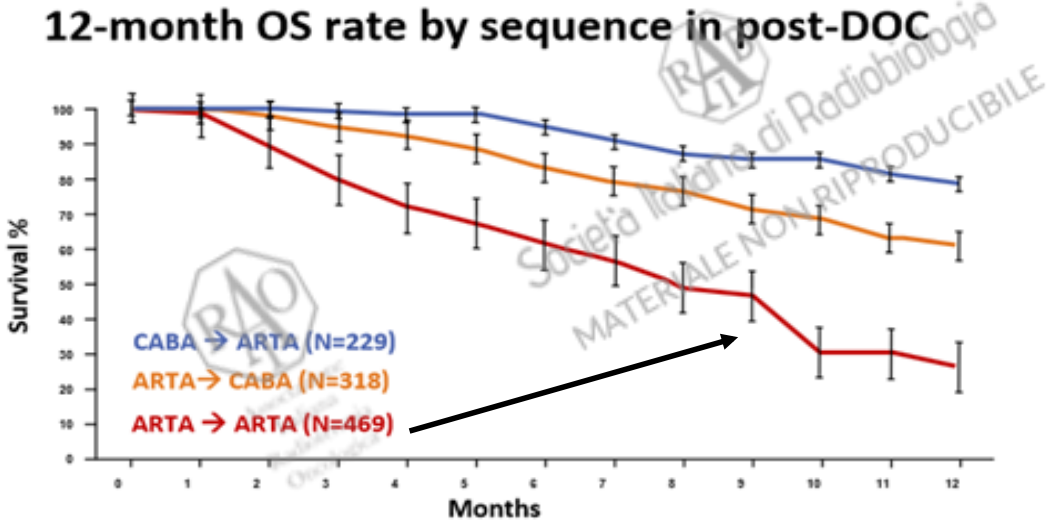
ARV+
ARV–
time to mCRPC<12
Time to mCRPC >12

Toxicity

Fatigue (Enza)
Cardiac Event (Abi)

And second –third line?

Systematic review of 13 published retrospective studies in mCRPC (N=1,016)

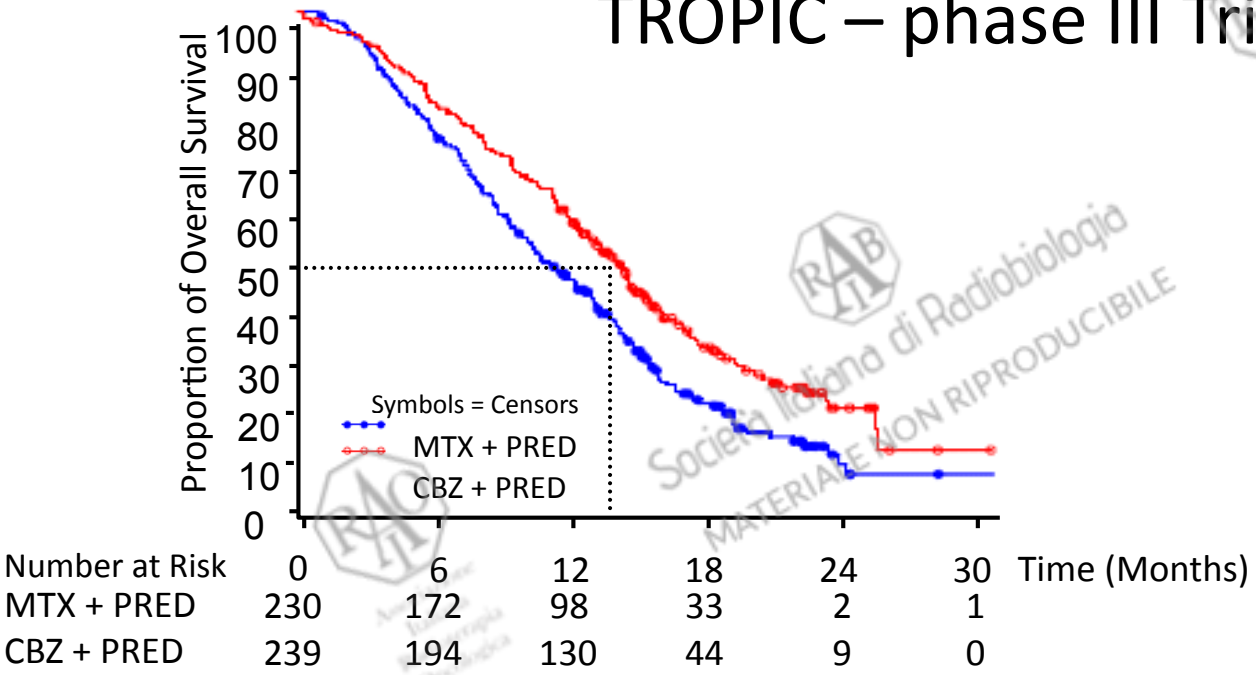


Poor survival with AR-targeted agents in sequence (post-DOC)

ARTA: androgen receptor targeted agent

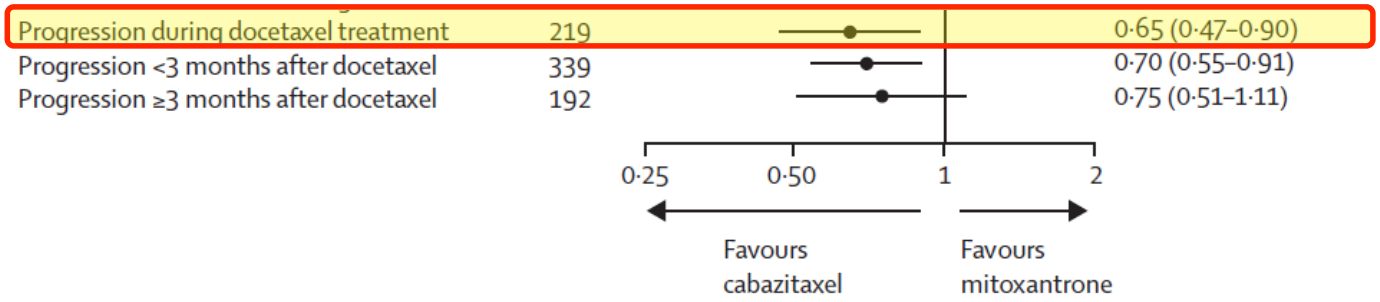
Maines F et al. Crit Rev Oncol Hematol 2015;96:498-506

Cabazitaxel: TROPIC – phase III Trial



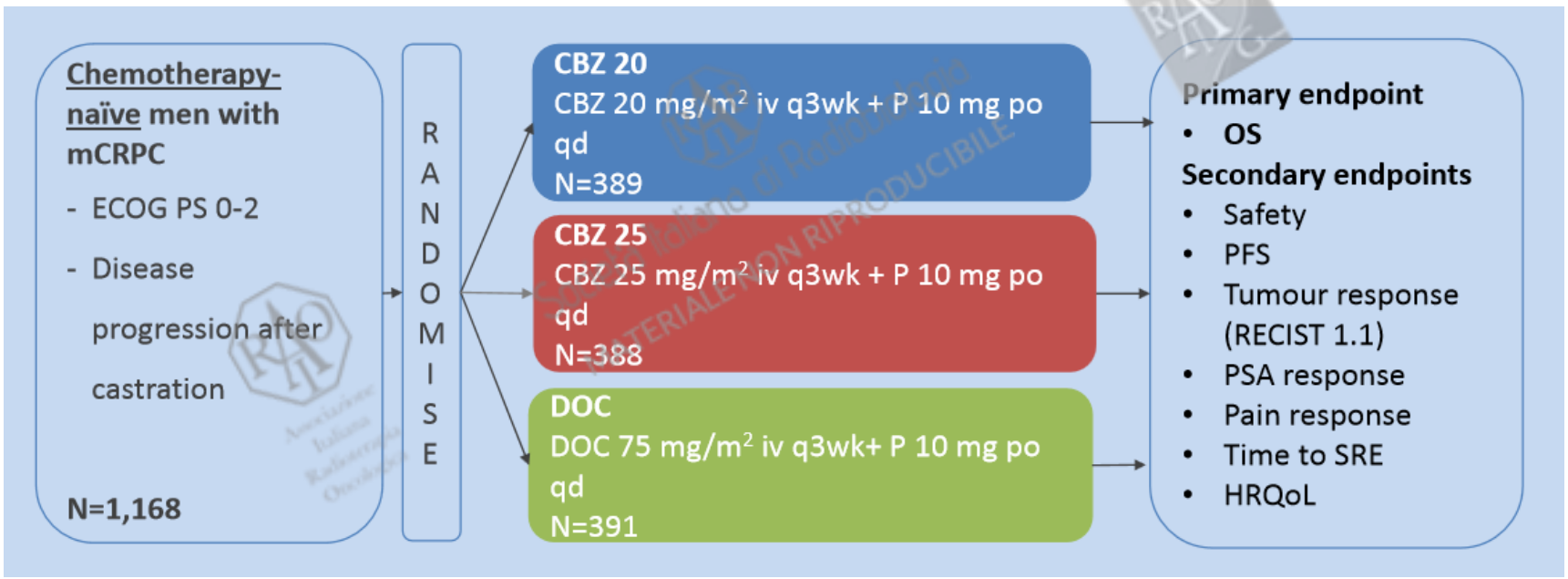
Median OS (Months)

MTX	CBZ
10.9	13.8



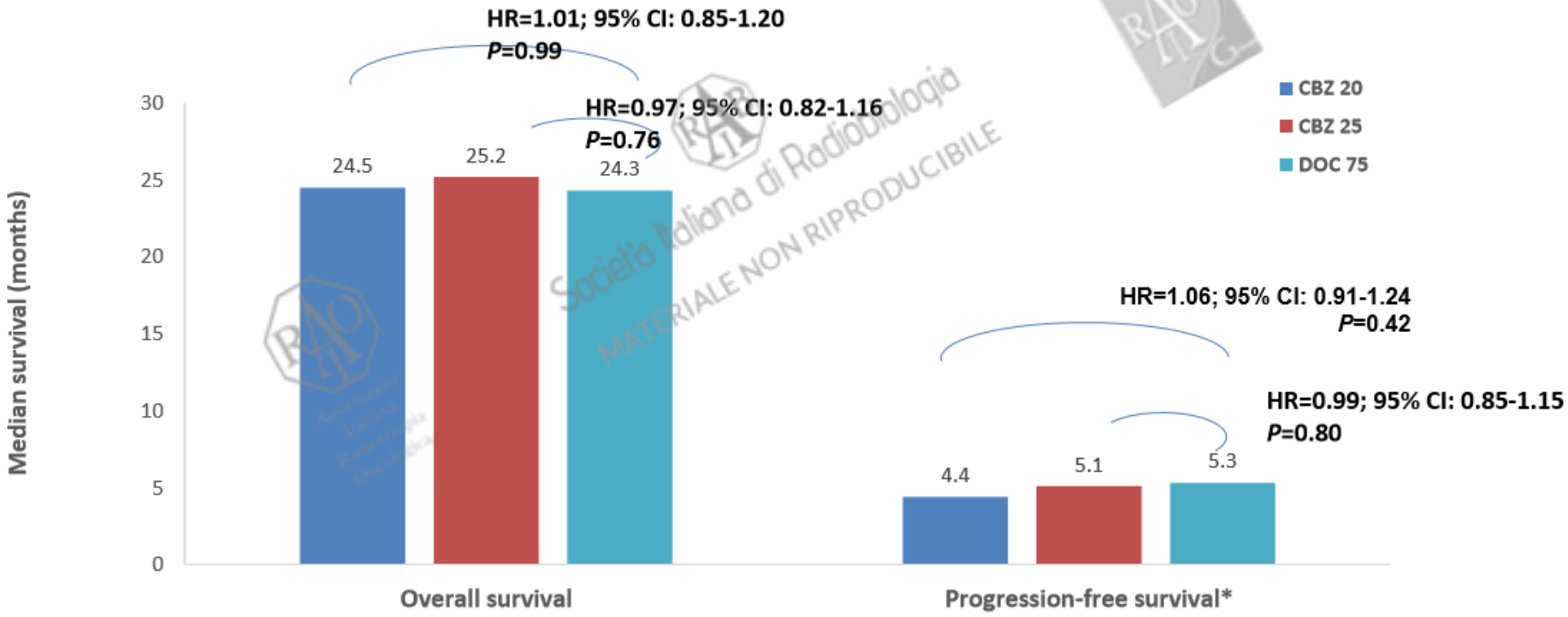
De Bono JS et al. 47° ASCO Annual Meeting. G.U.CANCER. ASCOSCANNER n°2 del 4/06/2011.

Cabazitaxel: FIRSTANA – phase III Trial



ASCO 2016 Sartor AO. J Clin Oncol 2016;34(15S):267s(abs.5006)

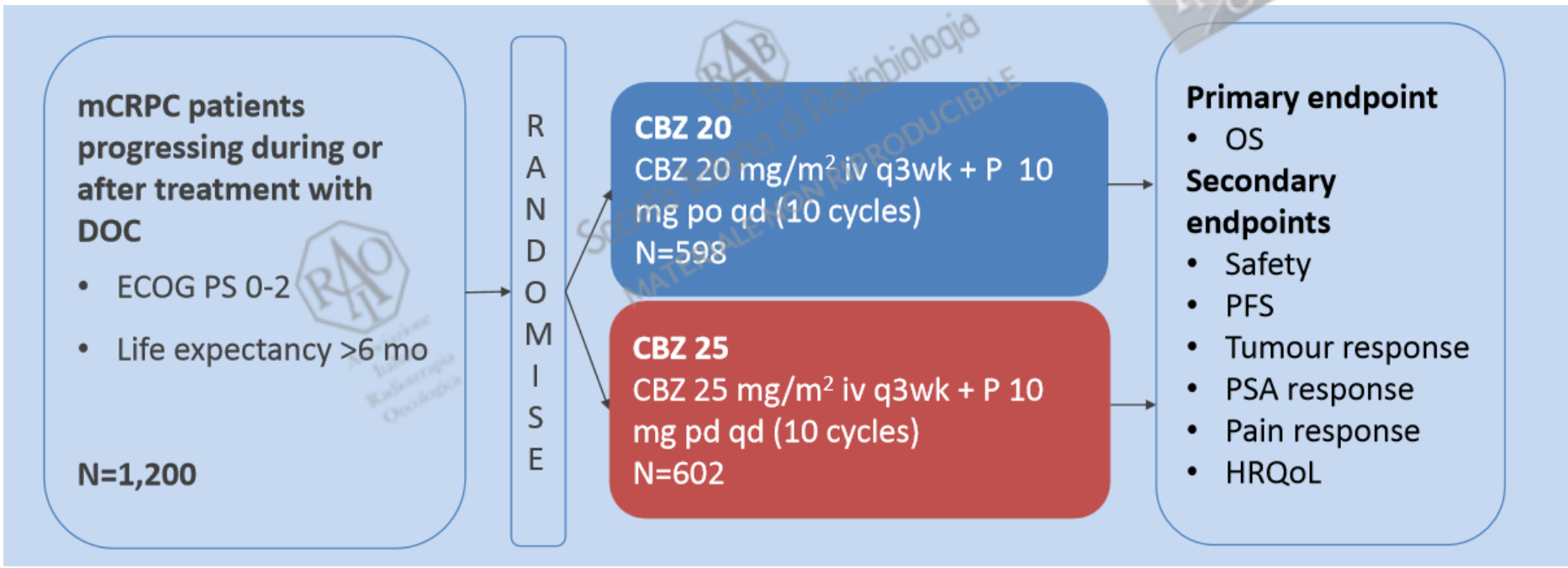
Cabazitaxel: FIRSTANA – results



ASCO 2016 Sartor AO. J Clin Oncol 2016;34(15S):267s(abs.5006)

PROSELICA Trial

multinational, non-inferiority, phase III study



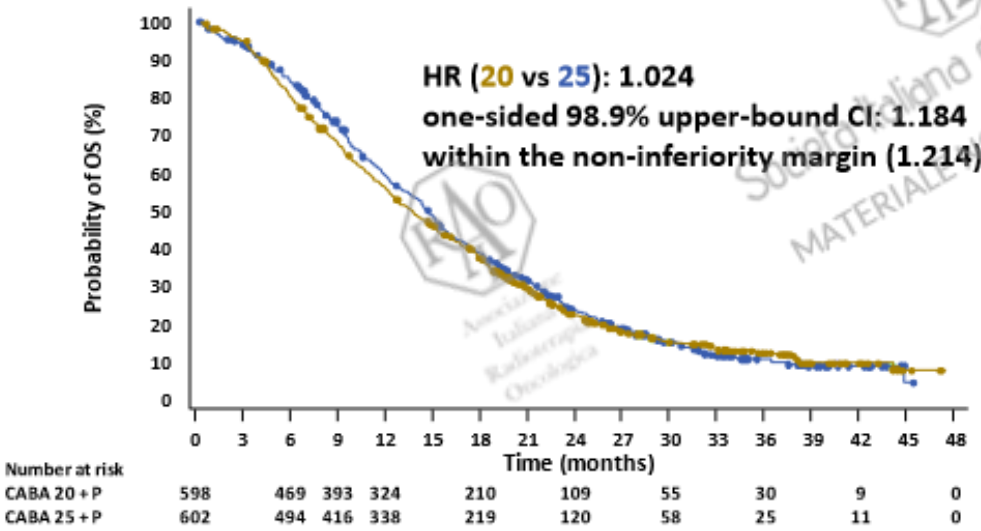
De Bono JS. ASCO 2016, abs 5008

PROSELICA Trial: Efficacy

Median OS, months (95% CI)

CABA 20 + P **13.4 (12.19-14.88)**

CABA 25 + P **14.5 (13.47-15.28)**

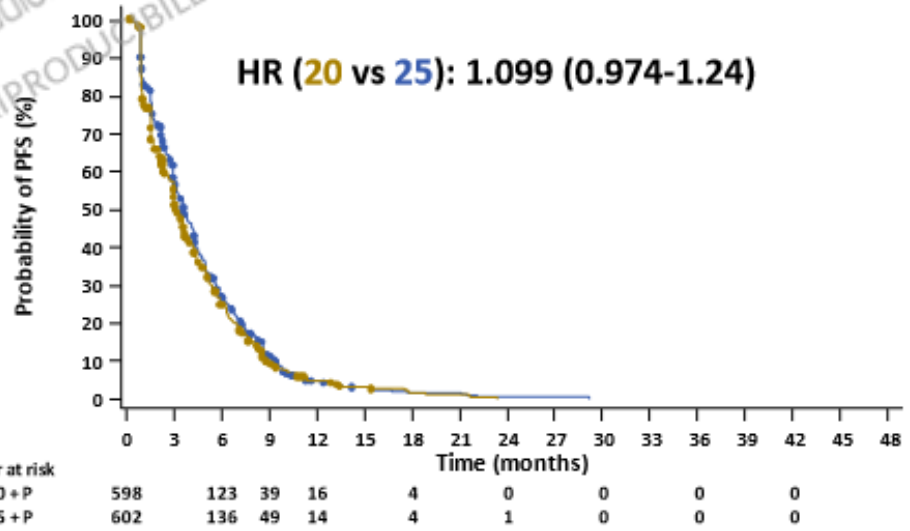


Number at risk										
CABA 20 + P	598	469	393	324	210	109	55	30	9	0
CABA 25 + P	602	494	416	338	219	120	58	25	11	0

Median PFS, months (95% CI)

CABA 20 + P **2.9 (2.79-3.45)**

CABA 25 + P **3.5 (3.12-3.94)**



Number at risk										
CABA 20 + P	598	123	39	16	4	0	0	0	0	
CABA 25 + P	602	136	49	14	4	1	0	0	0	

De Bono JS. ASCO 2016, abs 5008

PROSELICA Trial: Safety

AE (%)	CBZ 20 Grade 3-4	CBZ 25 Grade 3-4
Treatment-emergent AE	40	55
Febrile neutropenia	2.1	9.2
Diarrhoea	1.4	4.0
Haematuria	1.9	4.2
Fatigue	2.6	3.7
Anaemia	10	14
Neutropenia	42	73
Thrombocytopenia	2.6	4.2

De Bono JS. ASCO 2016, abs 5008

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- SEQUENCING CURRENT THERAPIES IN THE TREATMENT OF METASTATIC PROSTATE CANCER: Should all mCRPC patients receive all available treatments ?

- DOCETAXEL + ADT UPFRONT IN METASTATIC HORMONE SENSITIVE PROSTATE CANCER

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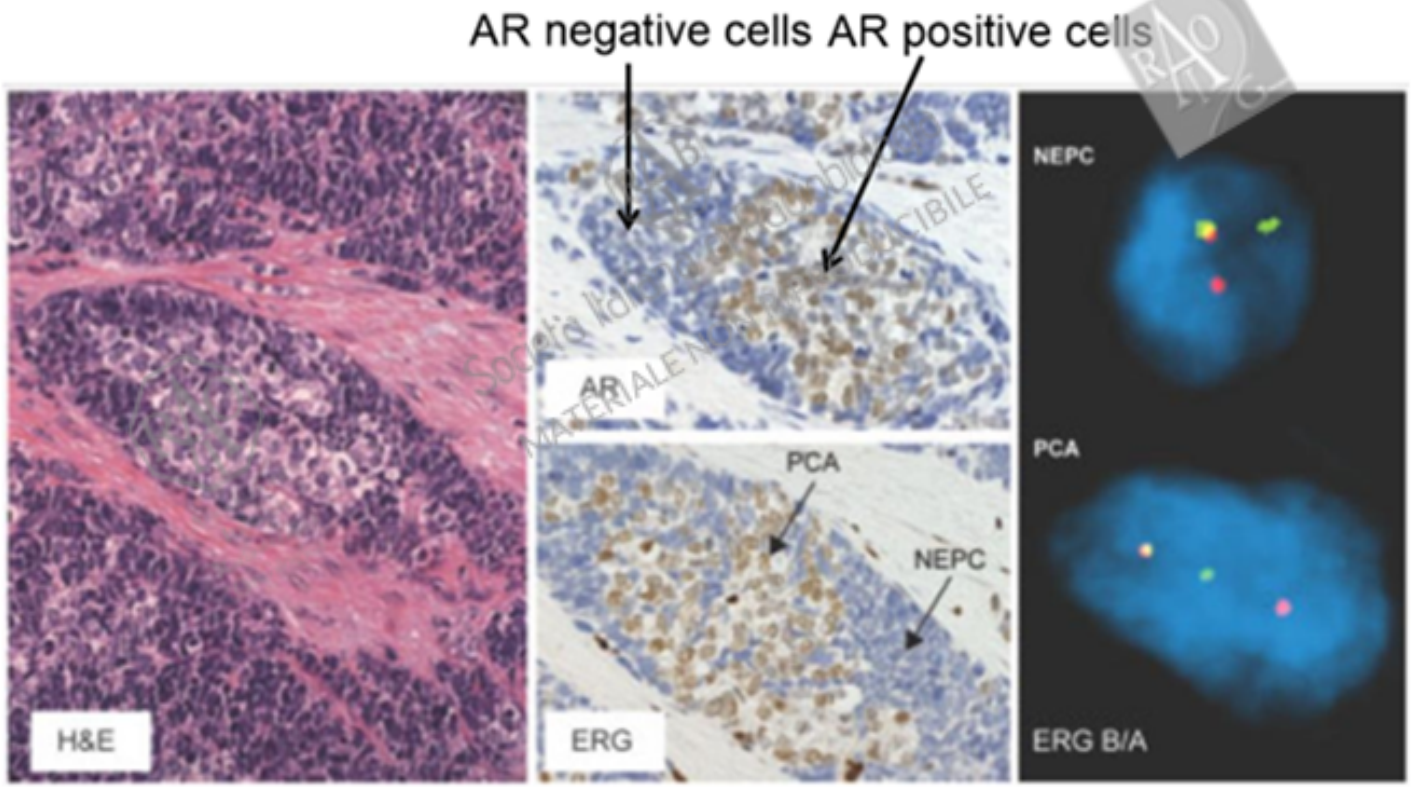
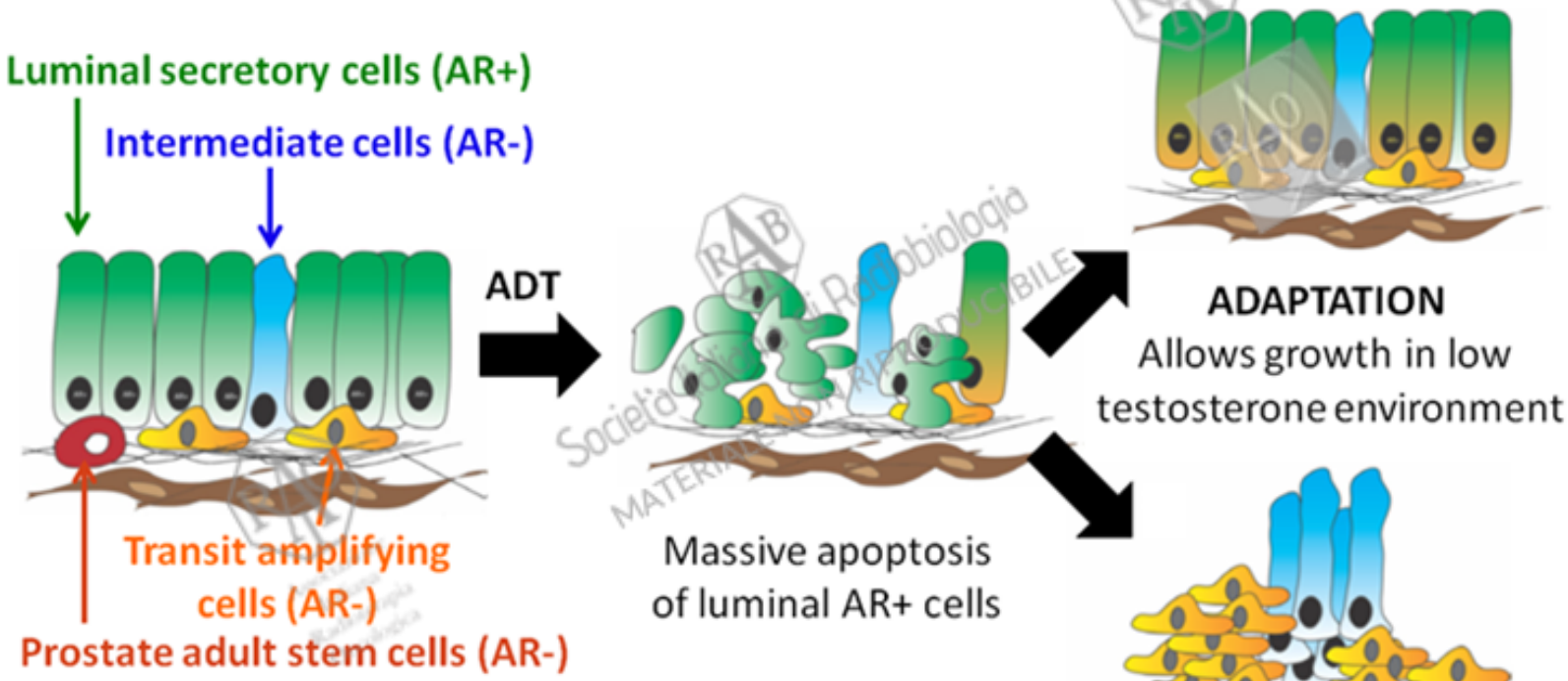
Co-existence of AR positive and AR negative tumour cells in a same patient



Beltran H. Cancer discovery 2011; 1: 487-495

The CHAARTED hypothesis



In most patients, both theories coexist: ADT response in some mets may be associated with radiological/clinical progression of other mets

Impact of Docetaxel in mHSPC

	OS control (months)	OS gain (months)	HR
Chaarted (all M1)[8]	**44**	**13.6**	**0.73**
Stampede (M1)[9]	**43**	**22**	**0.61**
Abiraterone/P vs. placebo/P[1] (post docetaxel)	11,2	4,6	0.74
Abiraterone/P vs. placebo/P[2] (pre docetaxel)	30,3	4,4	0.81
Enzalutamide vs. placebo[3] (post docetaxel)	13,6	4,8	0.63
Enzalutamide vs. placebo[4] (pre docetaxel)	31,3	4,0	0.77
Docetaxel(q3w)/P vs. mitoxantrone/P[5]	16,3	2,9	0.76
Cabazitaxel/P vs. mitoxantrone/P[6]	12,7	2,4	0.70
Ra-223* vs. placebo[7]	11,2	2,8	0.70

P, prednisone; q3w, every 3 weeks;

1. Fizazzi K, et al. Lancet Oncol 2012;13:983–92; 2. Ryan et al. Lancet Oncol. 2015 Feb;16(2):152-60 3. Scher HI, et al. N Engl J Med 2012;367:1187–97; 4. Tombal et al. EAU 2015, Madrid 5. JCO 2008 10;26(2):242-5; 6. de Bono JS, et al. Lancet 2010;76:1147–54;7. Kantoff PW, et al. N Engl J Med 2010;363:411–22; 8. Parker et al. N Engl J Med. 2013 Jul 18;369(3):213-23.8: Sweeney CJ et al. N Engl J Med. 2015 Aug 20;373(8):737-46; 9: James ND et al. Lancet. 2015 Dec 21. doi: 10.1016/S0140-6736(15)01037-5.

Guideline 2016

- ESMO

-ADT plus docetaxel is recommended as first-line of metastatic hormone-naïve disease in men fit enough for chemotherapy [1,A]

- NCCN

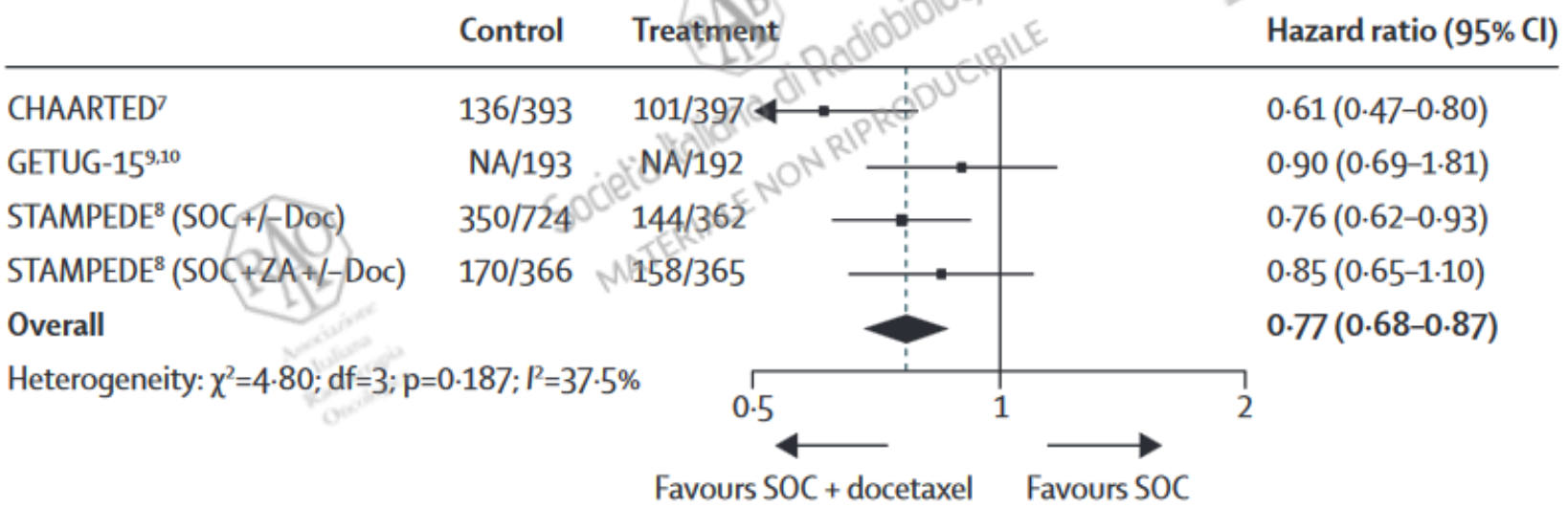
- Systemic therapy for progressive castration-naïve disease: Continuous ADT and docetaxel 75mg/m^2 with or without prednisone for 6 cycle

- EAU

- Offer castration combined with chemotherapy with ADT to all patients whose first presentation in M1 and are fit enough for chemotherapy

Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Claire L Vale, Sarah Burdett*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOpCaP Steering Group*



Addition of docetaxel to standard of care translates into

- an absolute improvement in 4-year OS of 9% (95% CI 5-14)
- an absolute 4-year failure rates of 16% (95% CI 12-19)

GETUG 15 vs CHAARTED: why this difference in outcome?

	GETUG-15	CHAARTED
N	385	790
Docetaxel exposure	Up to 9 cycles	6 cycles
High risk	22%	66%
Low/int risk	77%	34%
OS ADT + D	58.9 months	52.7 months
OS ADT	54.2 months	42.3 months
Time of follow-up	50 months	29 months
Deaths at analysis	175/385 (46%)	237/790 (30%)
Post-protocol docetaxel	62% ADT 28% ADT + D	33% ADT 12% ADT + D
Post-protocol abi, enza or other active novel AR tx	16% ADT + D 15% ADT	23% ADT + D 20% ADT

Courtesy of Morris M discussant at ASCO Annual Meeting 2014

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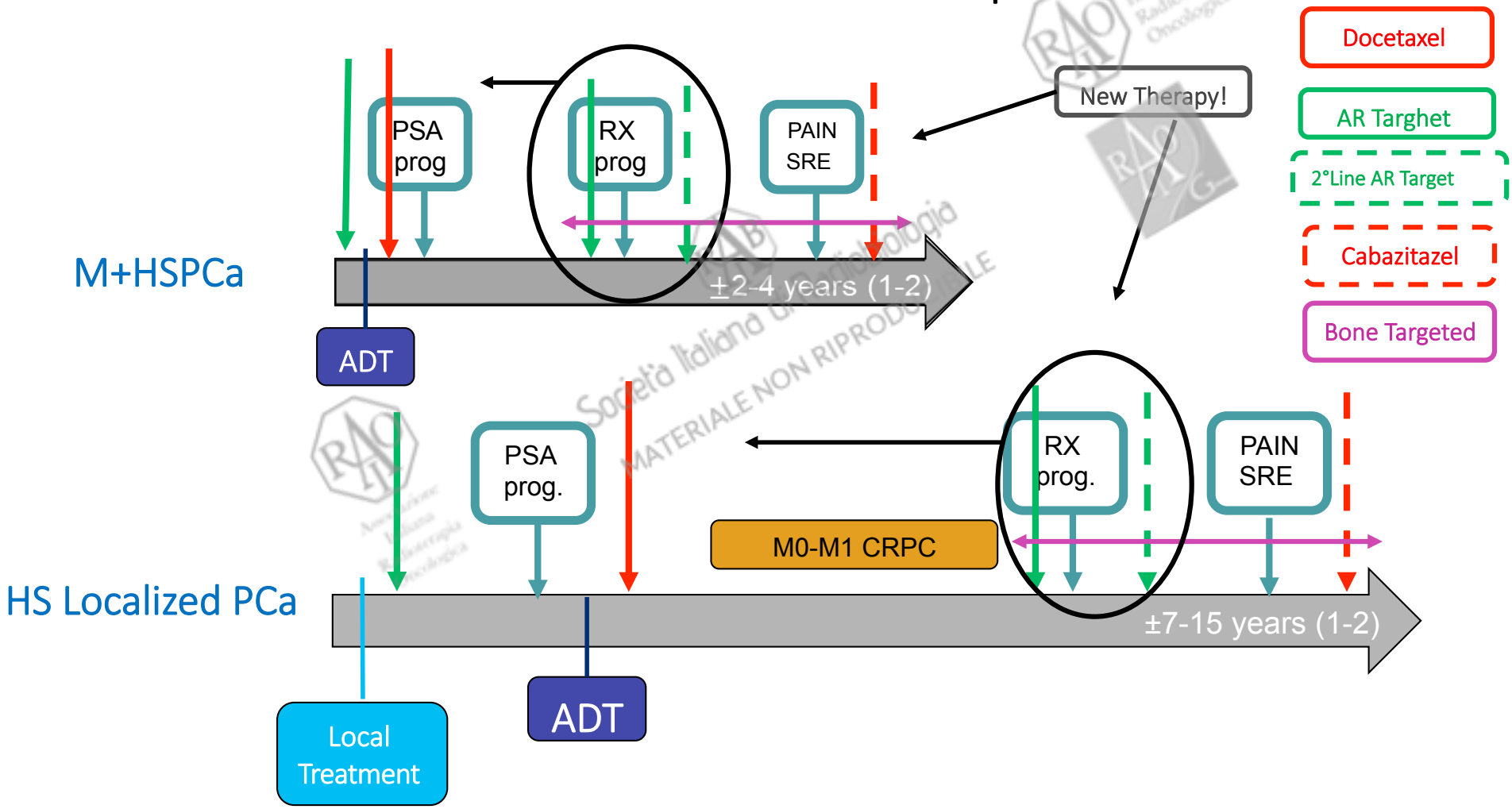
The advance PCa Landscape..NEWS?



HN PC: hormone naïve PCa; CRPC: Castration-Resistant Prostate Cancer; M0, non-metastatic; RX progression: radiological progression; SRE skeletal related events. 1. Gravis G, et al. Lancet Oncol 2013;14(2):149-58; 2. James ND, Eur Urol. 2014 Oct 6. pii: S0302-2838(14)00969-5; 3. Joniau S for EmPACT, Eur Urol. 2014 Jan 25. *epub*; 4. Widmark A, SPCG-7, Lancet. 2009 373(9660):301-8; Warde P, SPCG-7, Lancet. 2011 378(9809):2104-11.

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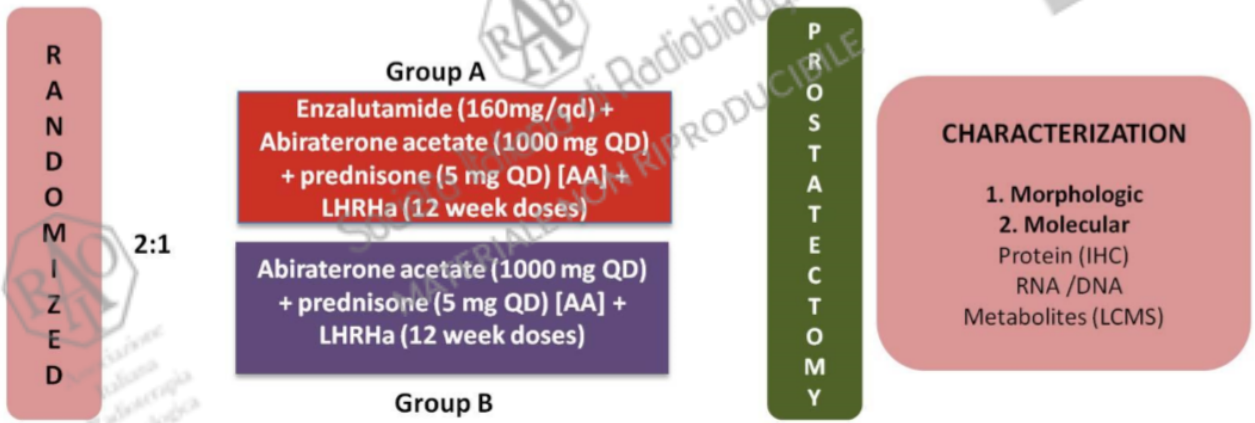
Neoadjuvant enzalutamide (ENZA) and abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus AA+ LHRHa in localized high-risk prostate cancer (LHRPC)

Eleni Efstathiou, John Davis, Mark Titus, Brian Chapin, Amado Zurita, Sijin Wen, Elsa Li Ning Tapia, Alexandros Tsikkinis, Anh Hoang, Ina Prokhorova, Patricia Troncoso, Christopher J Logothetis

The University of Texas MD Anderson Cancer Center, Houston, TX; University of Athens, Athens, Greece;

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®



Treatment: 6 months

Eligibility:

- Adenocarcinoma
- Gleason ≥ 8 *OR* Gleason 7 + ≥cT2b+PSA>10ng/ml
- Absent metastases

End points:

- Cytoreduction (Primary: ypT2N0 vs >ypT2N0)
- Residual cancer characterization
- PSA recurrence
- Safety

Efstathiou, 2016 ASCO Annual Meeting

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The University of Texas MD Anderson Cancer Center, Houston, TX; University of Athens, Athens, Greece;

Non è la specie più forte o la più intelligente
a sopravvivere, ma quella
che si adatta meglio al cambiamento.

Surgery	Group A AA+ENZA+LHRHa	Group B AA+LHRHa	
N*(Robotic-assisted prostatectomy)	43	21	
Lymph nodes, mean (range)	21 (8-41)	19(10-42)	
Perioperative serious AE	1 Pelvic Bleeding	1 cardiac MI	
Blood loss, mL, median (range)	150(50-600)	75(50-400)	
Pathology			***P* value**
≤ ypT2N0, n (%)	**13 (30)**	**11 (52)**	**0.08**
ypT0N0 CR	1	1	
Surgical margin negative, n (%)	34 (77)	19 (90)	ns
Lymph nodes negative, n (%)	27(61)	17 (81)	ns
PSA nadir			
PSA ≤ 0.1 ng/mL, n (%)	39 (89)	19 (90)	ns

Efstathiou, 2016 ASCO Annual Meeting

Ongoing Phase III Trial with new AR pathways inhibitor

Study	N	Arms	Endpoints
ENZAMET: Enzalutamide in first line androgen deprivation therapy for metastatic prostate cancer: a randomised phase III trial (ANZUP 1304)	1100	ADT + enzalutamide or bicalutamide	OS
LATITUDE: A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naïve Pca (NCT01715285)	1270	ADT ± abiraterone	OS
PEACE 1: A Phase III of ADT +/- Local RT +/- Abiraterone Acetate in Metastatic Hormone-naïve Prostate Cancer.(NCT01957436)	916	ADT + abiraterone, EBRT, or abiraterone+EBRT	OS PFS
STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial (NCT00268476)	5000	ADT ± EBRT, zoledronic acid, docetaxel, abiraterone, celecoxib	OS

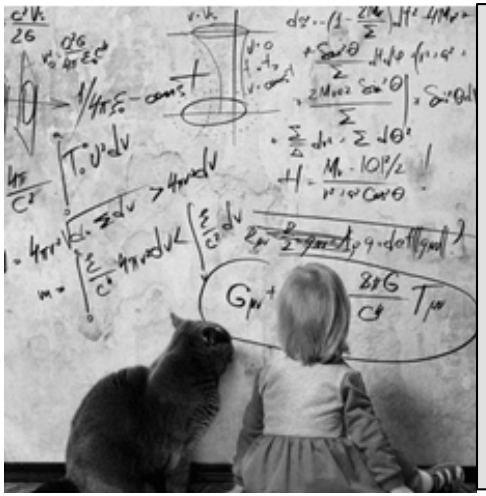
Conclusions…if possible…

- ✓ Prostate cancer treatment has dramatically changed…it's changing…and will change in the next future

- ✓ Future developments :
  - New drugs (hormonal…and not only…)
  - New indication "old drugs"
  - New combinations (EBRT!!!)

- ✓ More attention to the toxicity

- ✓ Need biomarkers!!!



Confusione è una parola inventata per indicare un ordine

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Grazie per l'attenzione