Per una vita come prima

Abiraterone nella Neoplasia Prostatica

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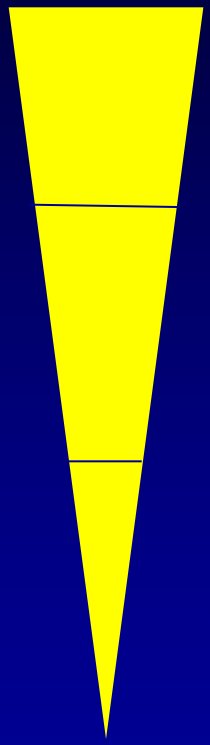
Negrar, 11 may 2013

Defining the problem …

- **Androgen Deprivation Therapy (ADT) till now Treatment of Choice for advanced Prostate Cancer with High overall Disease Control Rates (about 80-85%).**

- **However, almost all cases will progress to a Castration-Resistant status (CRPC)* within 24-36 months.**



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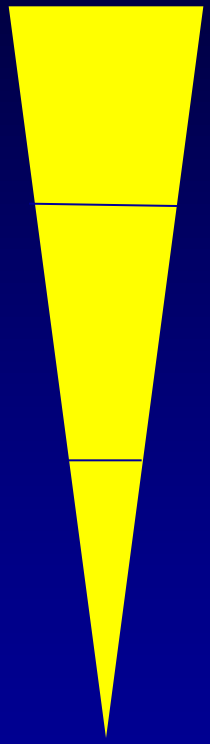
- **However, almost all cases will progress to a Castration-Resistant status (CRPC)* within 24-36 months.**

- **Large part of these cases actually evaluated and treated with a *First Line Docetaxel-based Chemoterapy* (mainly because of Phase III TAX 327 Study Data) with significant improvements in median OS.**



Docetaxel: nowadays, the standard of care for mCRPC In First Line

TAX 327: Study Design

Stratification:

Pain level
PPI ≥ 2 or AS ≥ 10
vs
PPI < 2 or AS < 10

KPS
≤70 vs ≥ 80

RANDOMIZE

- Docetaxel 75 mg/m² q 3 wk + Prednisone 5 mg bid
- Docetaxel 30 mg/m² wkly 5 of 6 wks + Prednisone 5 mg bid
- Mitoxantrone 12 mg/m² q 3 wk + Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

Eisenberger et al. *Proc ASCO.* 2004;23:2. Abstract 4.

Overall. More than 1.600 met HRPC pts treated !!

SWOG 9916: Study Design

R

- **D/E***
  Docetaxel 60 mg/m² IV D2 every 21 days
  Estramustine 280 mg po TID, D1-5
  Premedication: Dexamethasone 20 mg PO TID starting evening of D1
- **M/P**
  Mitoxantrone 12 mg/m² IV every 21 days
  Prednisone 5 mg po BID continuously

*Per protocol amendment January 15, 2001: Coumadin 2 mg PO daily + ASA 325 mg PO daily was added.
Docetaxel and mitoxantrone doses could be increased to 70 mg/m² and 14 mg/m², respectively, if no grade 3 or 4 toxicities were seen in cycle 1.

Petrylak et al. *Proc ASCO.* 2004;23:2. Abstract 3.

Treatment of Choice for HRPC since 2004: Docetaxel (>OS)

Comparison of initial and updated OS analysis

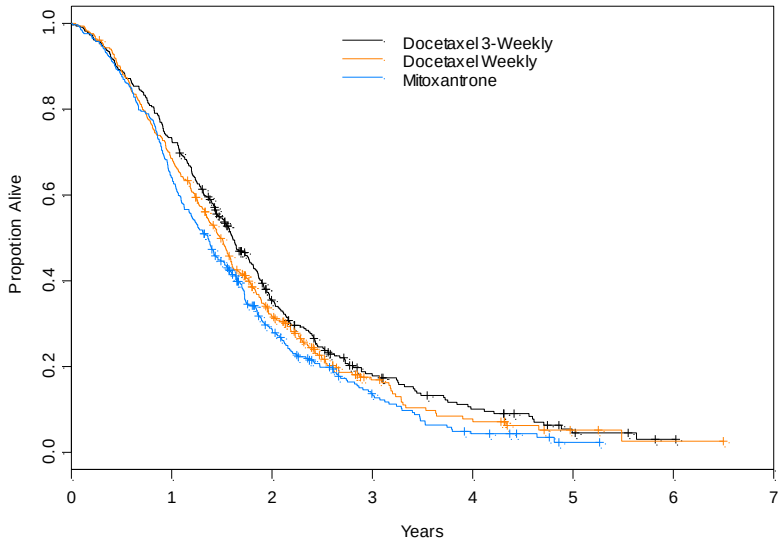
OS = +2.9 m

	Median OS			
	2003 Data	p-value	Update 2007	p-value
- DCT Q3w	18.9 (17.0-21.2)	0.009	**19.2** (17.5-21.3)	0.004
- DCT wk	17.4 (15.7-19.0)		**17.8** (16.2-19.2)	
- Mitox.	16.5 (14.4-18.6)		**16.3** (14.3-17.9)	

*** 95% confidence interval indicated**

3-yr Survival Rate

	Docetaxel Q3W (n=335)	Docetaxel Weekly (n=334)	Mitoxantrone (n=337)
3-yr survival rate	17.9%	16.7%	13.7%



2° Line Scenario: Defining the problem …

- **At a further Progression patients remaining in good general conditions should be evaluated for a second Line Option:**

1. **Some part of these patients could be initially retreated with Docetaxel (so called "Rechallenge"); *at the moment not according to general rules.***

2. **Some others should be evaluated for "really efficacious" second Line Options (… not simply for a second Line Option ..)**

Bracarda S, et Al. BJUI 2011

…. what's new about … ?

... We recently moved from a definition of **HRPC**
(Hormone-Refractory Prostate Cancer)

to a definiton of "**CRPC**"

(Castration-Resistant Prostate Cancer):

- not simply a "formal" change !! -

An increasing amount of Data shows a persistent activity of the AR Pathway in CRPC Cells

Because of:

- **Persistent high levels of Androgens in Tumoral Cells, despite circulating T at castration levels.**
  - T, DHT and AD levels sufficient to stimulate AR
  - Increased expression of genes/enzymes involved in steroid (androgen) biosynthesis[1,2]

- **Adaptive mechanisms allowing for an AR signalling *despite a "castrate-level" androgen environment***
  - AR over-expression
  - AR mutations
  - AR "promiscuity"

1. Locke, et al. *Cancer Res.* 2008; 2. Holzbeierlein, et al. *Am J Pathol.* 2004;

An increasing amount of Data shows a persistent activity of the AR Pathway in CRPC Cells

Two important following treatment considerations:

1) Possible activity of further Innovative Agents targeting the AR or other targets, mainly in the Bone (c-Met, VEGFR, Other)

2) Possible activity of further CT agents with a demonstrated efficacy in DCT-Refractory Disease (because of a persistent induced mitotic activity).

New Possible available Options:

Abiraterone Acetate Enzalutamide, Other

Bone Targeting Agents: Alpharadin, Cabozantinib, Other

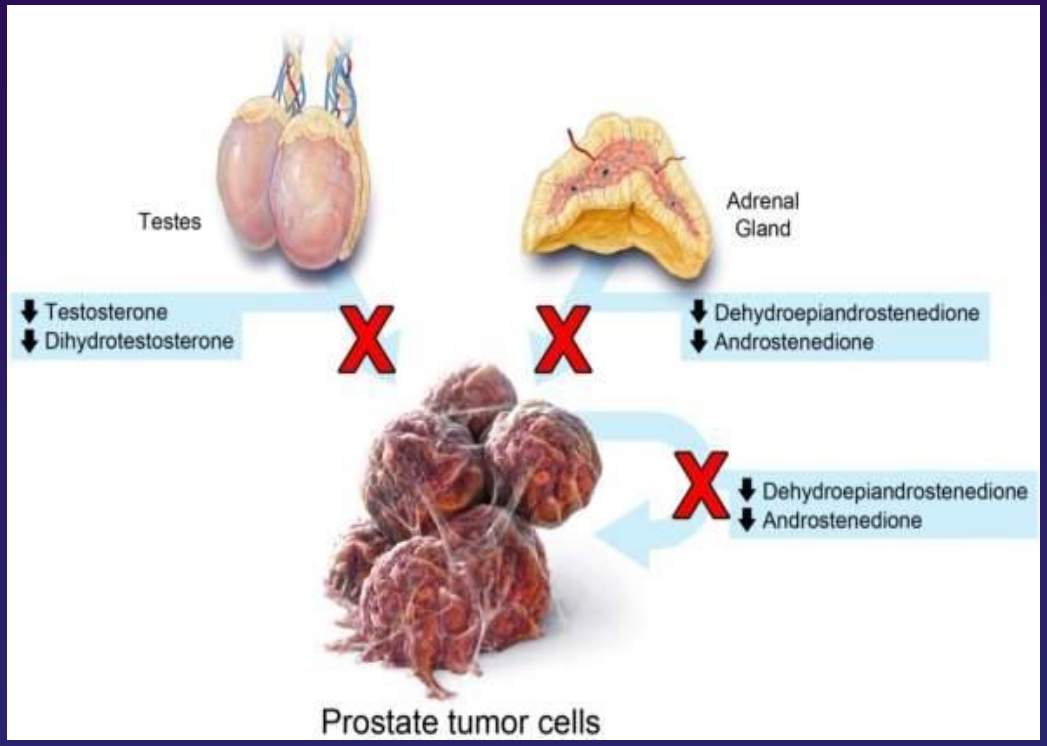
Cabazitaxel

Abiraterone Acetate:
An Androgen Biosynthesis Inhibitor

- ***Androgens** produced at three critical sites **lead to tumor proliferation***:
  - Testes
  - Adrenal gland
  - Prostate tumor cells

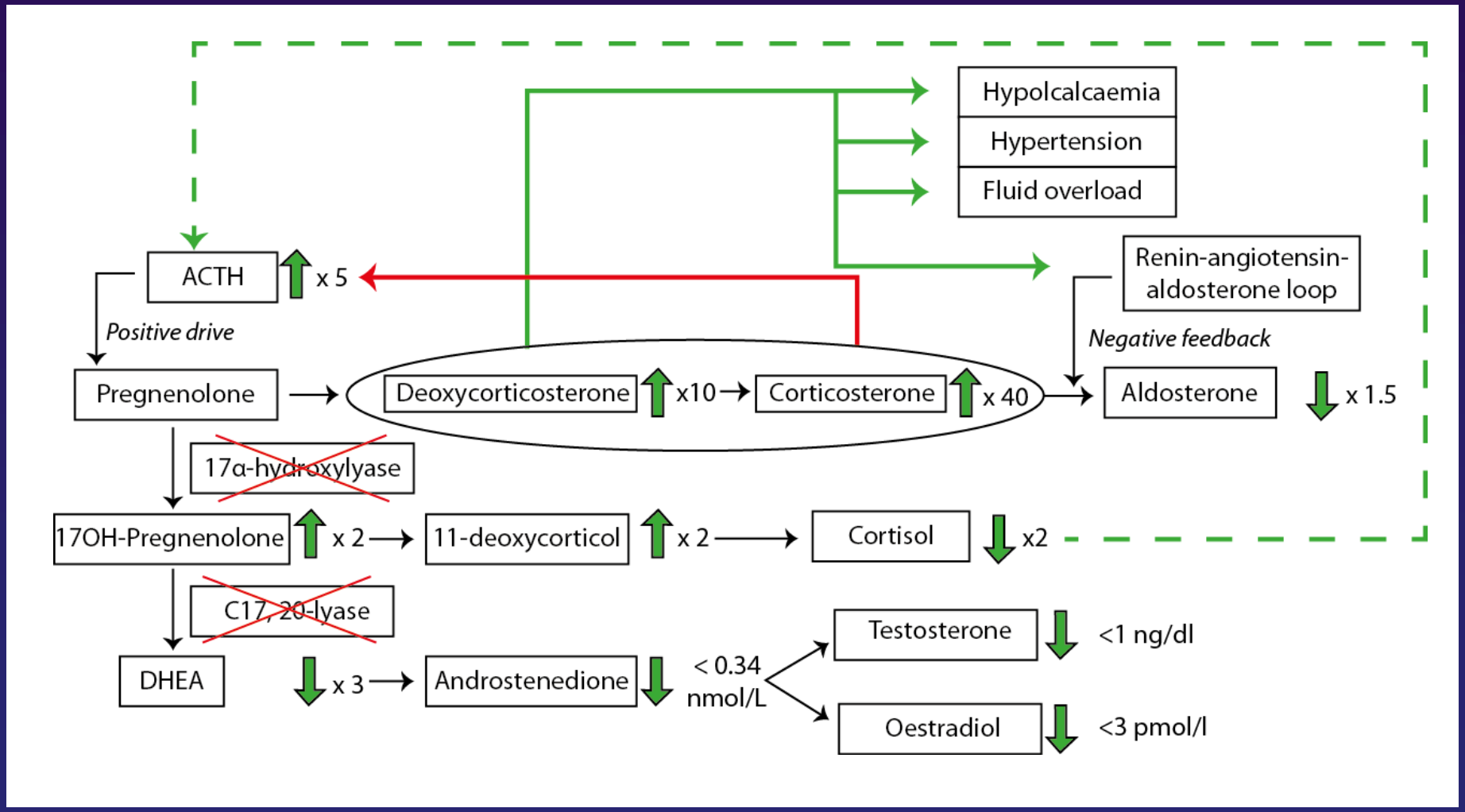
- **ADT reduce androgen synthesis**

- **Abiraterone,** *an Oral, selective inhibitor of the key enzyme CYP17,* **inhibits biosynthesis of androgens (T, DHT)** that stimulate tumor cell growth,



1. Attard G et al, *J Clin Oncol*, 2008; 2. Attard G et al. *J Clin Oncol*. 2009;
3. Reid AH et al. *J Clin Oncol*. 2010;
4. Ryan C et al, *J Clin Oncol*, 2009; 5. Danila D et al, *J Clin Oncol*, 2010.

Abiraterone Acetate: MOA



Abiraterone Acetate plus Pdn vs Placebo plus Pdn in Docetaxel progressive mCRPC pts. Results of the phase III Randomized Study AA-301.

(147 sites in 13 countries; USA, Europe, Australia, Canada)

- **1195 pts with progressive mCRPC**
- **Failed 1 or 2 CT Regimens, one of which contained Docetaxel**
- **Randomised 2:1**
- **Stratification by:**
- ECOG PS (0-1 vs. 2)
- Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
- Prior CT (1 vs. 2)
- Type of progression (PSA only vs. Rx PD with or without PSA PD)

Abiraterone acetate 1000 mg daily

Prednisone 5mg twice daily

Placebo daily

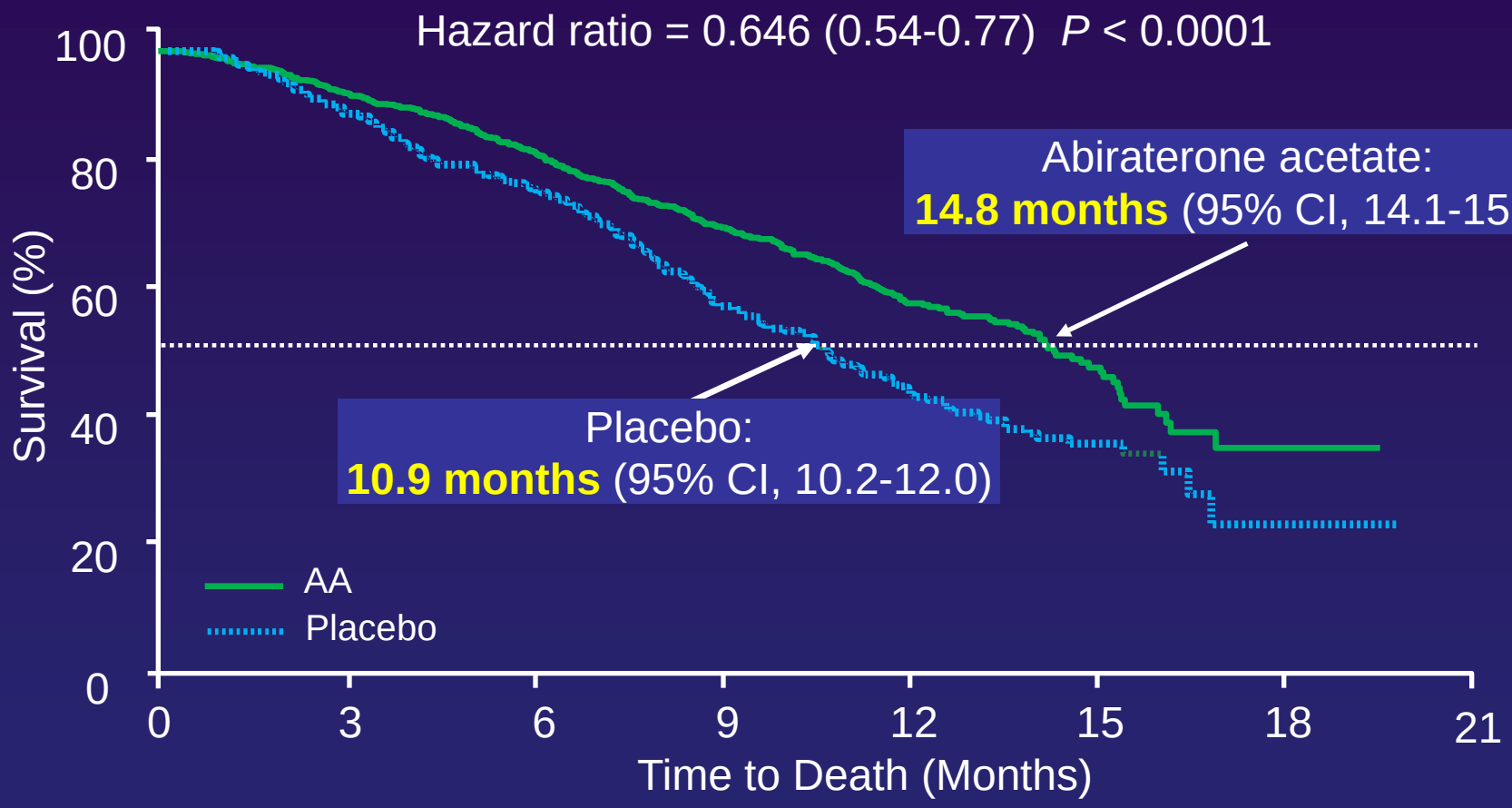
Prednisone 5mg twice daily

TREAT UNTIL PROGRESSION

Primary endpoint: OS (25% improvement; HR 0.8)

de Bono et al. Ann Oncol 2010: Abstract LBA5 (Oral presentation at ESMO)
Scher et al. J Clin Oncol 2011; 29(7S):Abstract 4 (Oral presentation at ASCO GU)

Abiraterone Acetate: Improved OS in mCRPC

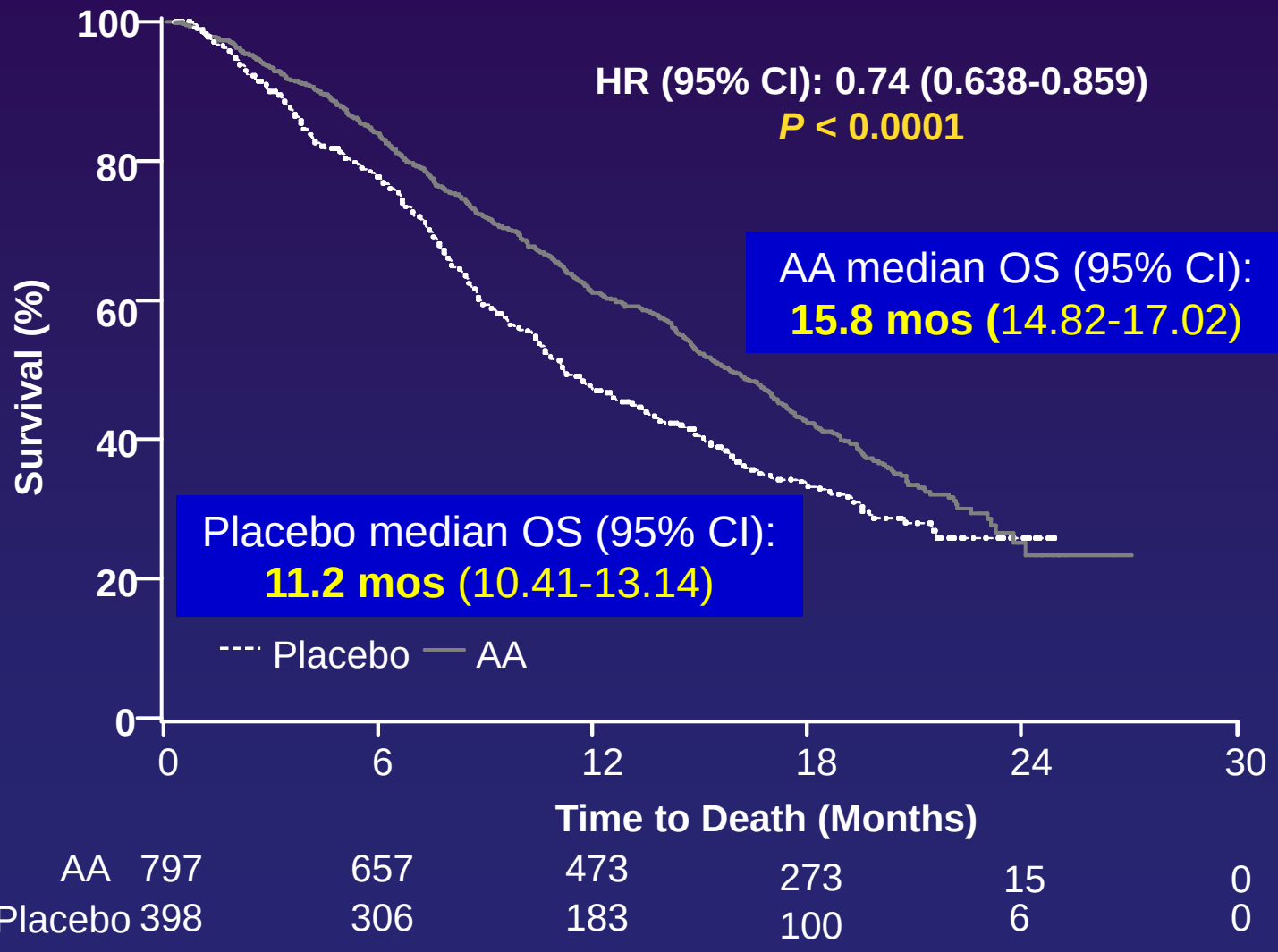


AA	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

de Bono et al. Ann Oncol 2010: Abstract LBA5 (Oral presentation at ESMO)
Scher et al. J Clin Oncol 2011; 29(7S):Abstract 4 (Oral presentation at ASCO GU)

V2.0

Study 301. second pre-planned analysis (775 Events): median OS Increase from 3.9 to 4.6 Months

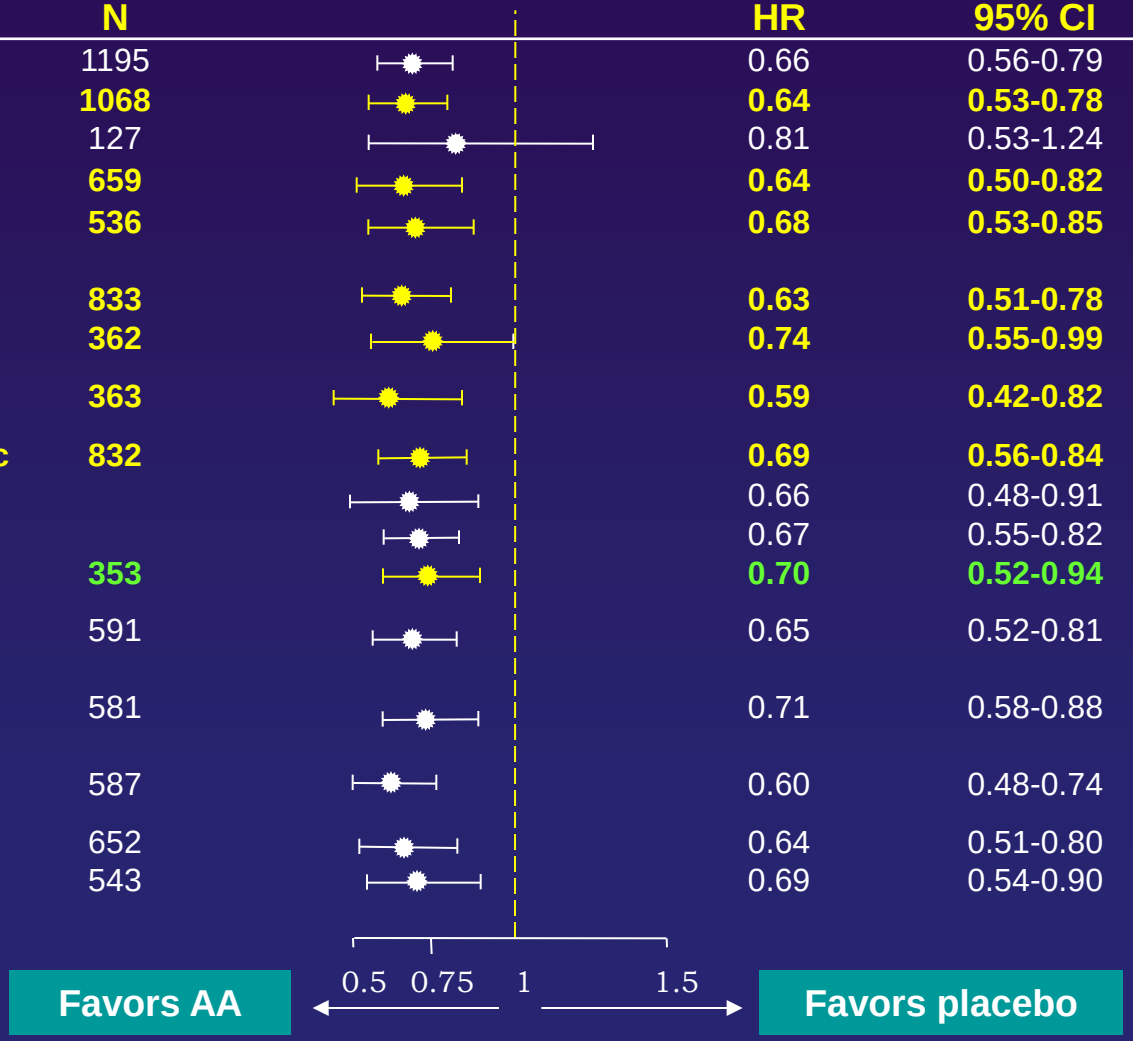


Scher et al. J Clin Oncol 2012; 29 (suppl): Abs A4517 (oral presentation)

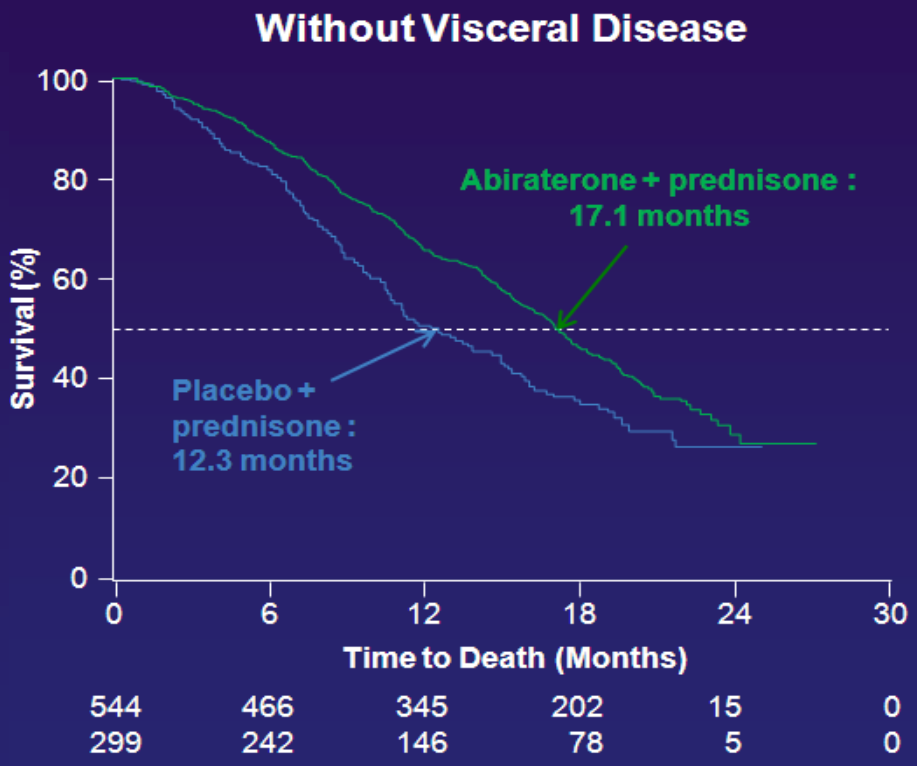
V2.0

Observed Survival Benefit consistent across Patient Subgroups

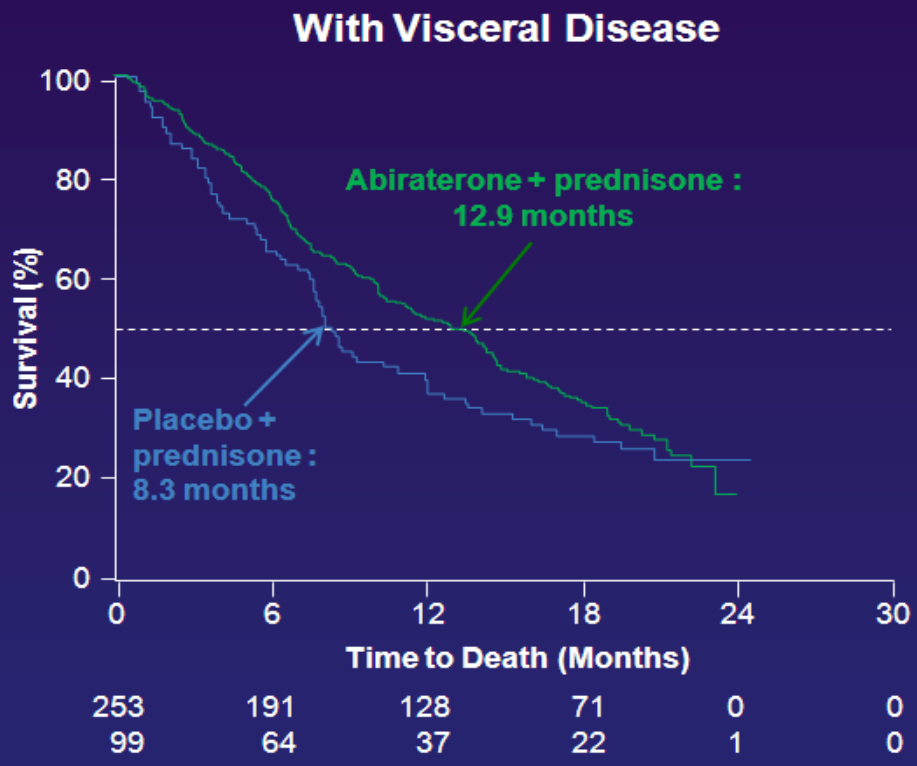
Variable	Subgroup	N	HR	95% CI
All subjects	All	1195	0.66	0.56-0.79
Baseline ECOG	**0-1**	**1068**	**0.64**	**0.53-0.78**
	2	127	0.81	0.53-1.24
Baseline BPI	**< 4**	**659**	**0.64**	**0.50-0.82**
	≥ 4	**536**	**0.68**	**0.53-0.85**
No of prior chemotherapy regimens	**1**	**833**	**0.63**	**0.51-0.78**
	2	**362**	**0.74**	**0.55-0.99**
Type of progression	**PSA only**	**363**	**0.59**	**0.42-0.82**
	Radiographic	**832**	**0.69**	**0.56-0.84**
Age, years	< 65		0.66	0.48-0.91
	≥ 65		0.67	0.55-0.82
Visceral disease at entry	**Yes**	**353**	**0.70**	**0.52-0.94**
Baseline PSA above median	Yes	591	0.65	0.52-0.81
Baseline LDH above median	Yes	581	0.71	0.58-0.88
Baseline ALK-P above median	Yes	587	0.60	0.48-0.74
Region	N America	652	0.64	0.51-0.80
	Other	543	0.69	0.54-0.90



Vantaggio in OS mantenuto nei pazienti con metastasi viscerali



HR 0,69; 95% CI 0.58-0.82



HR 0,79; 95% CI 0.59-1.05

Fizazi et al; ECCO 2011, abstract 7000 (oral presentation)

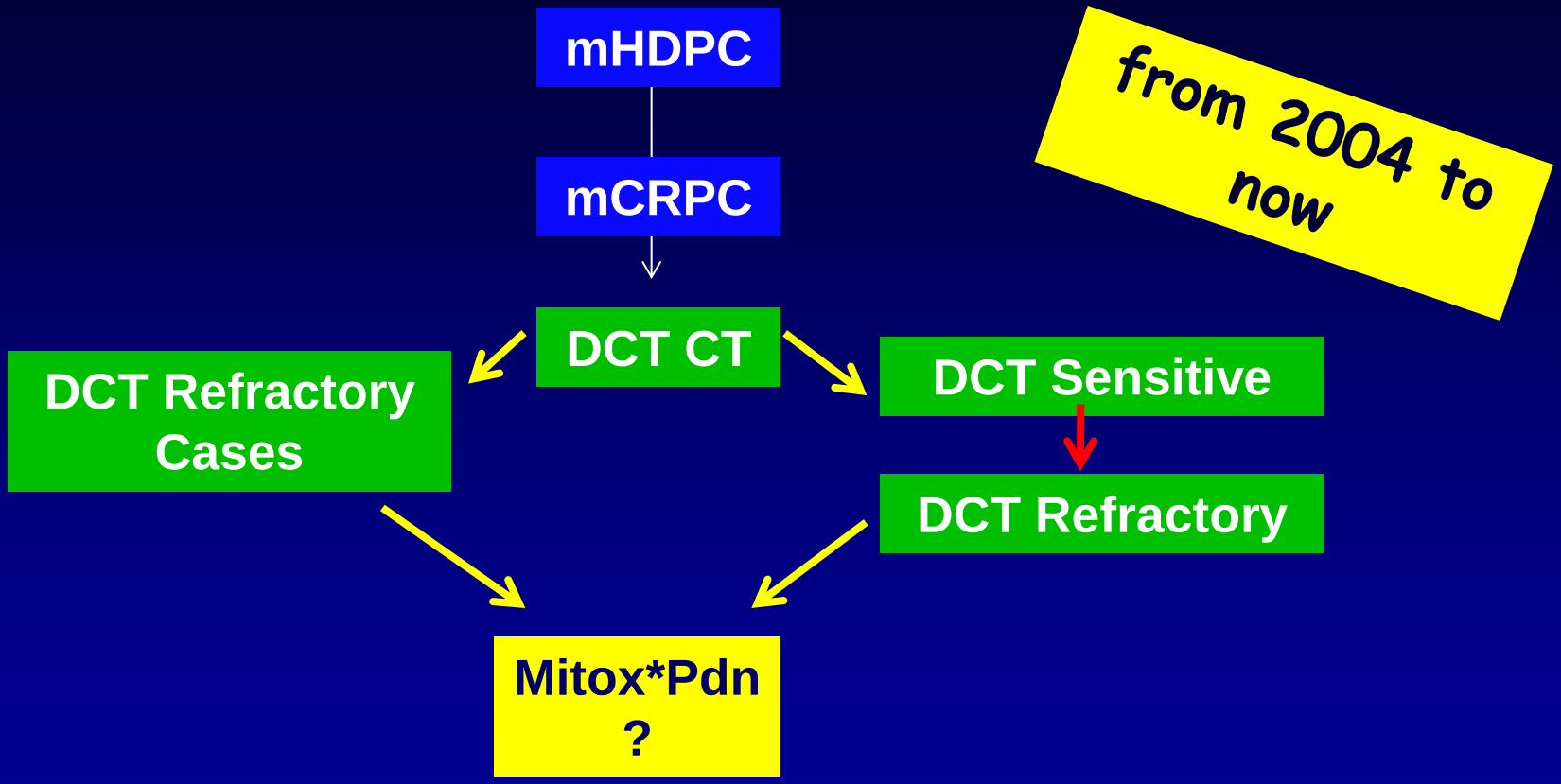
V2.0

AEs of Special Interest

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	30.5%	**2.3%**	22.3%	**1.0%**
Hypokalaemia	17.1%	**3.8%**	8.4%	**0.8%**
LFT abnormalities	10.4%	**3.5%**	8.1%	**3.0%**
Hypertension	9.7%	**1.3%**	7.9%	**0.3%**
Cardiac disorders	13.3%	**3.0%**	10.4%	**2.0%**

de Bono et al. Ann Oncol 2010: Abstract LBA5 (Oral presentation at ESMO)
Scher et al. J Clin Oncol 2011; 29(7S):Abstract 4 (Oral presentation at ASCO GU)

…. what's change in CRPC Scenario with Abiraterone and other New Drugs Availability



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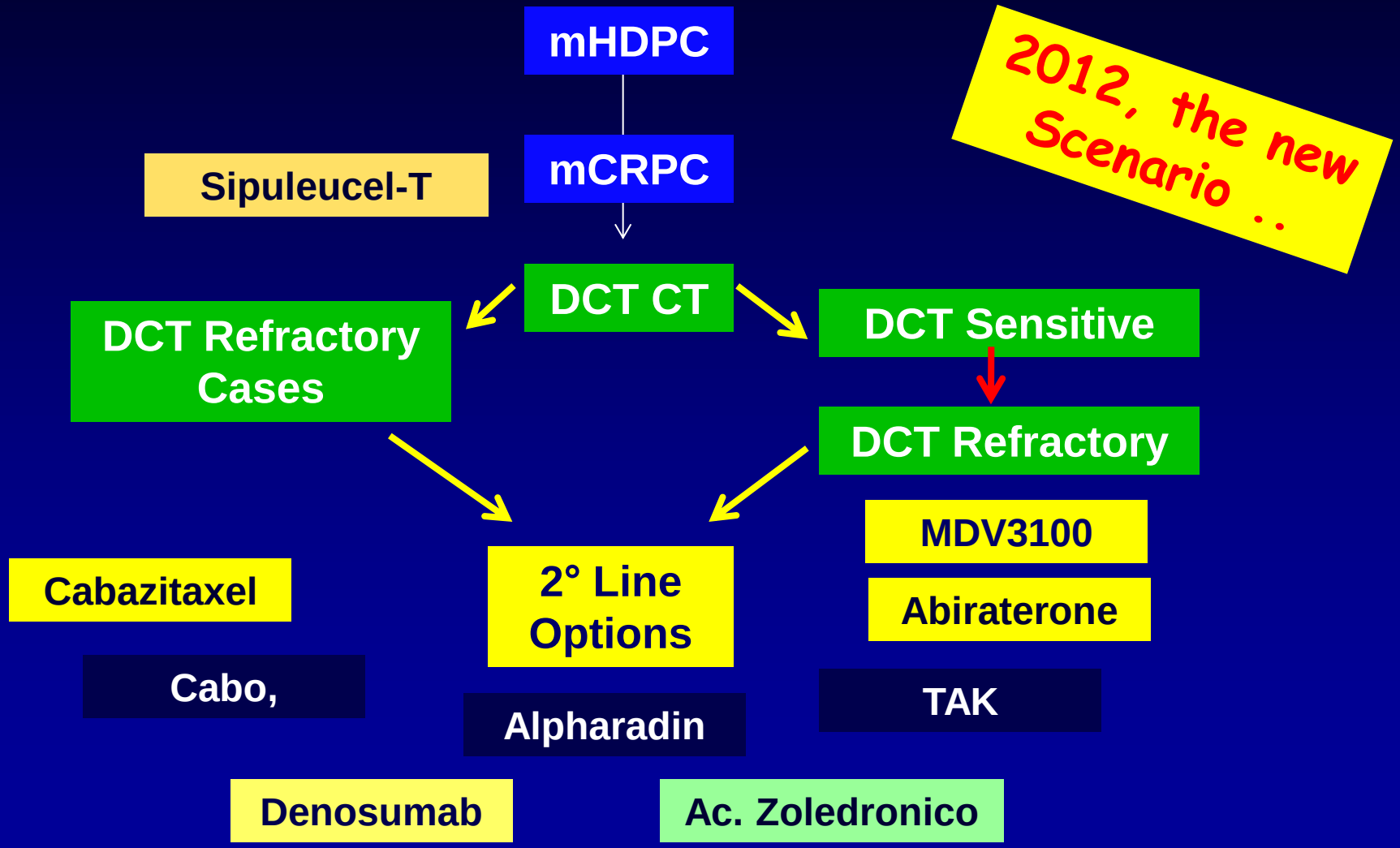
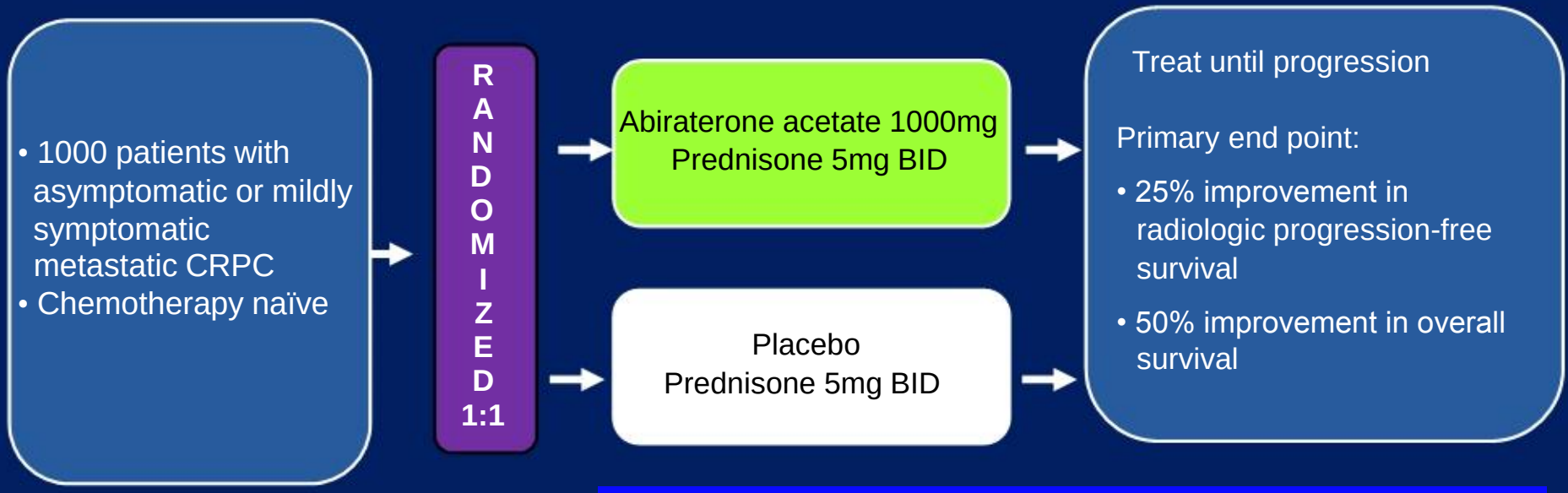


Phase III Trial of Abiraterone Acetate in asymptomatic or mildly symptomatic metastatic CT-naïve CRPC: Study AA-302



Stratified by:
ECOG PS (0 vs 1)

	AA plus Pdn	vs PL plus Pdn
Median PFS	**NR**	**8.3m**
Median OS	**NR**	**27.2m**

Accrual completed 4/2009

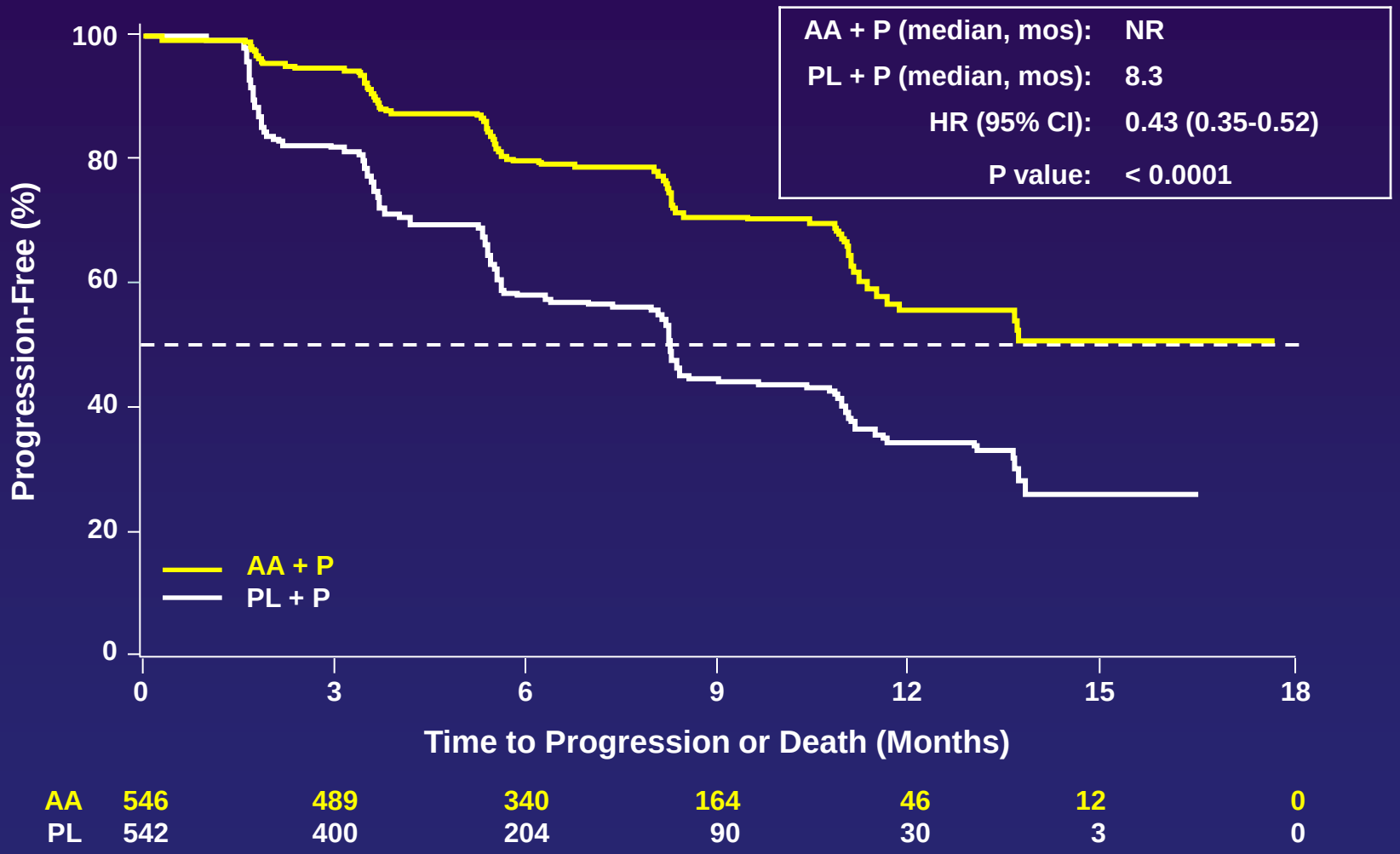
www.clinicaltrials.gov Identifier: NCT00887198

Study 302: Treatment Arms Evenly Matched

	AA + P (n = 546)	Placebo + P (n = 542)
Median age, years (range)	71 (44-95)	70 (44-90)
Median time from initial diagnosis to first dose (years)	5.5	5.1
Median PSA (ng/mL)	42.0	37.7
Median testosterone (ng/dL)	40.0	40.0
Median alkaline phosphatase (IU/L)	93.0	90.0
Median hemoglobin (g/dL)	13.0	13.1
Median lactate dehydrogenase (IU/L)	187.0	184.0
Gleason score (≥8) at initial diagnosis	54%	50%
Extent of disease		
Bone metastases	83%	80%
>10 bone lesions	49%	47%
Soft tissue or node	49%	50%
Pain (BPI Short Form)		
0-1	66%	64%
2-3	32%	33%

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

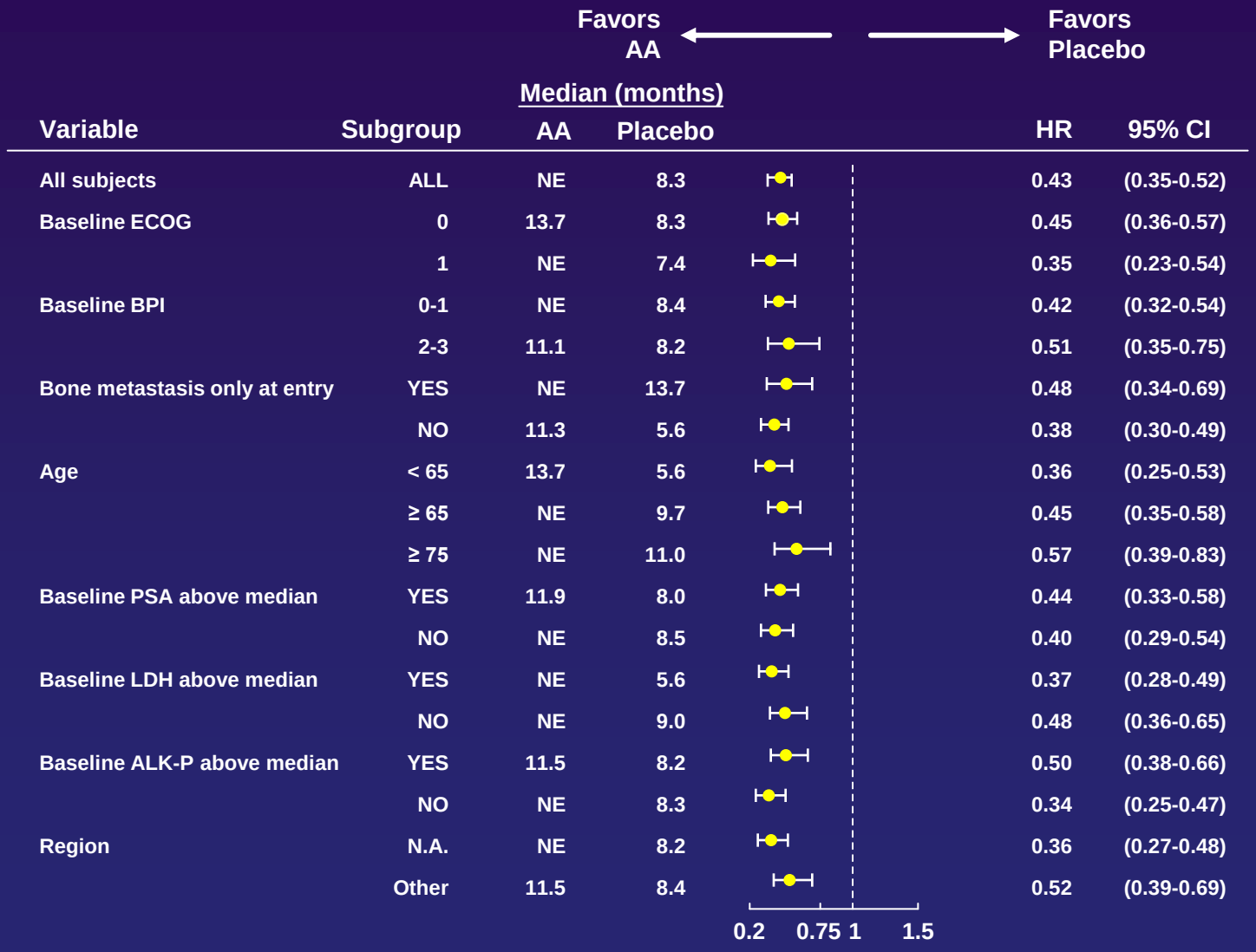
Statistically Significant Improvement in rPFS Primary End Point



Data cutoff 20/12/2010

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

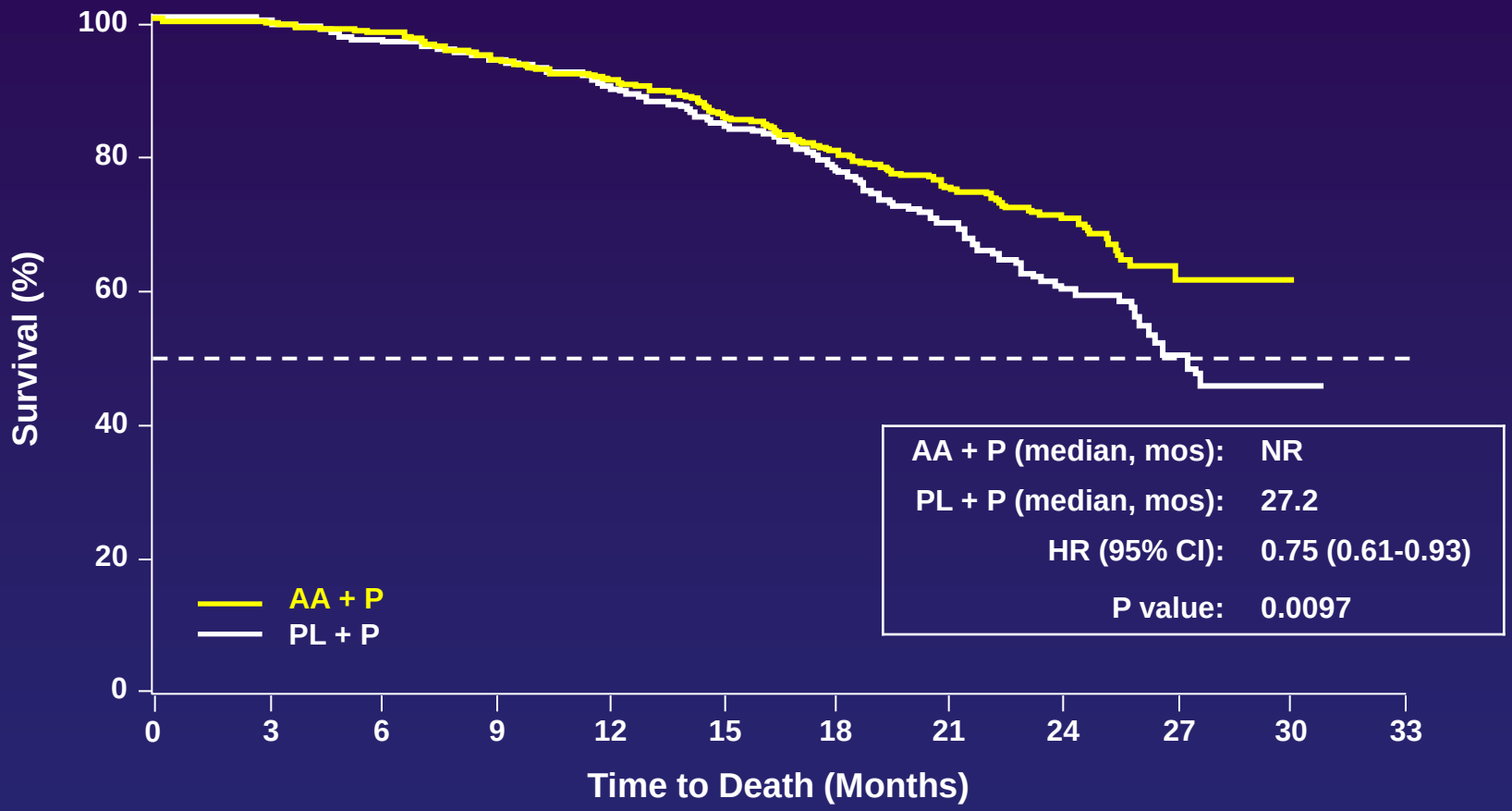
rPFS Benefit Demonstrated Across Full Spectrum of Patient Subgroups



Variable	Subgroup	Median (months) AA	Median (months) Placebo	HR	95% CI
All subjects	ALL	NE	8.3	0.43	(0.35-0.52)
Baseline ECOG	0	13.7	8.3	0.45	(0.36-0.57)
	1	NE	7.4	0.35	(0.23-0.54)
Baseline BPI	0-1	NE	8.4	0.42	(0.32-0.54)
	2-3	11.1	8.2	0.51	(0.35-0.75)
Bone metastasis only at entry	YES	NE	13.7	0.48	(0.34-0.69)
	NO	11.3	5.6	0.38	(0.30-0.49)
Age	< 65	13.7	5.6	0.36	(0.25-0.53)
	≥ 65	NE	9.7	0.45	(0.35-0.58)
	≥ 75	NE	11.0	0.57	(0.39-0.83)
Baseline PSA above median	YES	11.9	8.0	0.44	(0.33-0.58)
	NO	NE	8.5	0.40	(0.29-0.54)
Baseline LDH above median	YES	NE	5.6	0.37	(0.28-0.49)
	NO	NE	9.0	0.48	(0.36-0.65)
Baseline ALK-P above median	YES	11.5	8.2	0.50	(0.38-0.66)
	NO	NE	8.3	0.34	(0.25-0.47)
Region	N.A.	NE	8.2	0.36	(0.27-0.48)
	Other	11.5	8.4	0.52	(0.39-0.69)

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Strong Trend in OS (*co-Primary End Point*)



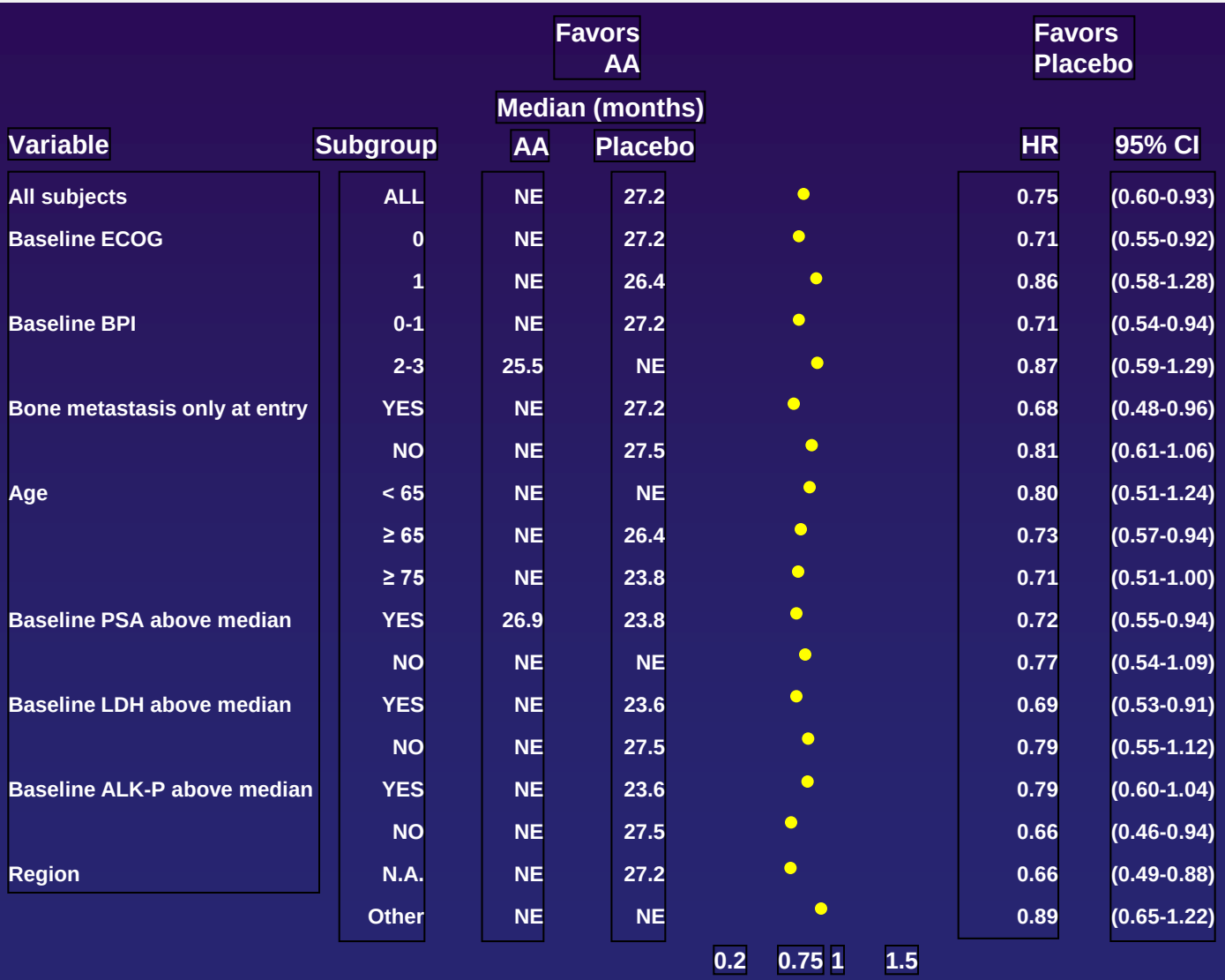
AA	546	538	524	503	482	452	412	258	120	27	0	0
PL	542	534	509	493	465	437	387	237	106	25	2	0

Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008

Data cutoff 20/12/2011

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Point Estimates for OS Favor AA in All Patient Subgroups



Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Statistically Significant Improvement in All Secondary End Points

	AA + P	Placebo + P		
	Median (months)	Median (months)	HR (95% CI)	P Value
Time to opiate use (cancer related pain)	NR	23.7	0.69 (0.57, 0.83)	0.0001
Time to chemotherapy initiation	25.2	16.8	0.58 (0.49, 0.69)	<0.0001
Time to ECOG PS deterioration	12.3	10.9	0.82 (0.71, 0.94)	0.0053
Time to PSA progression	11.1	5.6	0.49 (0.42, 0.57)	<0.0001

Note: All secondary end points remain significant after adjusting for multiplicity testing

Patient Reported Outcomes favored AA +P vs. Placebo +P
Full data to be reported

Data cut off 20/12/2011

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

No New Safety Concerns Identified with Longer AA Treatment than in 301 Study

	AA + P (n = 542) %		Placebo + P (n = 540) %	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fatigue	39	2	34	2
Fluid retention/edema	28	0.7	24	1.7
Hypokalemia	17	2	13	2
Hypertension	22	4	13	3
Cardiac disorders	19	6	16	3
Atrial fibrillation	4	1.3	5	0.9
ALT increased	12	5.4	5	0.7
AST increased	11	3.0	5	0.9

Most ALT and AST increases occurred during the first 3 months of treatment

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Subsequent Therapies Data

	AA + P (n = 546) n (%)	Placebo + P (n = 542) n (%)
No. with selected subsequent therapy for mCRPC	242 (44.3)	327 (60.3)
Docetaxel	**207 (37.9)**	**287 (53.0)**
Cabazitaxel	**45 (8.2)**	**52 (9.6)**
Ketoconazole	39 (7.1)	63 (11.6)
Sipuleucel-T	27 (4.9)	24 (4.4)
Abiraterone Ac*	**26 (4.8)**	**54 (10.0)**

*Prior to unblinding (e.g. not per protocol)

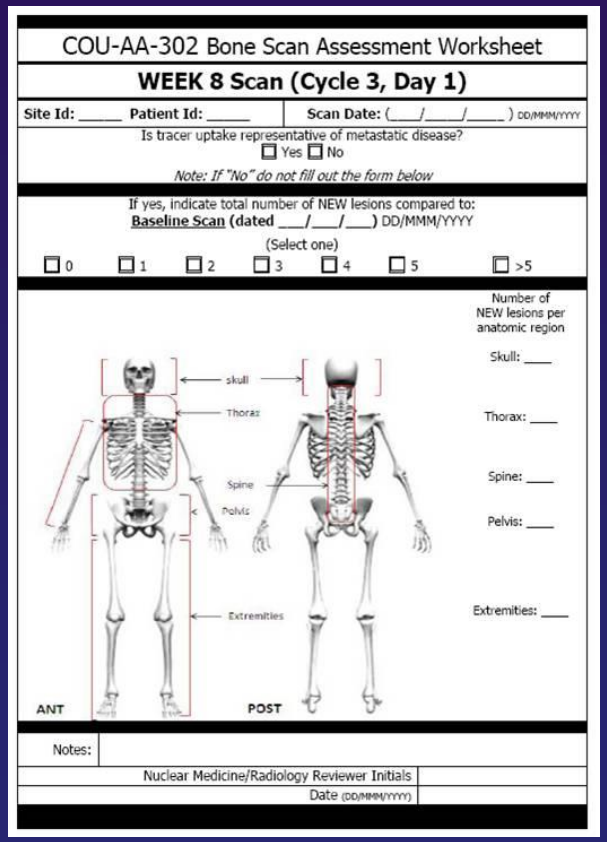
Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Adaptation of PCWG2 Consensus Criteria

COU-AA-302 Definition

- Progressive disease (PD) by bone scan: Adapted from PCWG2 consensus criteria1
  - Review < 12 weeks after randomization
    - ≥ 2 new bone lesions plus 2 additional lesions on a subsequent scan (“2+2”)
  - ≥ 12 weeks after randomization
    - ≥ 2 new bone lesions with new lesions confirmed at subsequent scan
- PD (soft tissue lesions) by CT/MRI by modified Response Evaluation Criteria in Solid Tumors (RECIST)
- Death from any cause

Prostate Cancer Clinical Trials Consortium (PCCTC) Bone Scan Form[2]



COU-AA-302 Bone Scan Assessment Worksheet

WEEK 8 Scan (Cycle 3, Day 1)

Site Id: _____ Patient Id: _____ Scan Date: (___/___/___) DD/MMM/YYYY

Is tracer uptake representative of metastatic disease?
☐ Yes ☐ No

Note: If "No" do not fill out the form below

If yes, indicate total number of NEW lesions compared to:
Baseline Scan (dated ___/___/___) DD/MMM/YYYY

(Select one)
☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ >5

Number of NEW lesions per anatomic region

Skull: ___
Thorax: ___
Spine: ___
Pelvis: ___
Extremities: ___

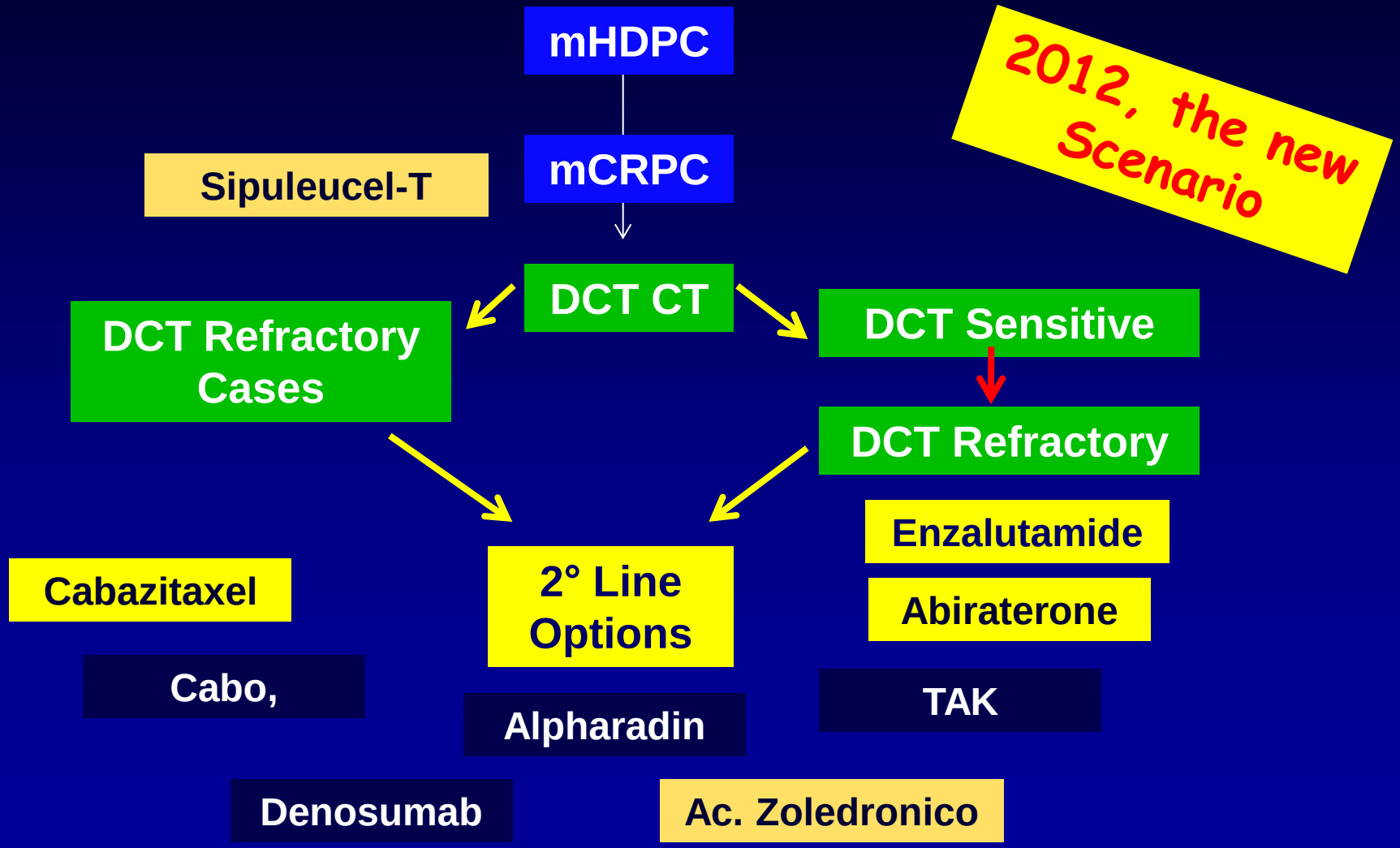
Notes:

Nuclear Medicine/Radiology Reviewer Initials

Date (DD/MMM/YYYY)

1. Scher HI, et al. *J Clin Oncol*. 2008;26:1148-1159.
2. Morris MJ, et al. *J Clin Oncol*. 2011;29(Suppl 7). Abstr 121.

…. what's moving in CRPC Scenario in the next few years… ?



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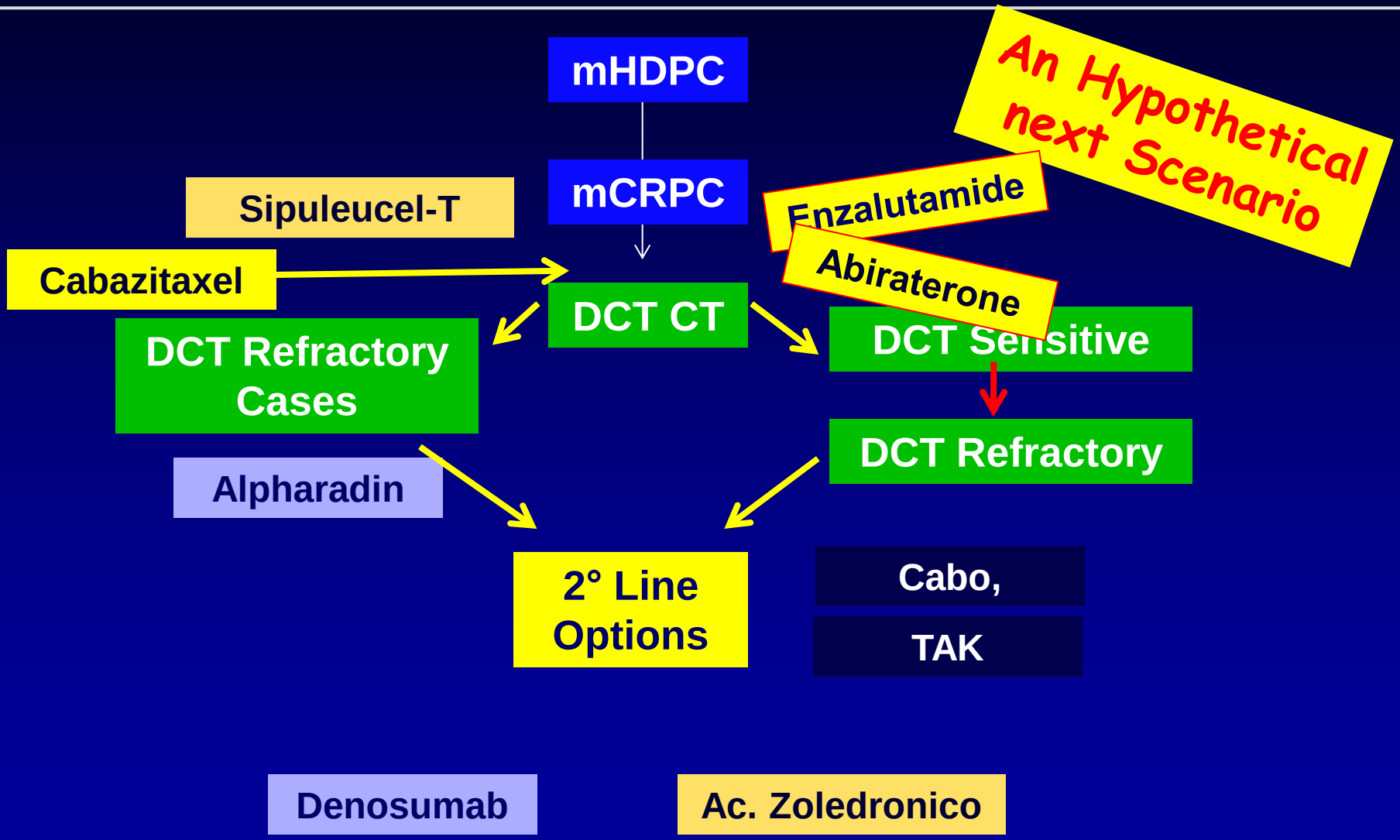

Conclusions

- After 7 years, We finally have *new* ***efficacious*** Treatment Options for CRPC, others are arriving.

- A significant percentage of these New Rx Options will move earlier phases of mCRPC and HDPC Treatment.

- The possibility of a personalized Treatment Approach, for mCRPC patients, it's arriving,

sb