Terapia Medica: quali nuove molecole nel paziente con Carcinoma della Prostata Resistente alla Castrazione metastatico (m-CRPC)?

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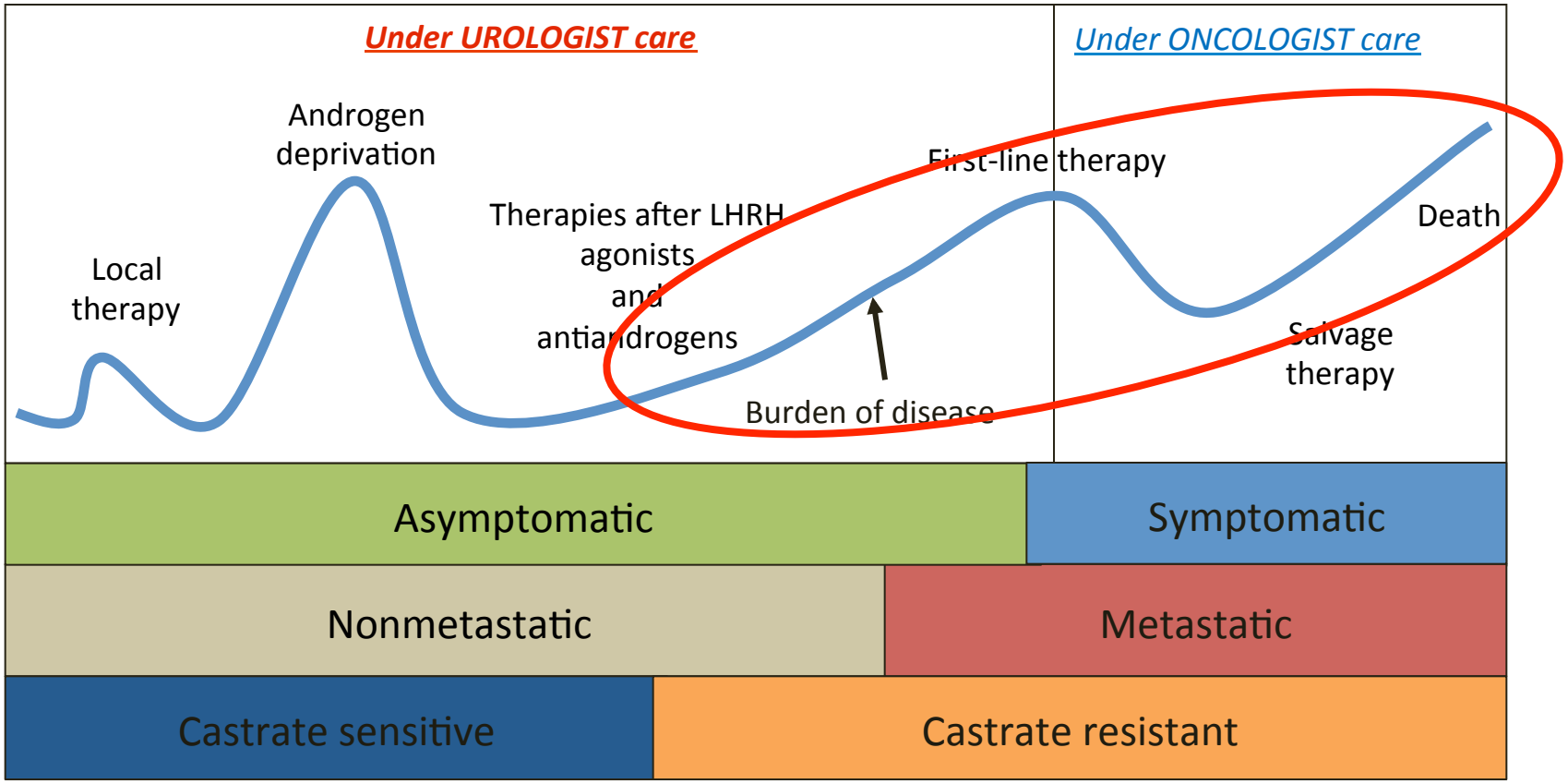
AIRO giovani incontra AIOM giovani – Rimini 18.05.2013

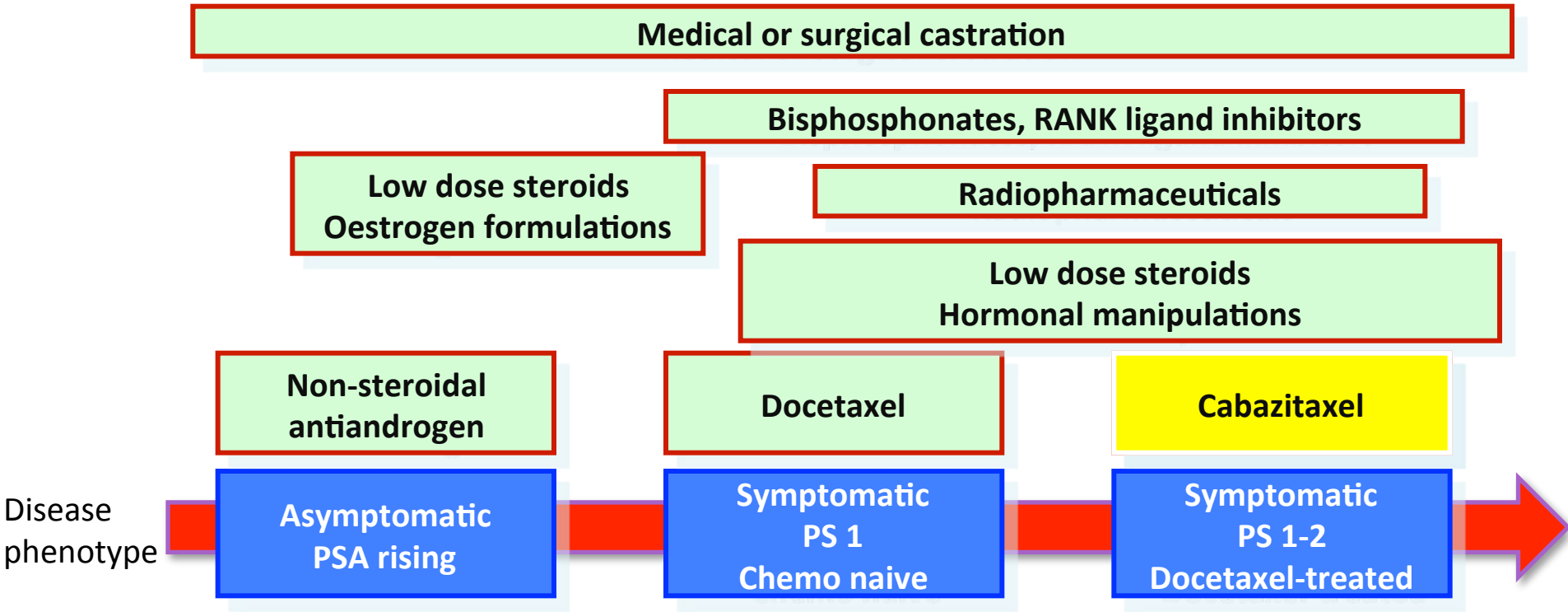
Natural History of Prostate Cancer

Typical patient presentation as they move through different stages



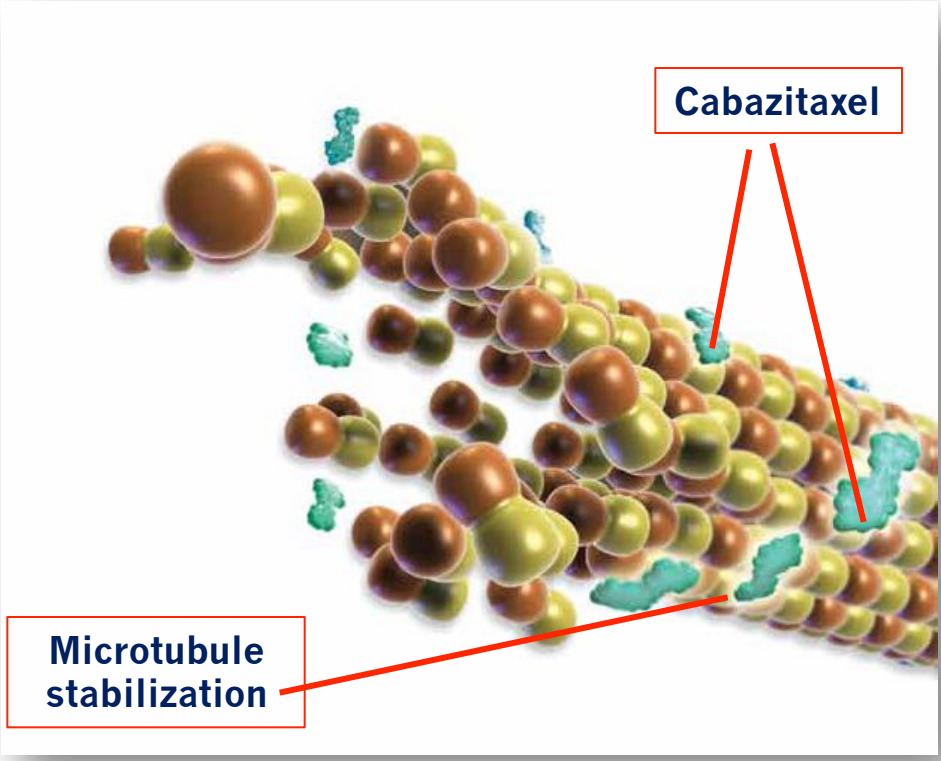
Higano C, et al. In: Figg WD, et al. Drug management of prostate cancer; 2010.

At the beginning of 2011



Cabazitaxel

- Selected over 450 docetaxel analogues for its ability to overcome taxane resistance
- As potent as docetaxel against sensitive cell lines and tumor models
- Active in vitro and in vivo against tumor models resistant to currently available taxanes



Cabazitaxel Preclinical Summary

	Docetaxel	Cabazitaxel
Stabilization of microtubules	√	√
Activity in taxane-sensitive cell lines	√	√
Activity in taxane-sensitive *in vivo* tumor models	√	√
Orally bioavailable in murine models		√
Active in chemotherapy-resistant or insensitive cell lines		√
Active in chemotherapy-resistant or insensitive *in vivo* tumor models		√
Crosses blood-brain-barrier *in vivo*		√

Phase III TROPIC trial

Cabazitaxel + prednisone (CBZP) versus mitoxantrone + prednisone (MP) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-based regimen

O. Sartor, S. Oudard, M. Ozguroglu, S. Hansen, J. P. H. Machiels, L. Shen, S. Gupta, J. S. De Bono, for the TROPIC Investigators

Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators

2010 ASCO Genitourinary Cancers Symposium & ASCO 2010

Phase III TROPIC trial

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors

ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)

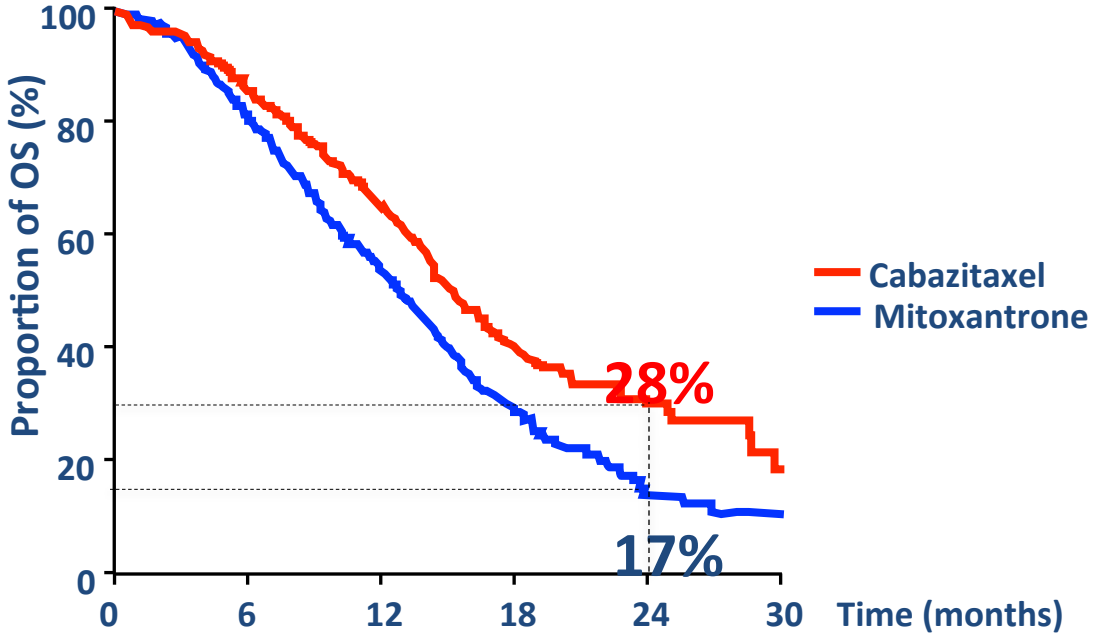
mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily

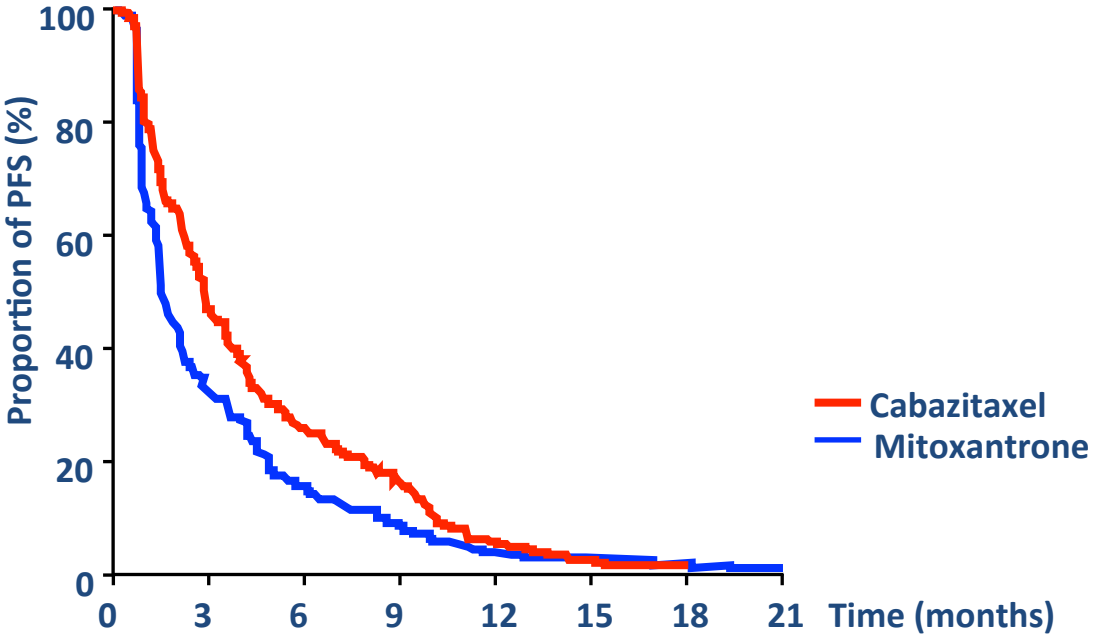
Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.70	
95% CI	0.59–0.83	
P value	<0.0001	



	MP	CBZP
Median PFS (months)	1.4	2.8
Hazard ratio	0.74	
95% CI	0.64–0.86	
P-value	<0.0001	

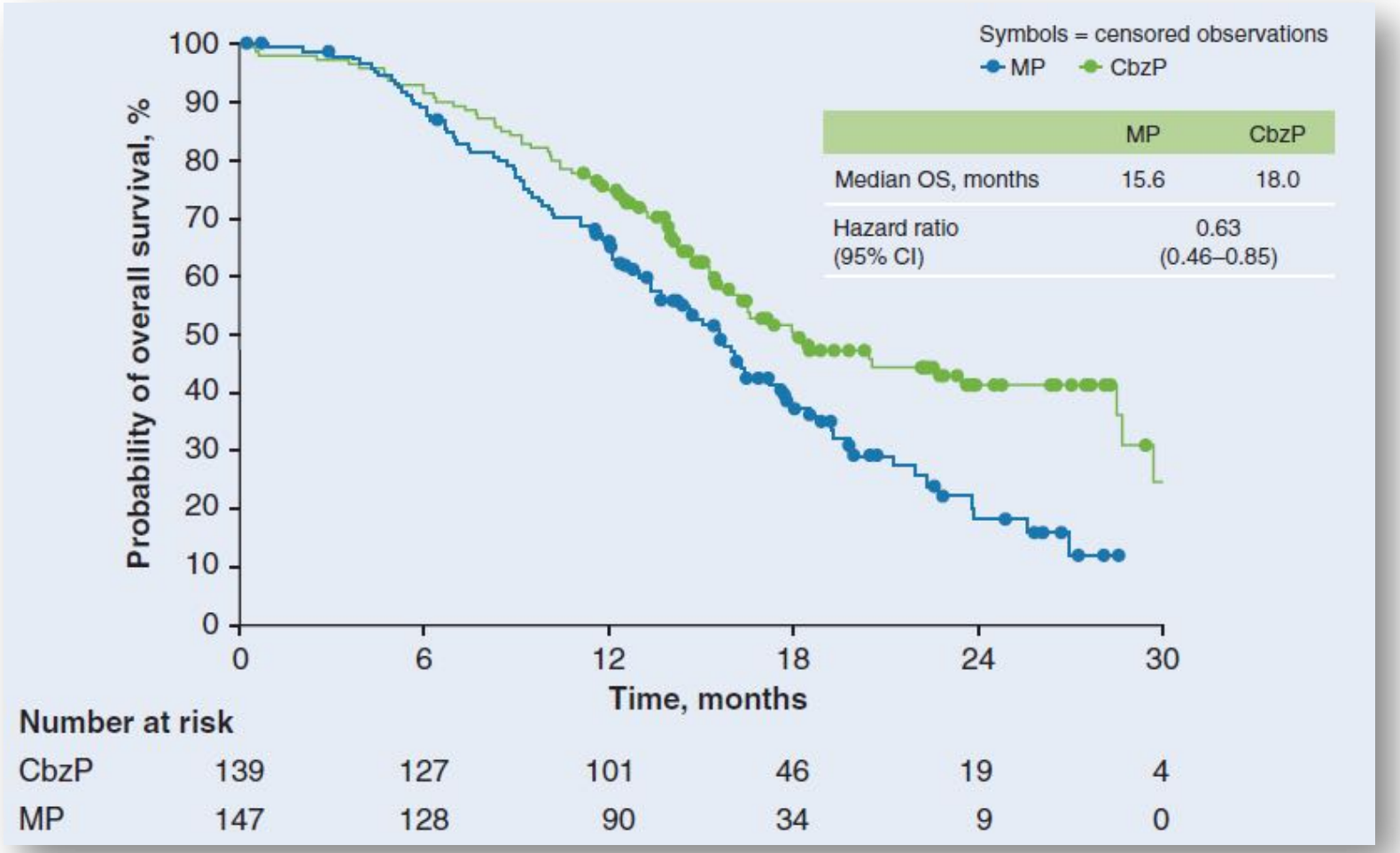
De Bono et al. *Lancet*, 2010, 376:1147-54

Response rate & time to progression

	MP (n=377)	CBZP (n=378)	Hazard ratio (95% CI)	*P*-value
Tumor assessment				
Response rate* (%)	4.4	14.4	–	0.0005
Median TTP (months)	5.4	8.8	0.61 (0.49–0.76)	<0.0001
PSA assessment				
Response rate* (%)	17.8	39.2	–	0.0002
Median TTP (months)	3.1	6.4	0.75 (0.63–0.90)	0.001
Pain response rate				
(N patients)	(168)	(174)		
Response rate (%)	7.7	9.2	0.91 (0.69-1.19)	0.63

De Bono et al. *Lancet*, 2010, 376:1147-54

OS in Patients Discontinuing Prior Docetaxel for Other Reason than Disease Progression



De Bono et al. *ASCO 2011*, abstract 4526

Non hematological Adverse Events

	MP (n=371)		CBZP (n=371)	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Any adverse event	88	39	96	57
Febrile neutropenia	1	1	8	8
Diarrhea	11	<1	47	6
Fatigue	27	3	37	5
Back pain	12	3	16	4
Nausea	23	<1	34	2
Vomiting	10	0	23	2
Hematuria	4	1	17	2
Abdominal pain	4	0	12	2

De Bono et al. *Lancet*, 2010, 376:1147-54

Hematological Adverse Events

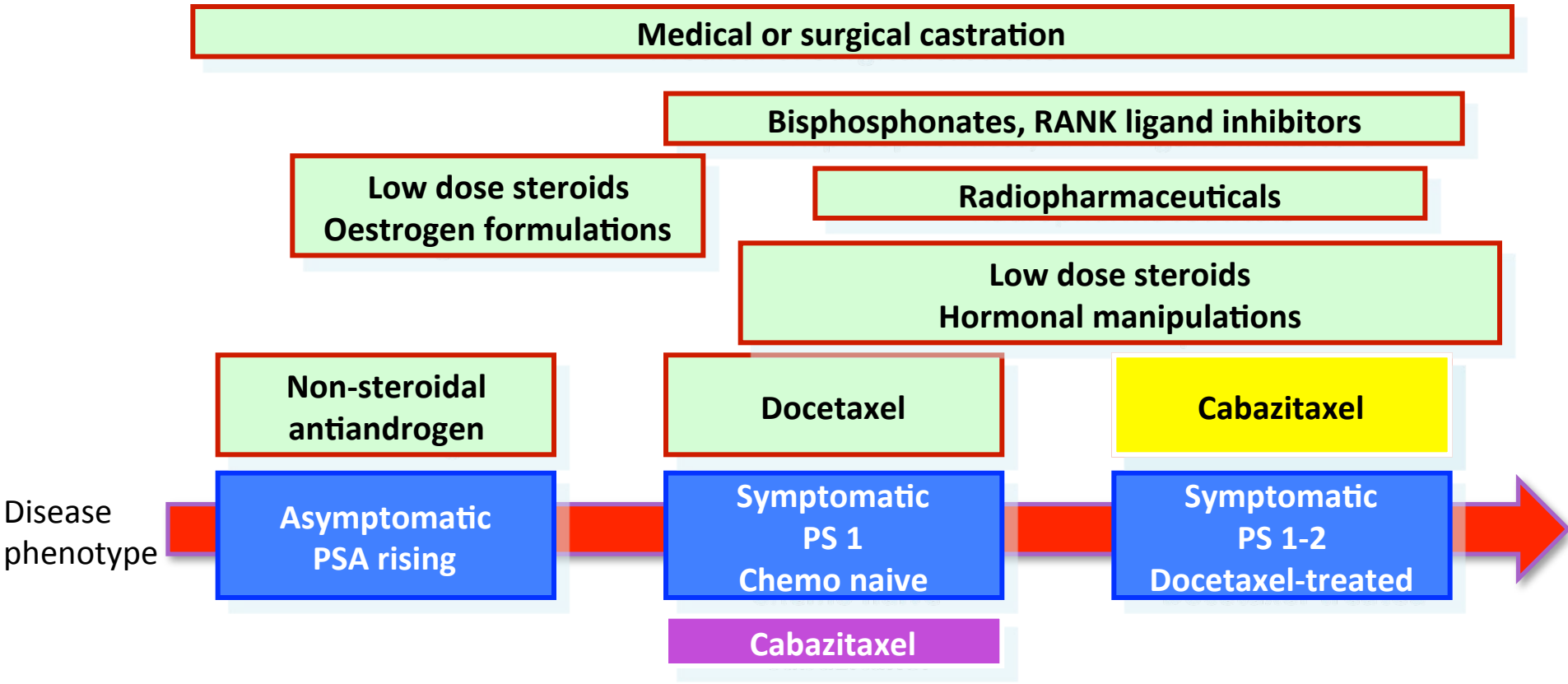
	MP (n=371)		CBZP (n=371)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Anemia	81	5	97	11
Leukopenia	92	42	96	68
Neutropenia*	88	58	94	82
Thrombocytopenia	43	2	47	4

De Bono et al. *Lancet*, 2010, 376:1147-54

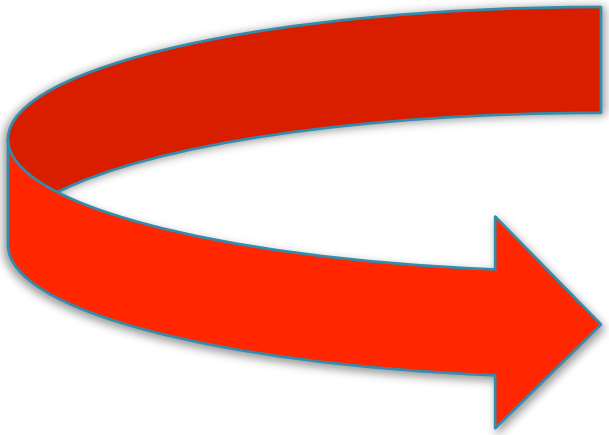
Cabazitaxel key issues

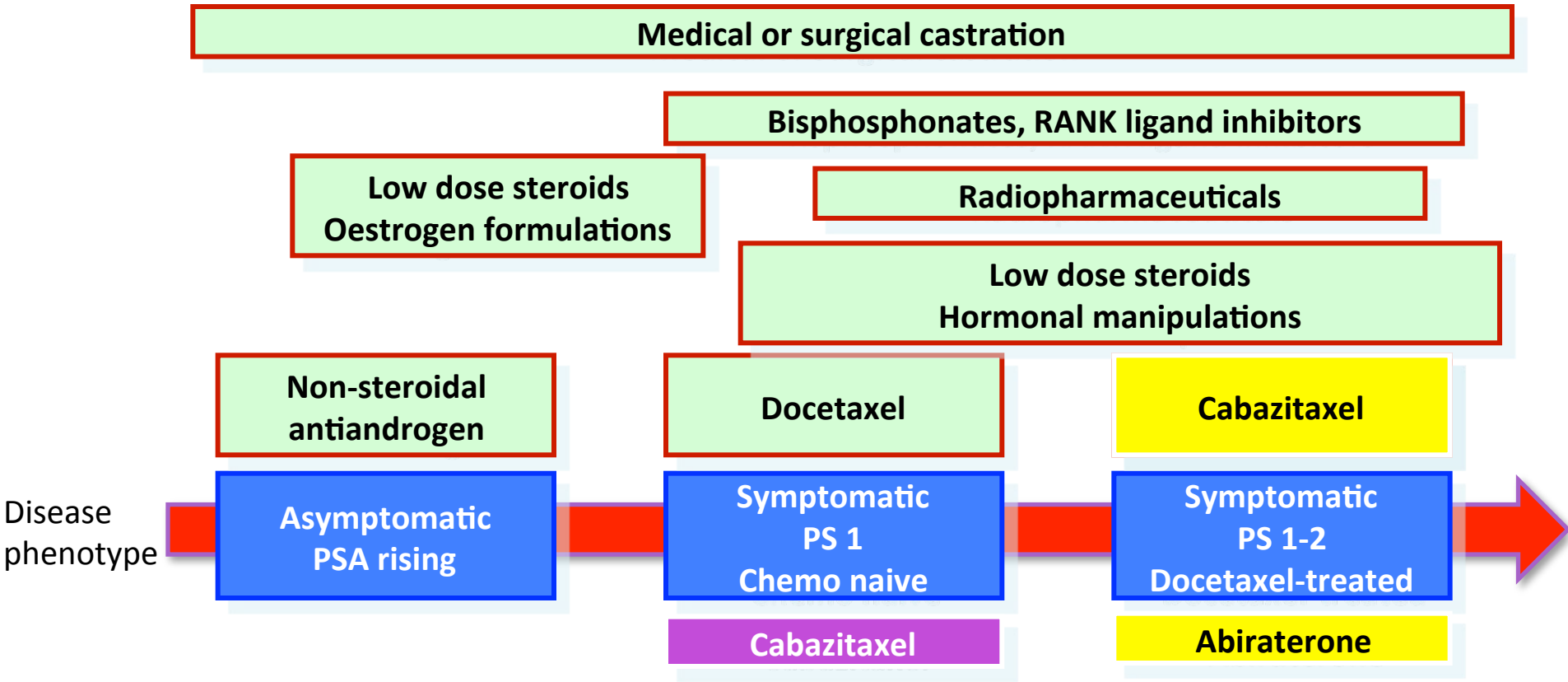
- Efficacy
  - The first approved drug in second line setting
  - Significantly prologs CRPC pts survival
  - Contributes to change disease history
- Toxicity
  - To pay attention to critical toxicities
  - Proactive management of critical toxicities
- Strategy placing
  - Vs rechallenge option in DOC sensitive pts
  - Pivotal trial in first line (FIRSTANA)

At the beginning of 2012

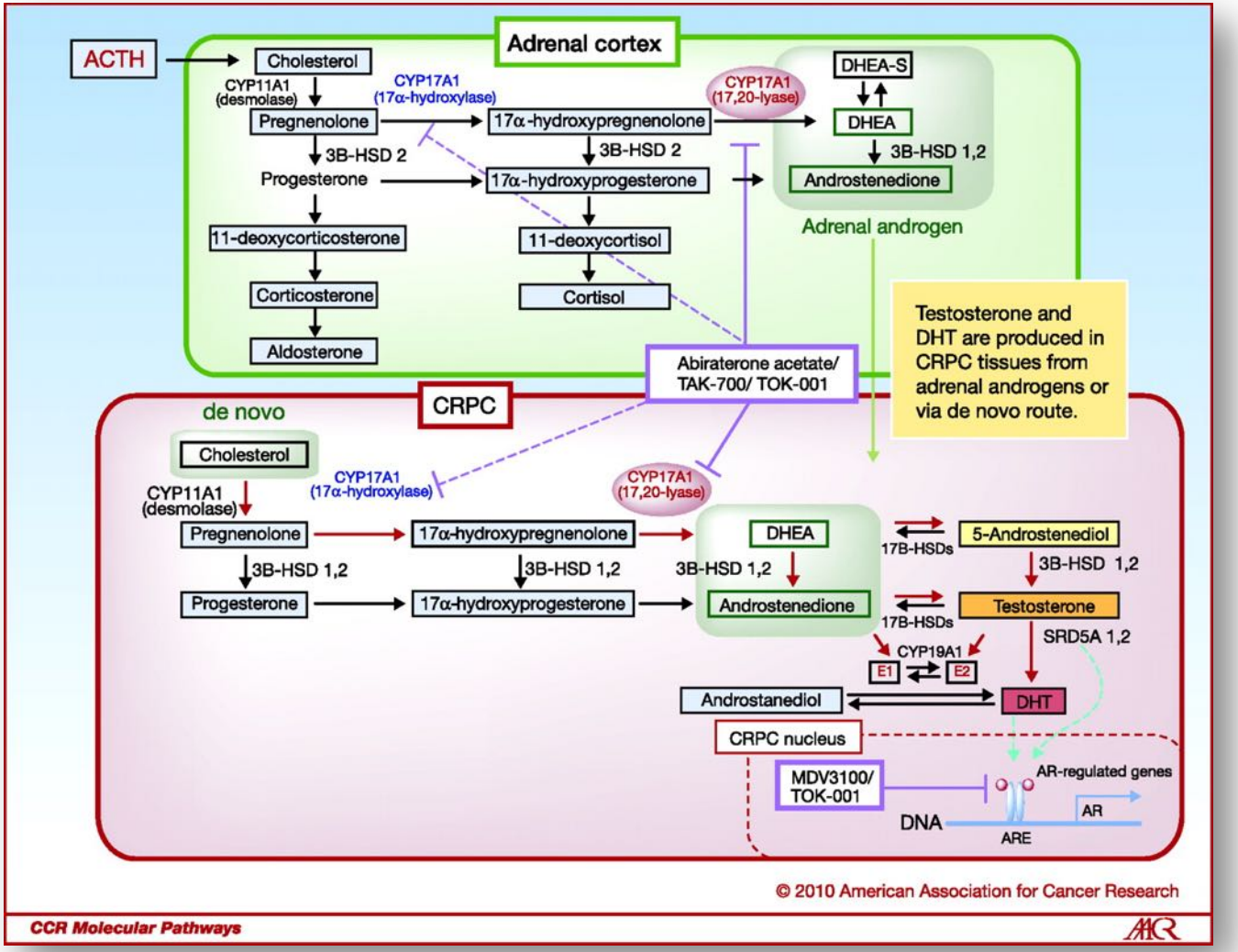


What's in 2012



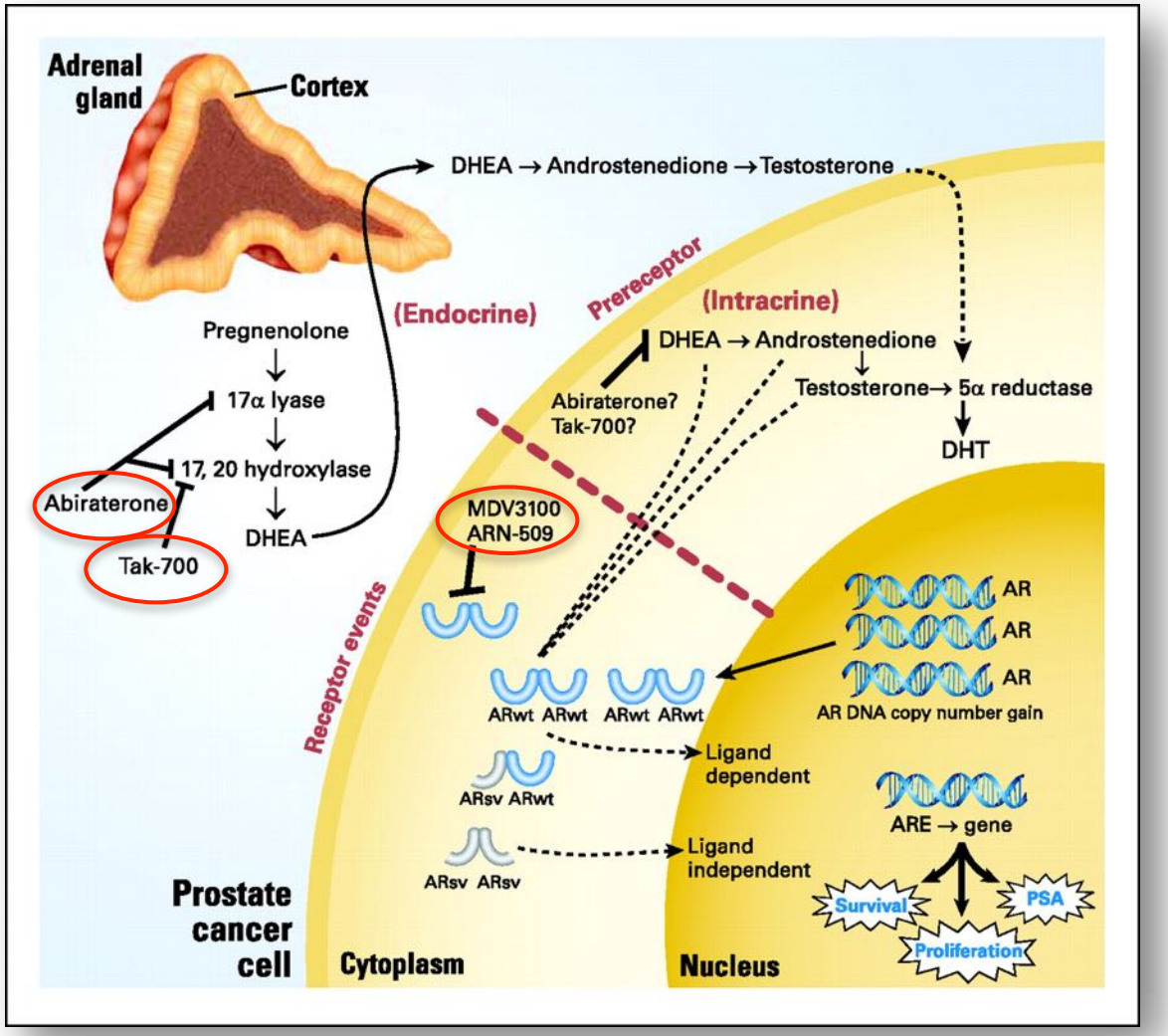

Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
Oestrogen formulations
Radiopharmaceuticals
Low dose steroids
Hormonal manipulations
Non-steroidal
antiandrogen
Docetaxel
Cabazitaxel
Disease
phenotype
Asymptomatic
PSA rising
Symptomatic
PS 1
Chemo naive
Symptomatic
PS 1-2
Docetaxel-treated
Cabazitaxel
Abiraterone

Androgen synthesis pathways in adrenal and CRPC tissues



Yamaoka M et al. Clin Cancer Res 2010;16:4319-4324

Schematic of the various androgen-receptor (AR) signaling aberrancies that may drive progressive prostate cancer.



Modified: Ryan C J , Tindall D J JCO 2011;29:3651-3658

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2011 VOL. 364 NO. 21

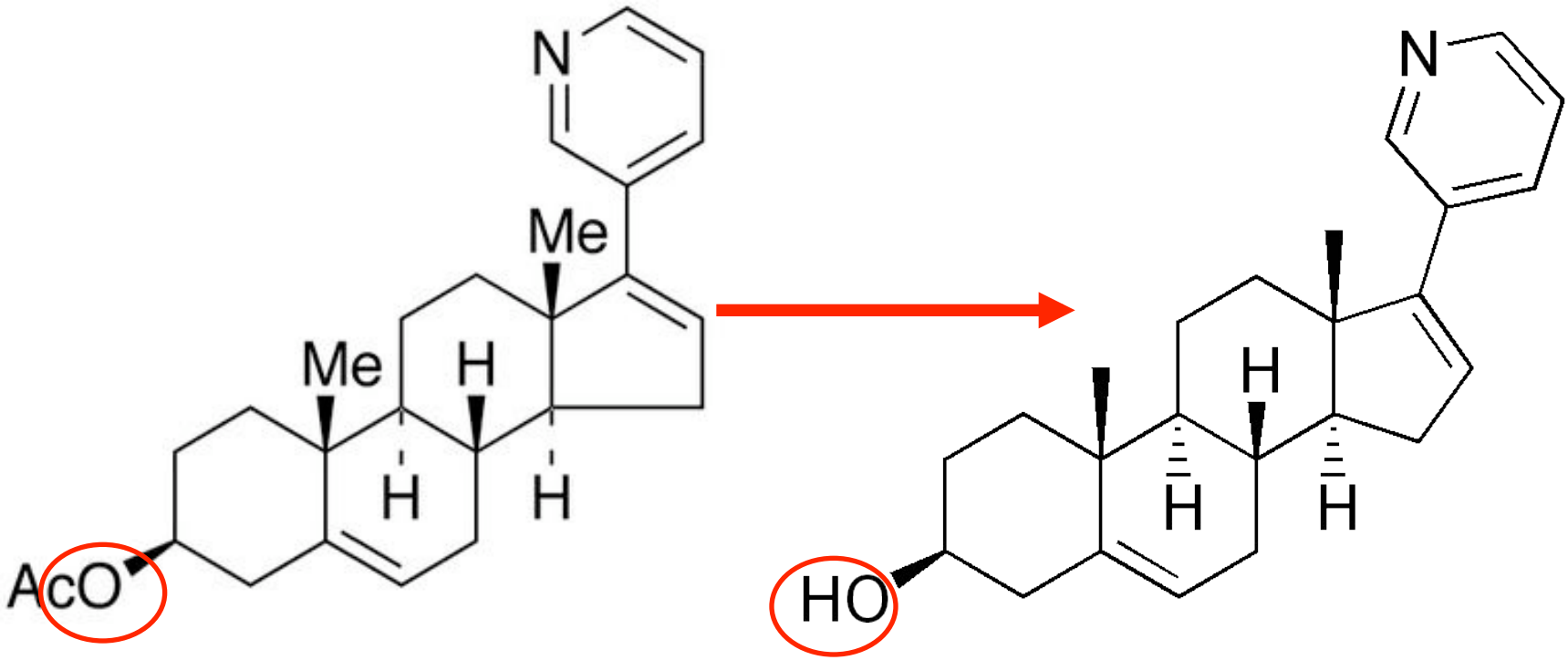
Abiraterone and Increased Survival in Metastatic Prostate Cancer

Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar B. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John N. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., Stephen Harland, M.D., Thomas W. Flaig, M.D., Thomas E. Hutson, D.O., Pharm.D., Tina Cheng, M.D., Helen Patterson, M.D., John D. Hainsworth, M.D., Charles J. Ryan, M.D., Cora N. Sternberg, M.D., Susan L. Ellard, M.D., Aude Fléchon, M.D., Ph.D., Mansoor Saleh, M.D., Mark Scholz, M.D., Eleni Efstathiou, M.D., Ph.D., Andrea Zivi, M.D., Diletta Bianchini, M.D., Yohann Loriot, M.D., Nicole Chieffo, M.B.A., Thian Kheoh, Ph.D., Christopher M. Haqq, M.D., Ph.D., and Howard I. Scher, M.D., for the COU-AA-301 Investigators*

ABIRATERONE ACETATE

Pro-drug

Drug

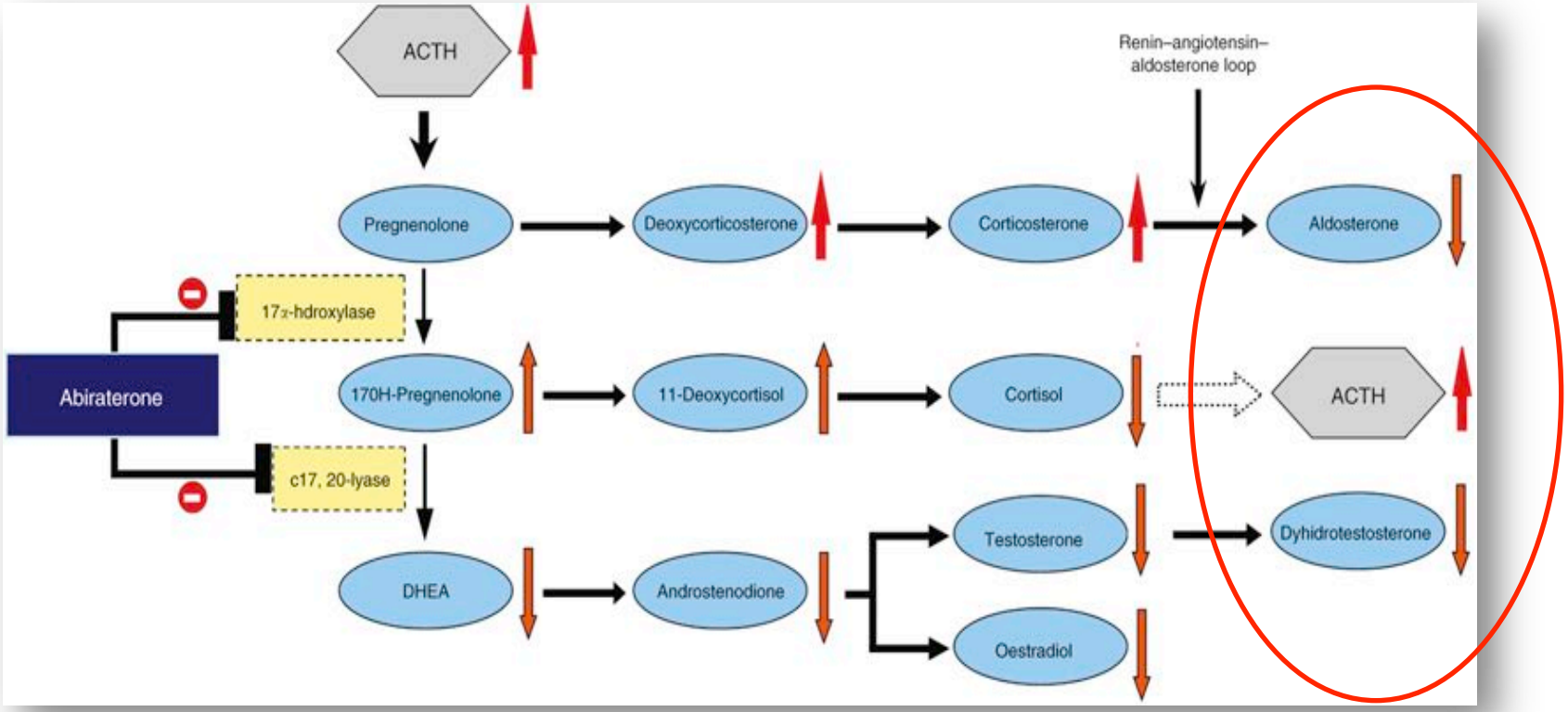


Abiraterone acetate

Abiraterone

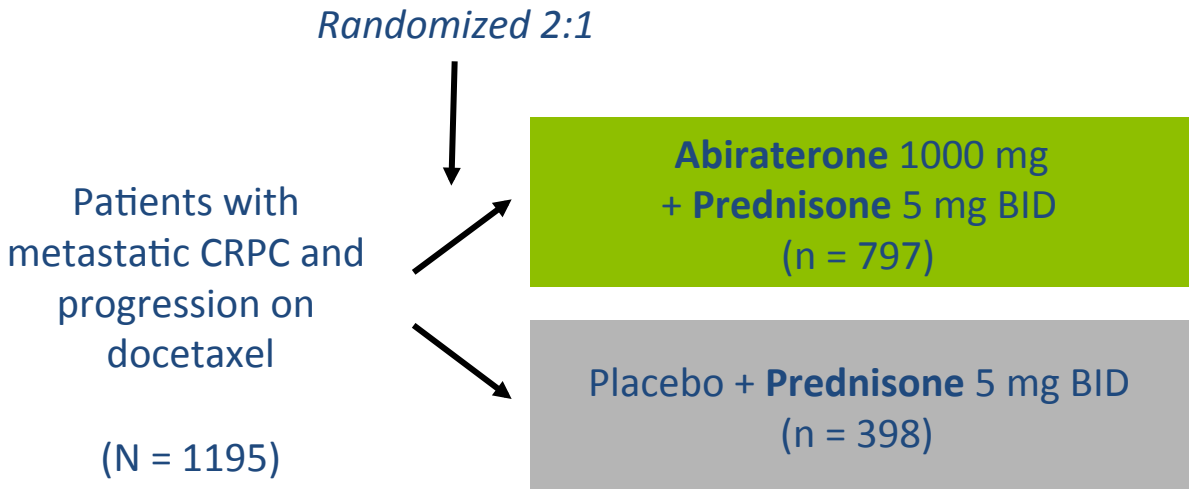
Potent and selective inhibitor of CYP17

Abiraterone effects on androgen biosynthesis



Ang et al. BJ Cancer 2009: 100, 671

COU-AA-301: Phase III Study of Abiraterone + Prednisone in mCRPC



- Primary endpoint: OS
- Secondary endpoints: time to PSA progression, radiographic PFS, PSA response rate

de Bono JS, et al. NEJM 2011

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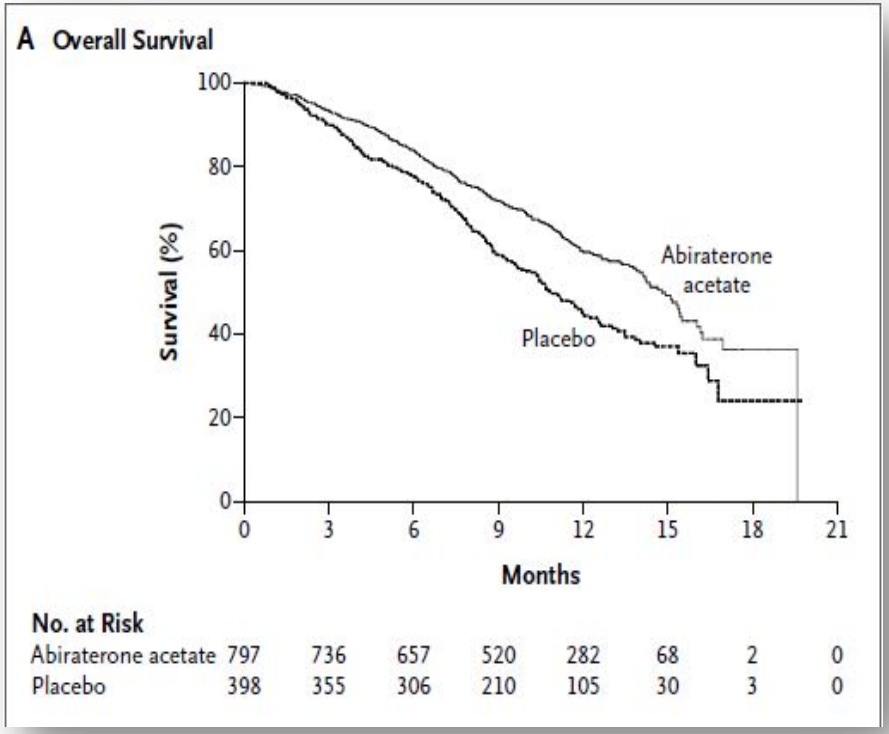
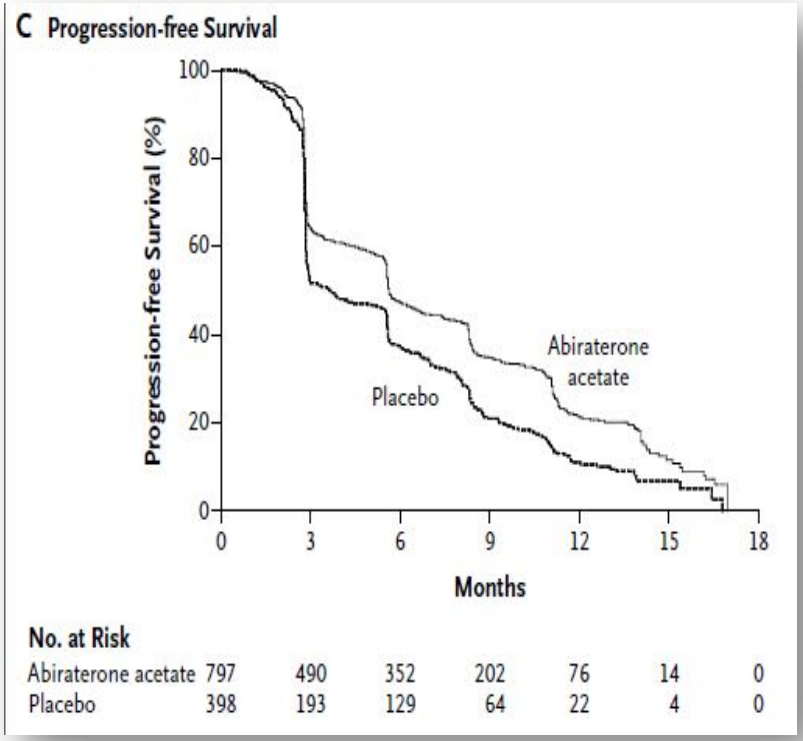
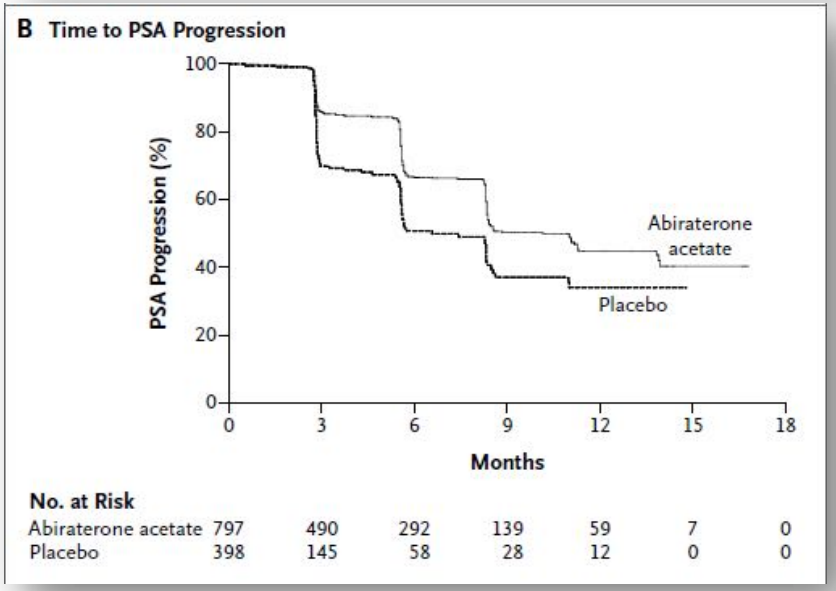






COU-AA-301: OS, Response

	AA (n = 797)	Placebo (n = 398)	HR (95% CI)	*P* Value
Median OS, mos	14.8	10.9	0.646 (0.54-0.77)	< .0001
TTPP, mos	10.2	6.6	0.58 (0.46-0.73)	< .0001
rPFS, mos	5.6	3.6	0.67 (0.59-0.78)	< .0001
PSA response rate				
• Total, %	38.0	10.1		< .0001
• Confirmed, %	29.1	5.5		< .0001

TTPP, time to PSA progression; rPFS, radiographic PFS.

de Bono JS, et al. NEJM 2011

COU-AA-301: Adverse Events

Adverse Event, %	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
All treatment-emergent AEs	98.9	54.5	99.0	58.4
Serious AEs	37.5	32.1	41.4	35.3
AEs leading to discontinuation	18.7	10.5	22.8	13.5
Fluid retention	30.5	2.3	22.3	1.0
Hypokalemia	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	4.1	10.4	2.3

de Bono JS, et al. NEJM 2011

Abiraterone key issues

- Efficacy
  - First hormonal agent with proven efficacy in CRPC pts
  - Efficacy magnitude similar to CABA [HR 0.65 (vs placebo) vs 0.70 (vs DOC)]
- Toxicity
  - Low acute toxicity profile
  - Long term toxicities?
- Strategy placing
  - The most appropriate sequencing of abiraterone and cabazitaxel remains to be determined
  - ...first line (COU-AA-302) 

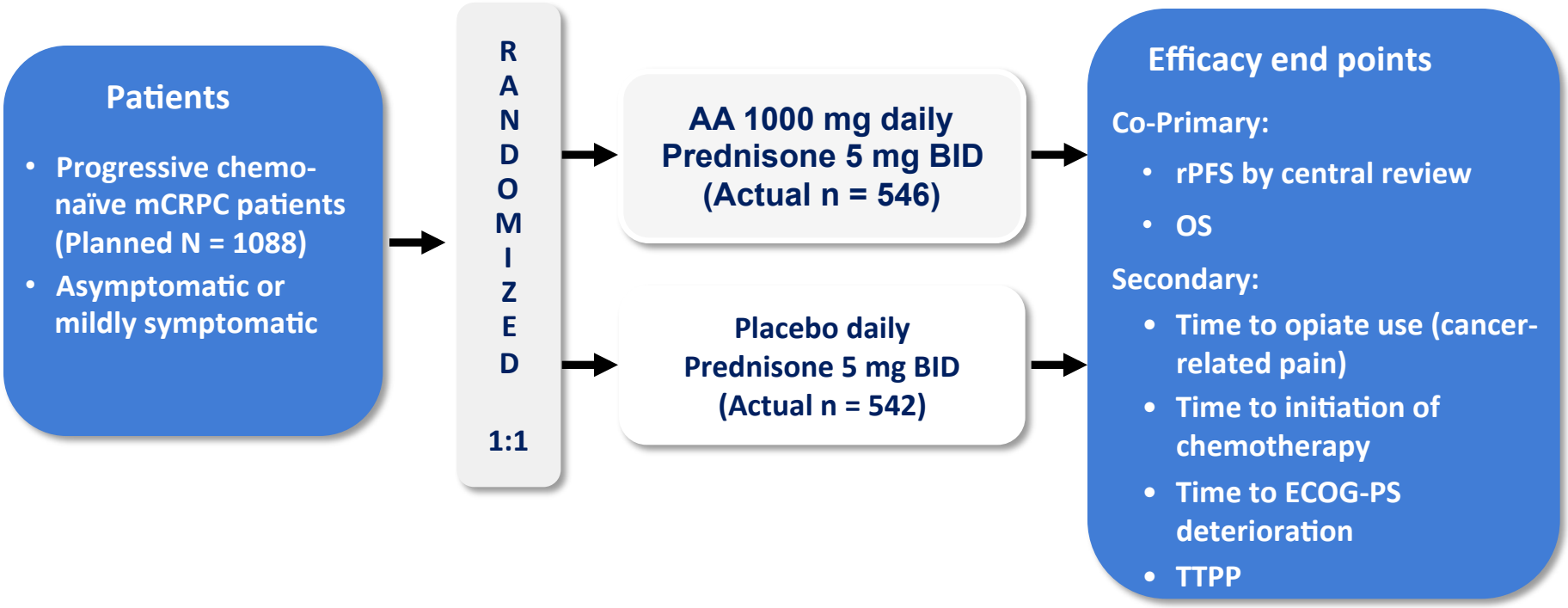
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D., Johann S. de Bono, M.B., Ch.B., Ph.D., Arturo Molina, M.D., Christopher J. Logothetis, M.D., Paul de Souza, M.B., Ph.D., Karim Fizazi, M.D., Ph.D., Paul Mainwaring, M.D., Josep M. Piulats, M.D., Ph.D., Siobhan Ng, M.D., Joan Carles, M.D., Peter F.A. Mulders, M.D., Ph.D., Ethan Basch, M.D., Eric J. Small, M.D., Fred Saad, M.D., Dirk Schrijvers, M.D., Ph.D., Hendrik Van Poppel, M.D., Ph.D., Som D. Mukherjee, M.D., Henrik Suttmann, M.D., Winald R. Gerritsen, M.D., Ph.D., Thomas W. Flaig, M.D., Daniel J. George, M.D., Evan Y. Yu, M.D., Eleni Efstathiou, M.D., Ph.D., Allan Pantuck, M.D., Eric Winquist, M.D., Celestia S. Higano, M.D., Mary-Ellen Taplin, M.D., Youn Park, Ph.D., Thian Kheoh, Ph.D., Thomas Griffin, M.D., Howard I. Scher, M.D., and Dana E. Rathkopf, M.D., for the COU-AA-302 Investigators*

COU-AA-302: Phase III Study of Abiraterone + Prednisone in mCRPC in patients without previous chemotherapy



- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs. 1

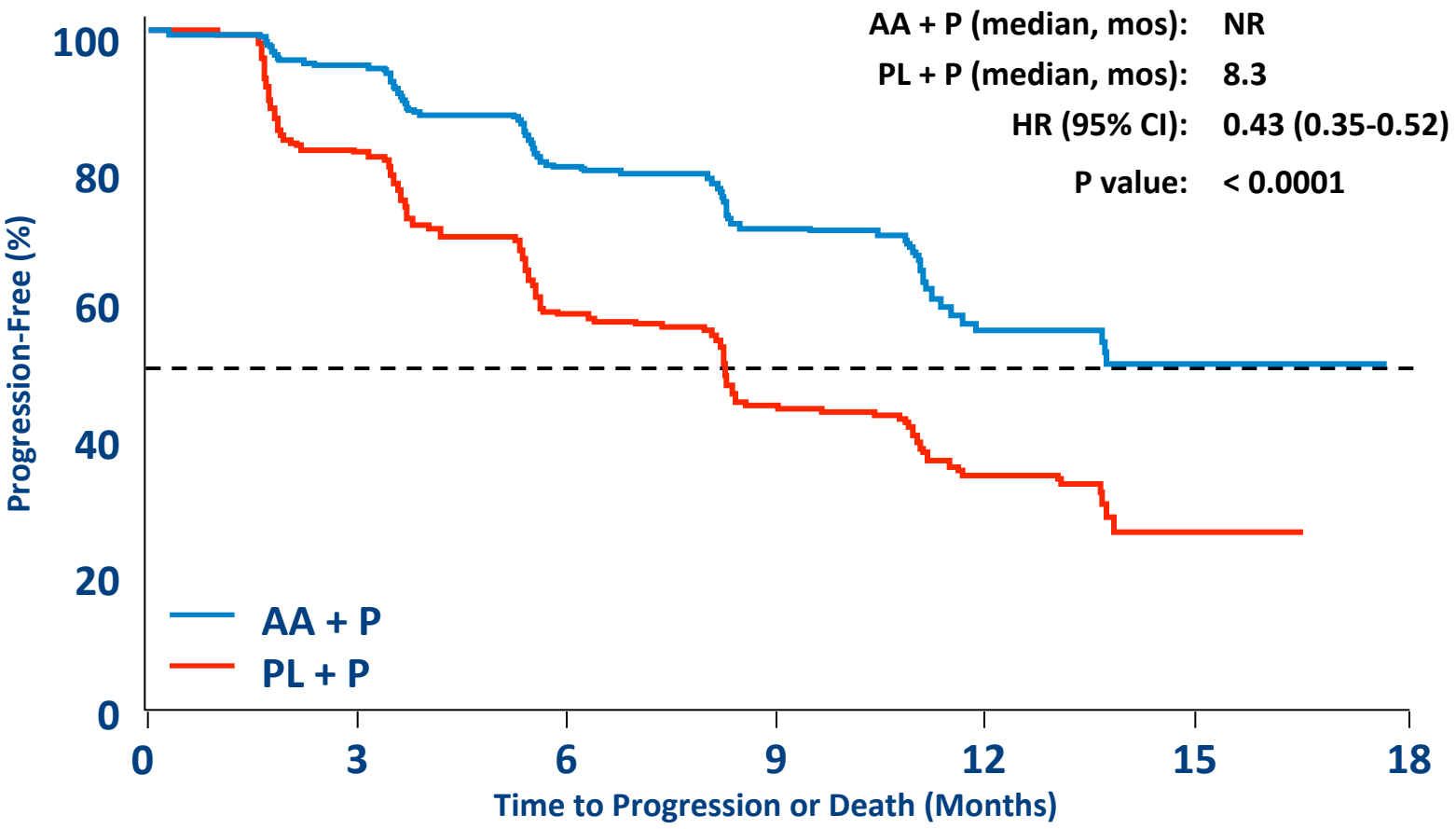
Ryan et al., NEJM 2012

COU-AA-302: patients' characteristics

	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)	4.0	4.0
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	48%	47%
Soft tissue or node	49%	50%
Pain (BPI Short Form)		
0-1	66%	64%
2-3	32%	33%

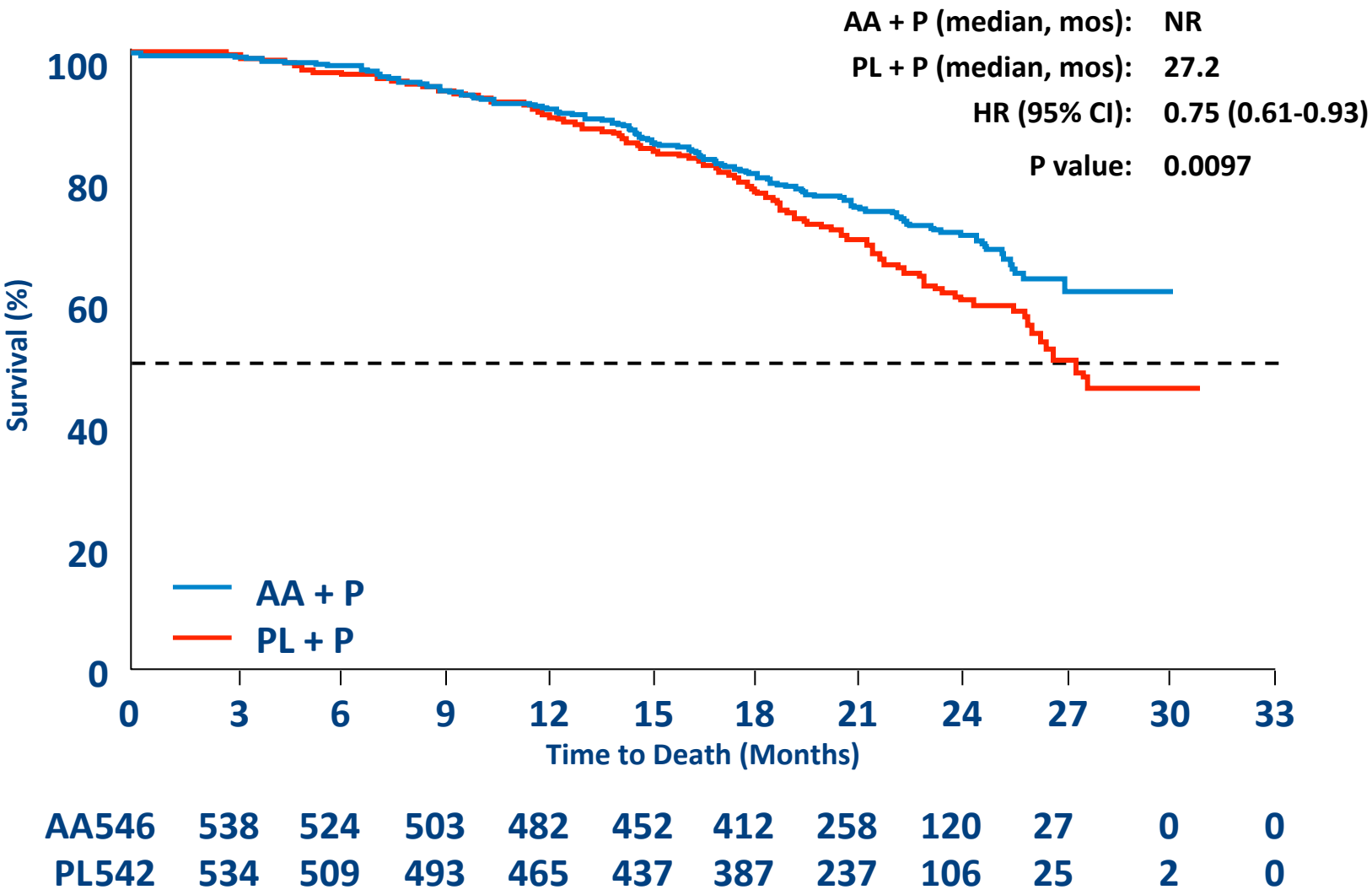
Ryan et al., NEJM 2012

COU-AA-302: PFS



Ryan et al., NEJM 2012

COU-AA-302: OS



Ryan et al., NEJM 2012

COU-AA-302: 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

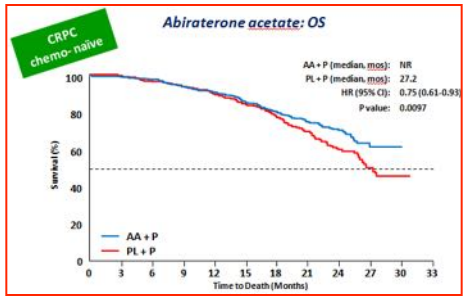
Note: All secondary end points remain significant after adjusting for multiplicity testing

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

Ryan et al., NEJM 2012

COU-AA-302: Subsequent Therapy Was Common

	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 acetate*	26 (4.8)	54 (10.0)

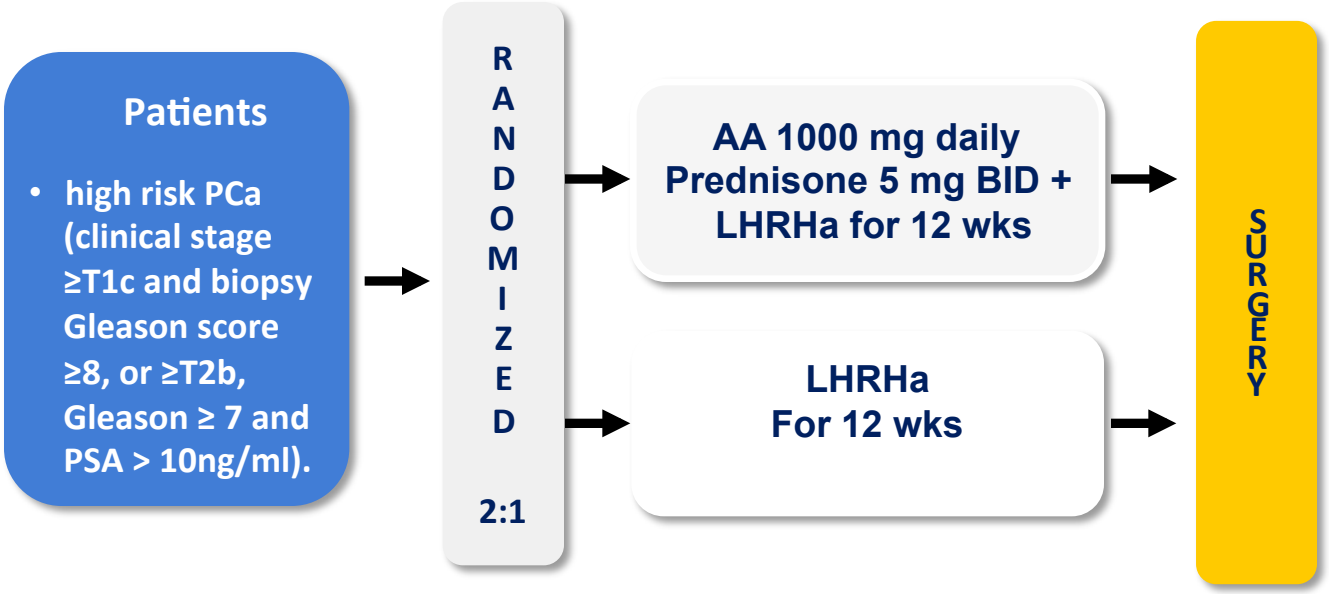


Despite 16% of patients did not receive subsequent therapy compared to placebo, AA increase OS!

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

Ryan et al., NEJM 2012

Cytoreduction and androgen signaling modulation by abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus LHRHa in localized high-risk prostate cancer (PCa): Preliminary results of a randomized preoperative study.



Efficacy end points

Co-Primary:

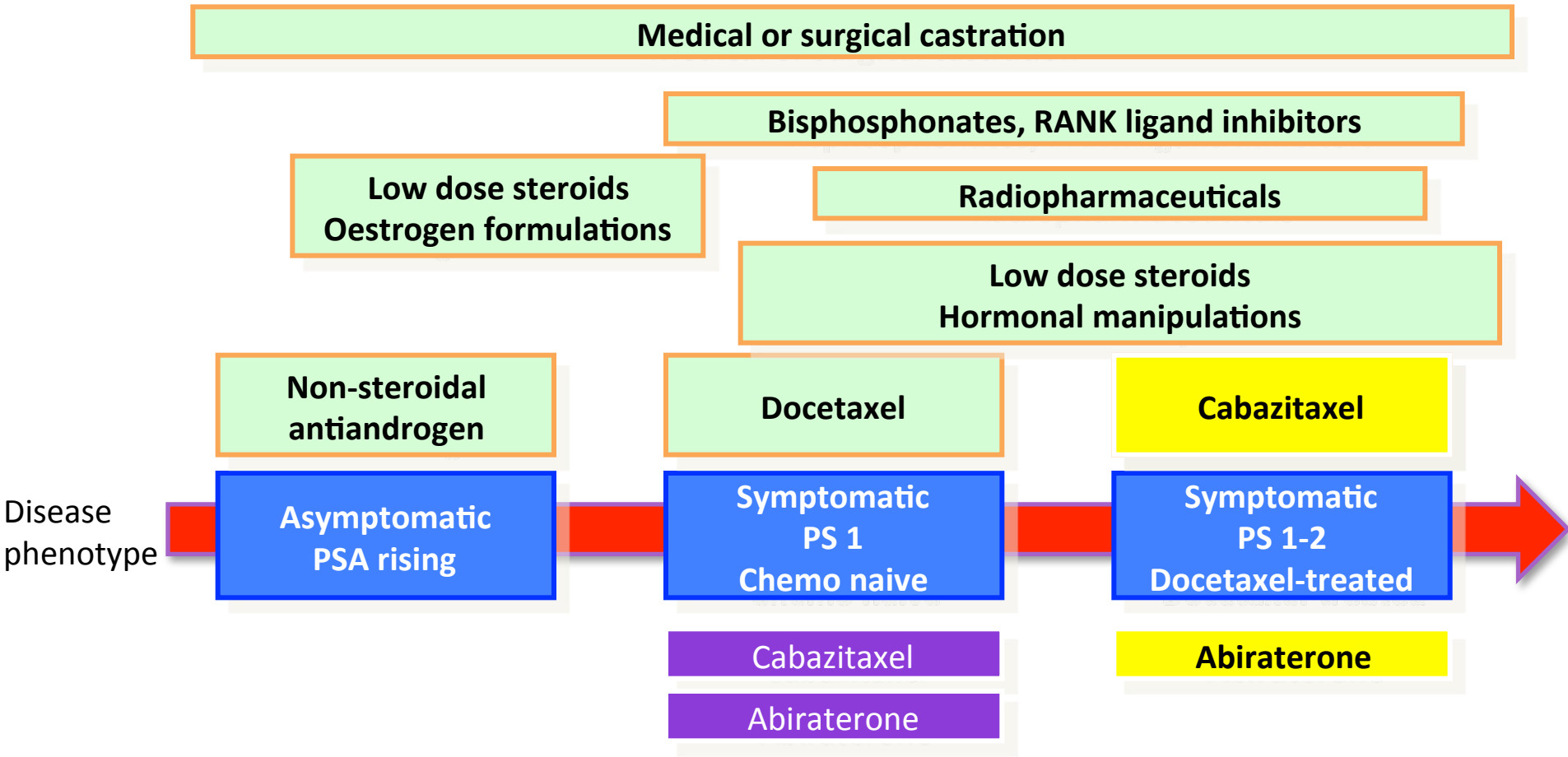
- difference in down staging (≤ ypT2)
- safety

Secondary:

- **difference in androgen biosynthesis, androgen signaling, proliferation apoptosis and candidate treatment resistance pathways.**

Results:

	AA+LHRHa	LHRHa
ypT2N0	60%	33%
Near pCR	24%	8%
N+	28%	50%
R1	8%	33%


Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
Oestrogen formulations
Radiopharmaceuticals
Low dose steroids
Hormonal manipulations
Non-steroidal antiandrogen
Docetaxel
Cabazitaxel
Disease phenotype
Asymptomatic PSA rising
Symptomatic PS 1 Chemo naive
Symptomatic PS 1-2 Docetaxel-treated
Cabazitaxel
Abiraterone
Abiraterone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

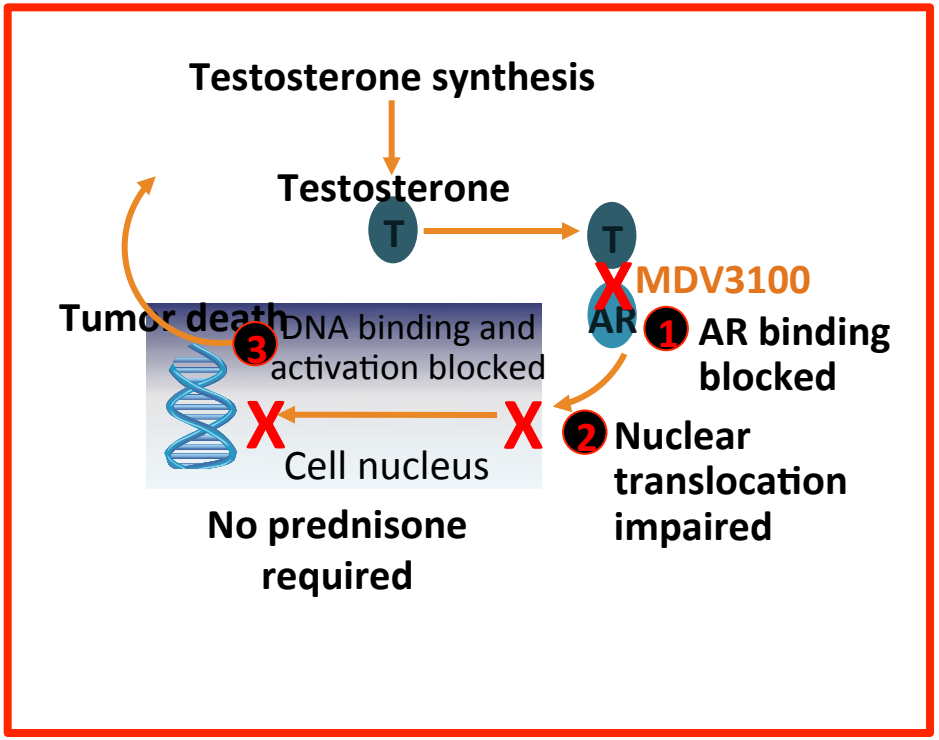
Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D. Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Aude Fléchon, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

MDV3100: ENZALUTAMIDE

Antiandrogen with three effects on Androgen Receptor:

- AR inhibition
- AR degradation
- Inhibition of AR transport into prostate cancer cell nucleus



Phase 3 Trial (AFFIRM) of Enzalutamide (MDV3100), an Androgen Receptor Signaling Inhibitor: Primary, Secondary, and Quality-of-Life Endpoint Results.

Johann de Bono MB ChB (Glasgow) FRCP MSc PhD
The Institute of Cancer Research and Royal Marsden, London, UK

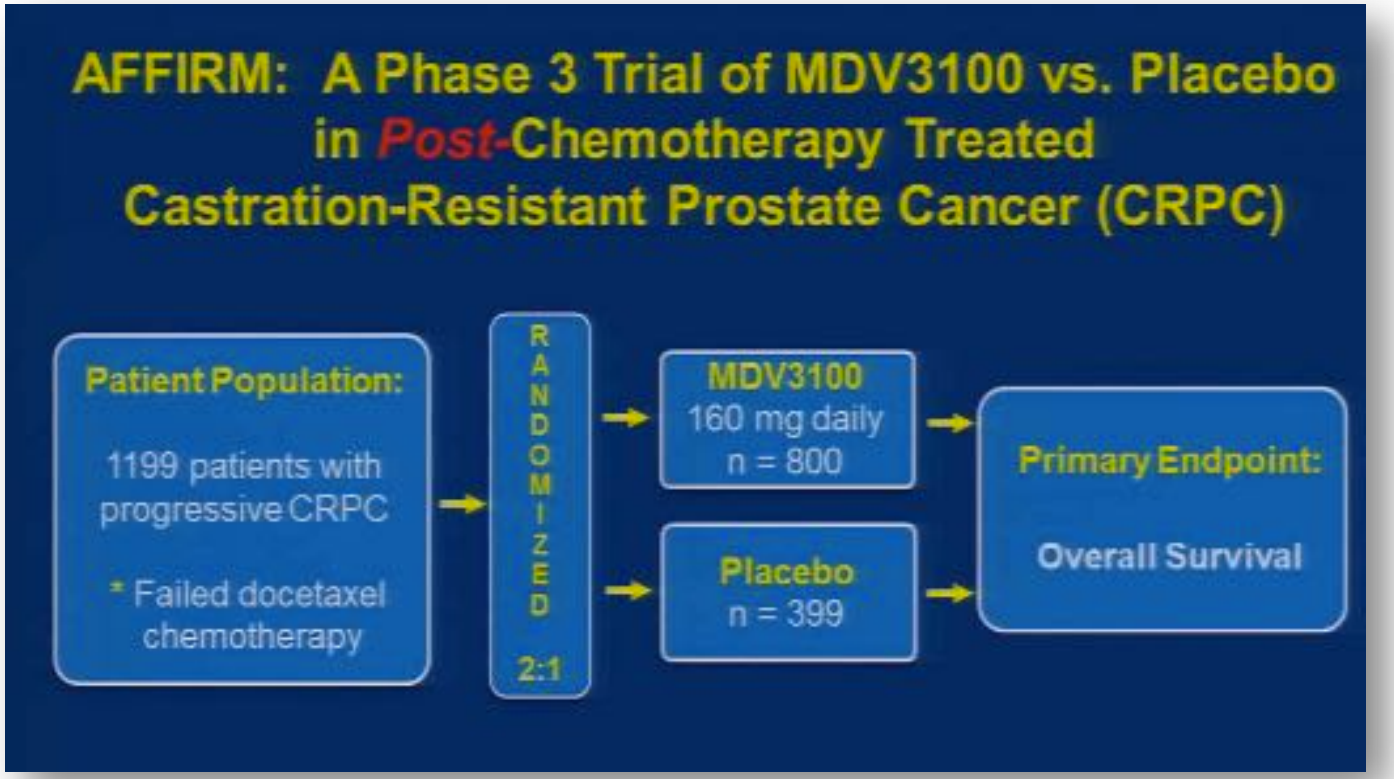
Karim Fizazi, Fred Saad, Mary-Ellen Taplin, Cora N. Sternberg, Kurt Miller, Peter Mulders, Kim N. Chi, Andrew J. Armstrong, Mohammad Hirmand, Brian Selby, Howard I. Scher, for the AFFIRM Investigators

ICR 1909 2009

THE ROYAL MARSDEN

Howard I. Scheret al, Abs LBA1, ASCO GU 2012

The AFFIRM Trial Design

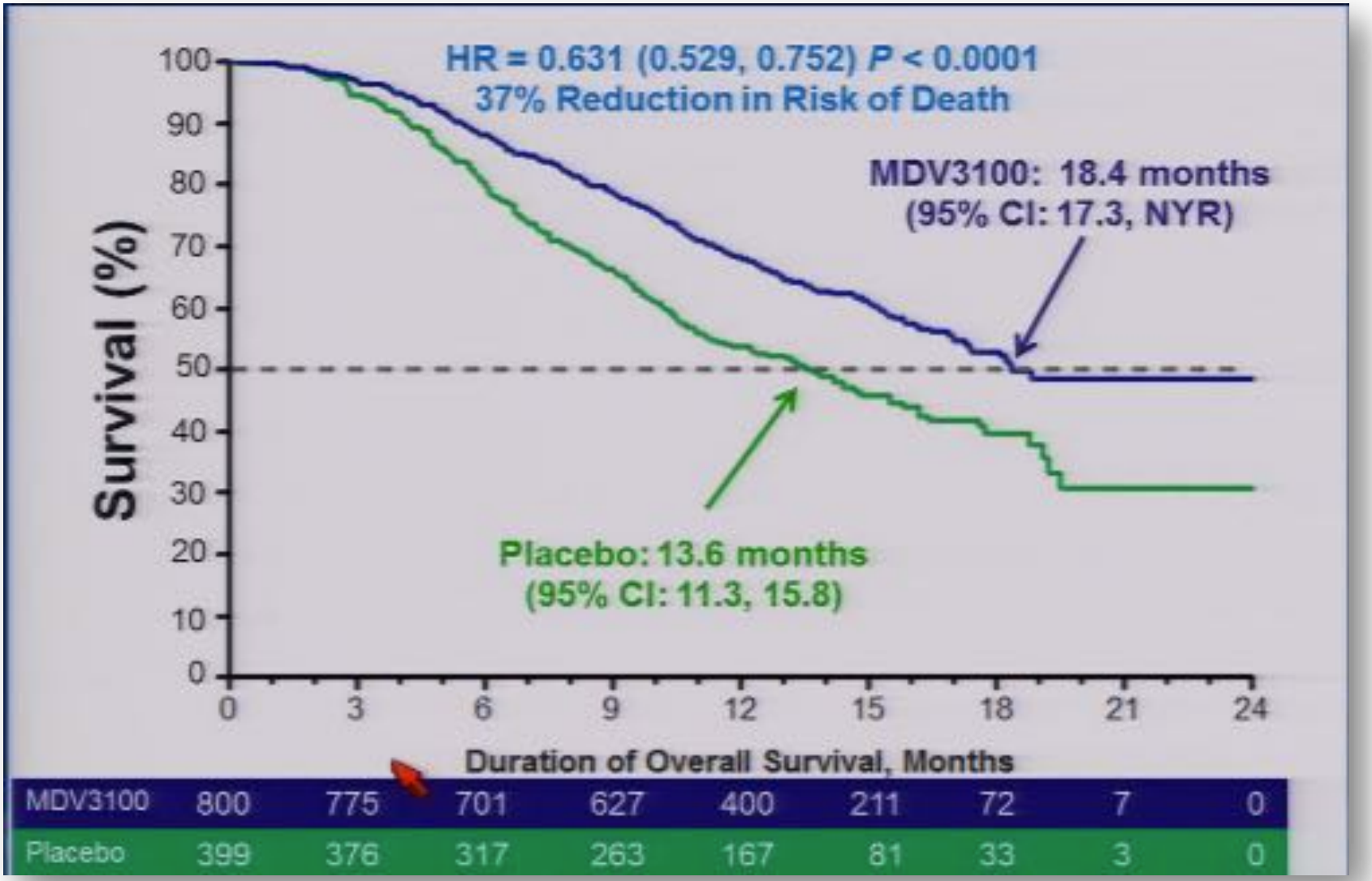


Primary End-Point: OS
Stratification variables: ECOG-PS, meand BPI (<4, ≥4)

Statistical design: power 90% to detect a 24% reduction in mortality (target HR= 0.76).

Howard I. Scheret al, Abs LBA1, ASCO GU 2012

MDV 3100 Prolonged Survival by a Median of 4.8 Months in the Phase III Study AFFIRM

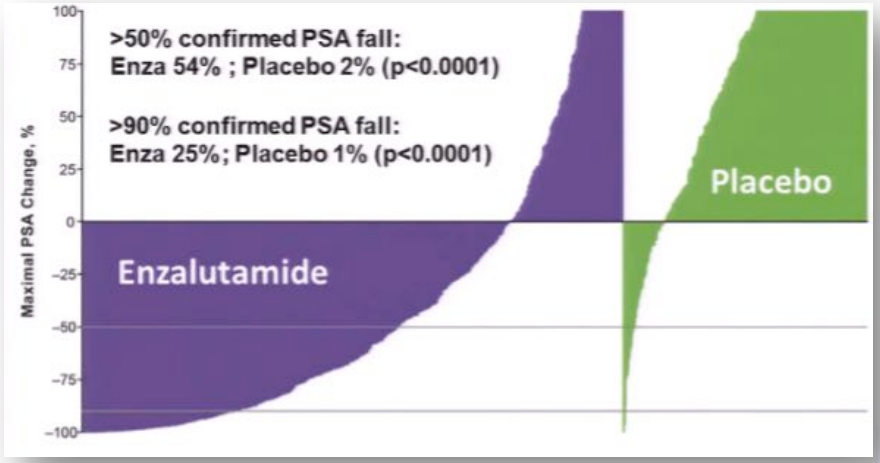


Howard I. Scheret al, Abs LBA1, ASCO GU 2012

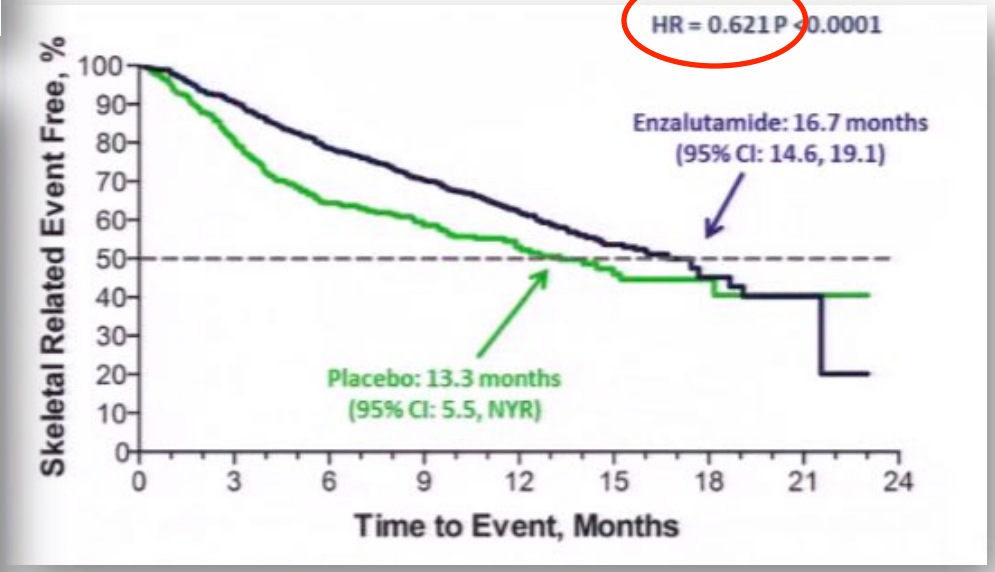
The AFFIRM Trial

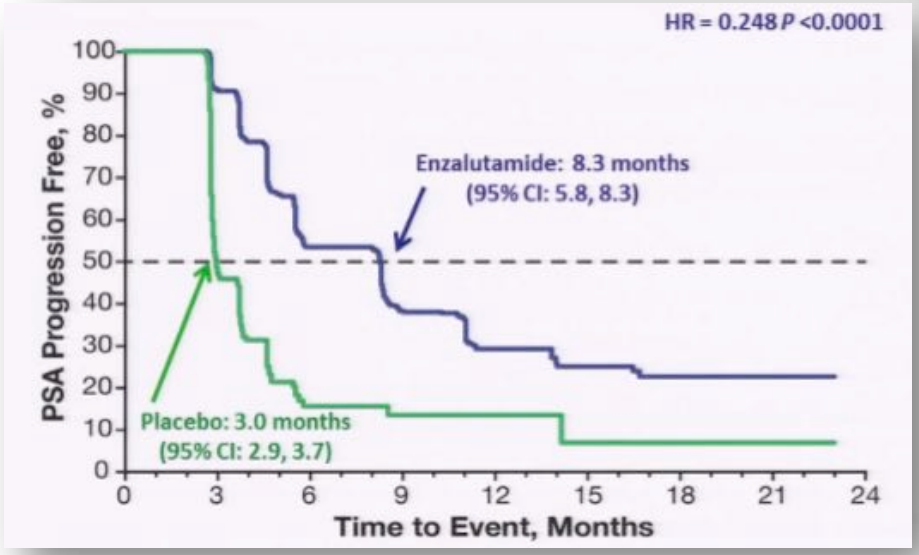
RESULTS:

PSA response rate, PSA-PFS and Time To First Skeletal Event



HR denosumab vs placebo 0.84!*



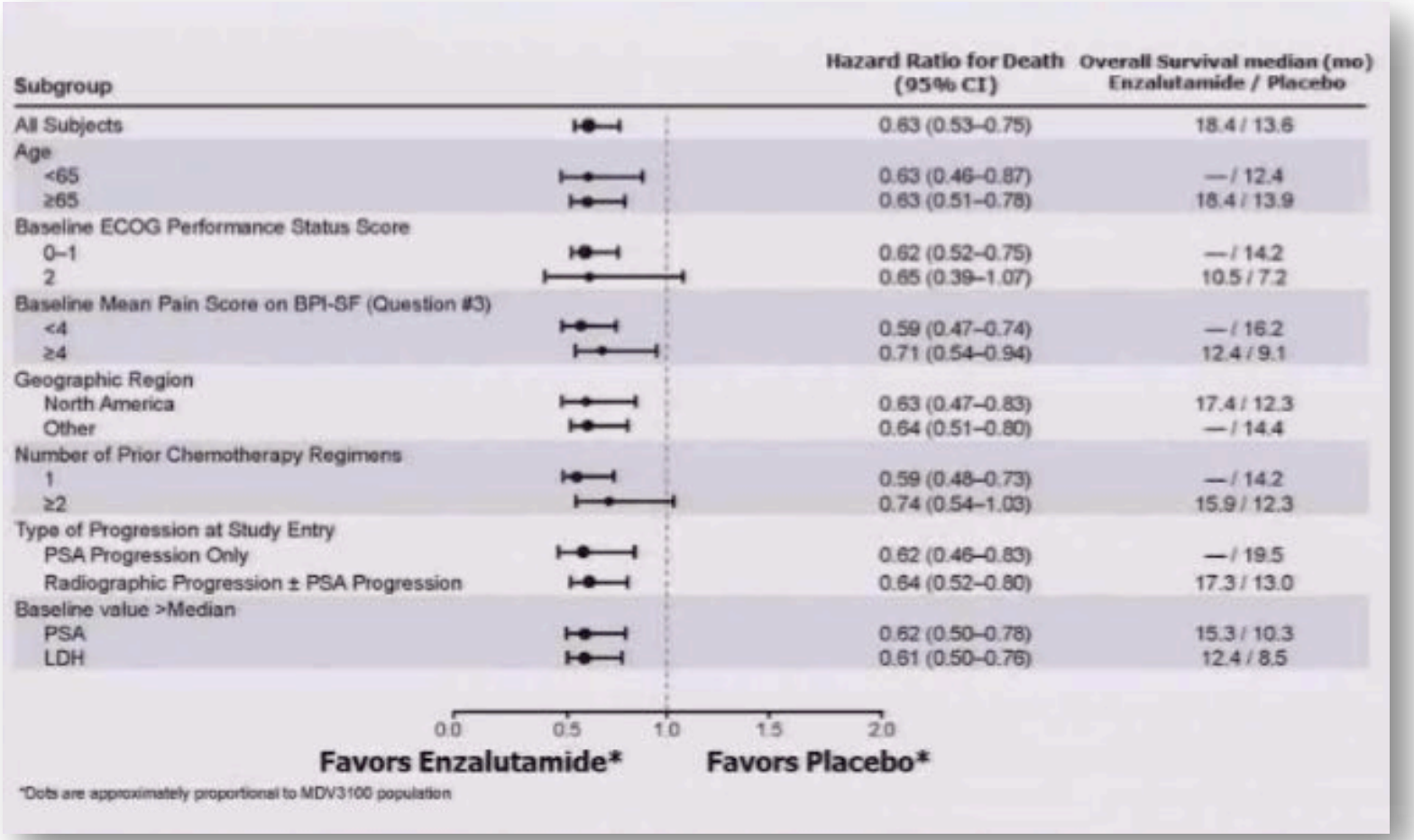


*Smith MR et al. Lancet 2012

The AFFIRM Trial

RESULTS:

Survival benefit across all subgroups



Smith MR et al. Lancet 2012

The AFFIRM Trial: Safety

	ENZALUTAMIDE		PLACEBO	
	Any Grade n° (%)	Grade ≥3 n° (%)	Any Grade n° (%)	Grade ≥3 n° (%)
≥ 1 Adverse event	785 (98)	362 (45)	390 (98)	212 (53)
FATIGUE	269 (34)	50 (6)	116 (29)	29 (7)
DIARRHEA	171 (21)	9 (1)	70 (18)	1 (<1)
HOT FLASH	162 (20)	0	41 (10)	0
MUSCULOSKELETAL PAIN	109 (14)	8 (1)	40 (10)	1 (<1)
HEADACHE	93 (12)	6 (<1)	22 (6)	0
CARDIAC DISORDER	49 (6)	7 (1)	30 (8)	8 (2)
ABNORMALITY ON LIVER FUNCTION	8 (1)	3 (<1)	6 (2)	3 (<1)
SEIZURE	5 (<1)	5 (<1)	0	0

Smith MR et al. Lancet 2012

The AFFIRM Trial: Safety

	All Grades		Grades ≥3*	
	Enzalutamide (n = 800)	Placebo (n = 399)	Enzalutamide (n = 800)	Placebo (n = 399)
AEs	98.1%	97.7%	45.3%	53.1%
Serious AEs	33.5%	38.6%	28.4%	33.6%
Discontinuations due to AEs	7.6%	9.8%	4.6%	7.0%
AEs leading to death	2.9%	3.5%	2.9%	3.5%

	All Grades		Grade ≥ 3 Events	
	Enzalutamide (n = 800)	Placebo (n = 399)	Enzalutamide (n = 800)	Placebo (n = 399)
Fatigue	33.6%	29.1%	6.3%	7.3%
Cardiac Disorders	6.1%	7.5%	0.9%	2.0%
Myocardial Infarction	0.3%	0.5%	0.3%	0.5%
LFT Abnormalities*	1.0%	1.5%	0.4%	0.8%
Seizure	0.6%	0.0%	0.6%	0.0%

Smith MR et al. Lancet 2012

Conclusions

1. MVD 3100 significantly prlonged survival by nearly 5 months in men with late-stage prostate cancer

2. The secondary measures of response and time to progression were consistent with the survival benefit

3. The results confirm the androgen receptor and androgen receptor signaling as a therapeutic target

4. MDV 3100 was well-tolerated and the benefit/risk profile will likely position it as the front-line agent post-docetaxel therapy

Trials of MDV 3100 in the earlier stages of prostate cancer are ongoing

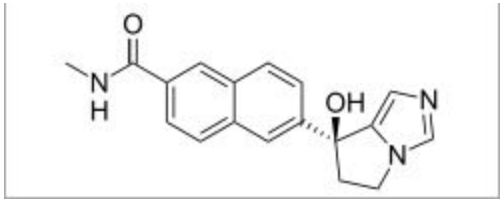
Howard I. Scheret al, Abs LBA1, ASCO GU 2012

TAK-700 (Orteronel)

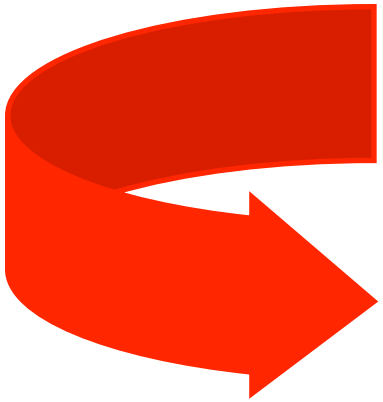
- Orteronel è un inibitore dell'enzima CYP17A1
- Studi di fase I/II
  - 52% bRR
  - Bassa incidenza di ipertensione ed ipocaliemia
  - fatigue (47%), emesi (30%), stipsi (21%) e anoressia(12%)

Studi in corso → **I linea**

Studi in corso → **II linea**

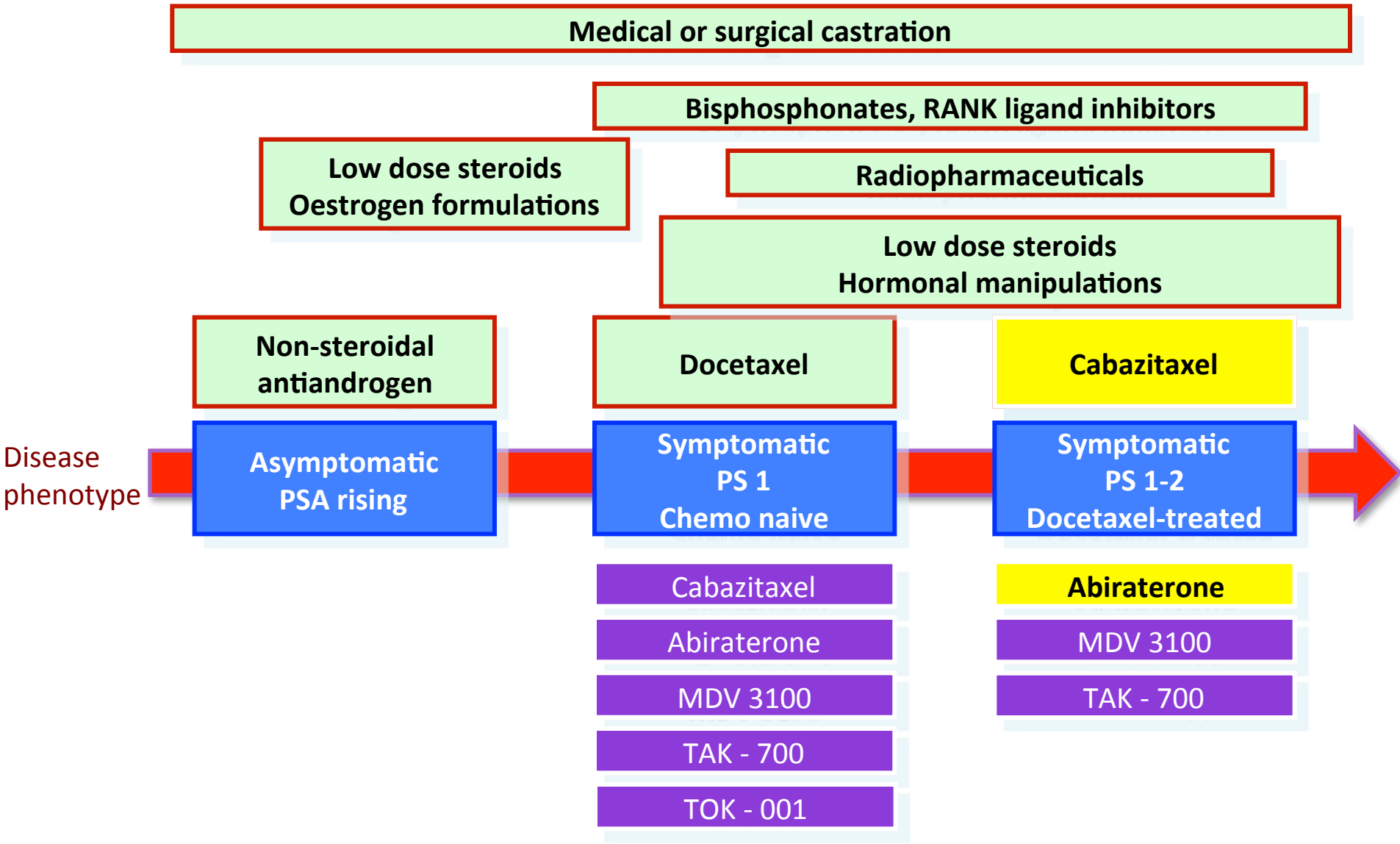


TOK-001: molecola ideale



TRIPLICE MECCANISMO D'AZIONE

1. Antagonizza il recettore androgenico (AR)
2. Inibisce il CYP17
3. Riduce i livelli di AR


Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
Oestrogen formulations
Radiopharmaceuticals
Low dose steroids
Hormonal manipulations
Non-steroidal antiandrogen
Docetaxel
Cabazitaxel
Disease phenotype
Asymptomatic
PSA rising
Symptomatic
PS 1
Chemo naive
Symptomatic
PS 1-2
Docetaxel-treated
Cabazitaxel
Abiraterone
MDV 3100
TAK - 700
TOK - 001
Abiraterone
MDV 3100
TAK - 700

VACCINI

Trial	Population	Comparator	Experimental arm	Results
IMPACT	Asymptomatic metastatic chemonaïve CRPC	Placebo	Sipuleucel-T	Improved overall survival with vaccine
VITAL-1	Asymptomatic metastatic chemonaïve CRPC	Docetaxel + prednisone	GVAX	Closed prior to completion for futility
VITAL-2	Symptomatic metastatic chemonaïve CRPC	Docetaxel + prednisone	GVAX + docetaxel	Closed after interim analysis showed inferiority for vaccine arm
Phase II	Asymptomatic metastatic chemonaïve CRPC	Placebo	Prostvac + co-stimulatory molecules	Improved survival with vaccine

Trial	Population	Comparator	Experimental arm	Results
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Phase II	Asymptomatic metastatic chemonaïve CRPC	Placebo	Prostvac + co-stimulatory molecules	Improved survival with vaccine

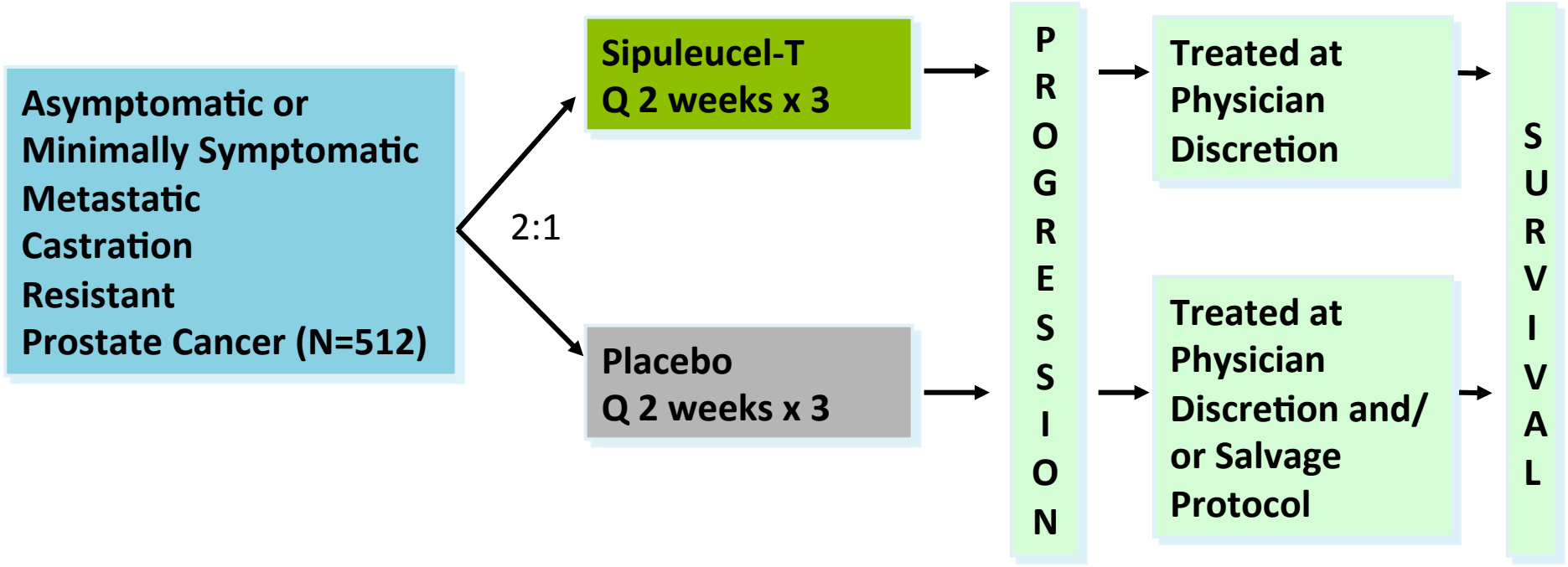
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

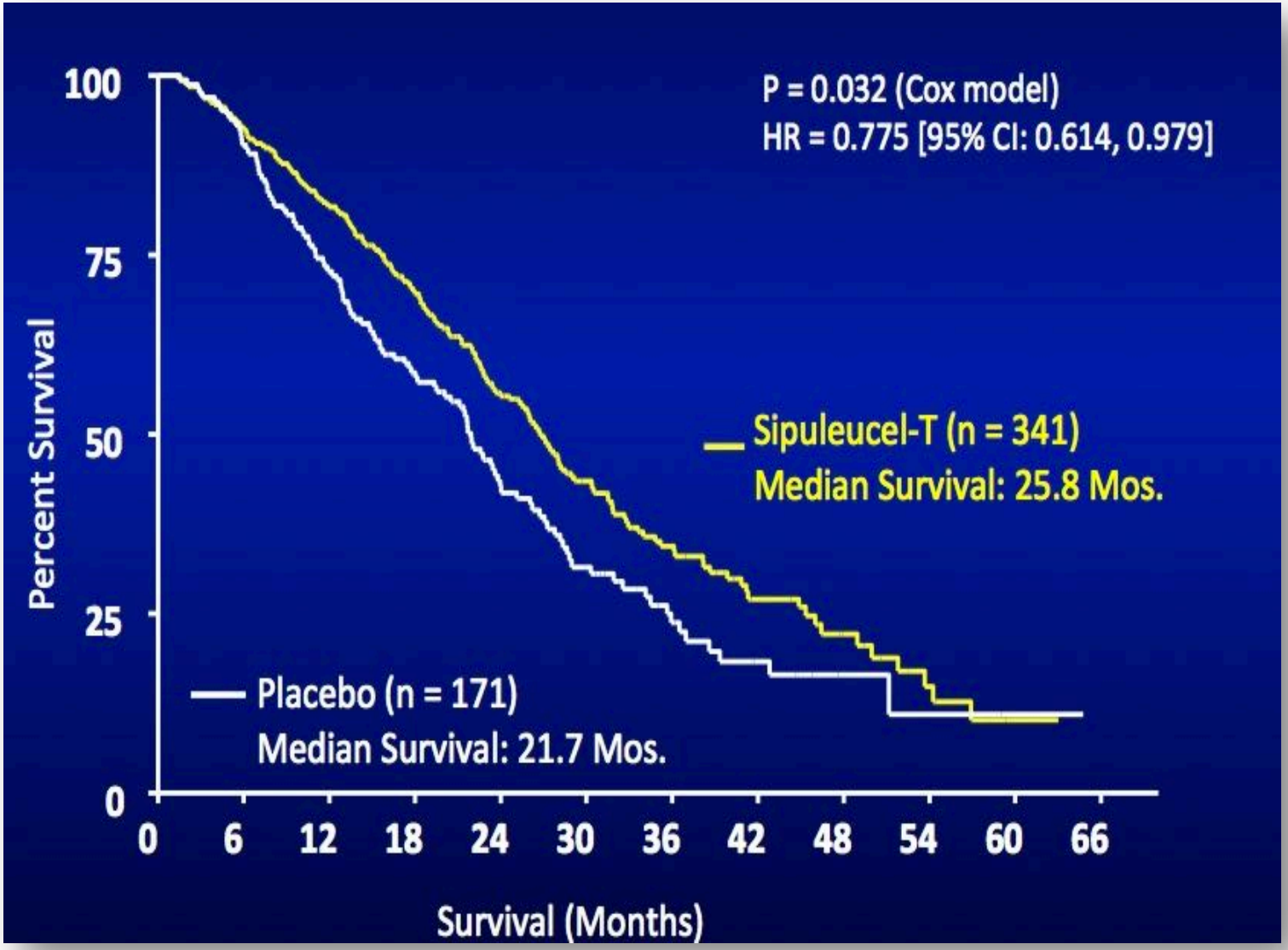
Randomized Phase 3 IMPACT Trial (IMmunotherapy Prostate AdenoCarcinoma Treatment)



Primary Endpoint: Overall Survival

Secondary Endpoint: Objective Disease Progression

Sipuleucel-T: IMPACT Overall Survival



VOLUME 28 · NUMBER 7 · MARCH 1 2010

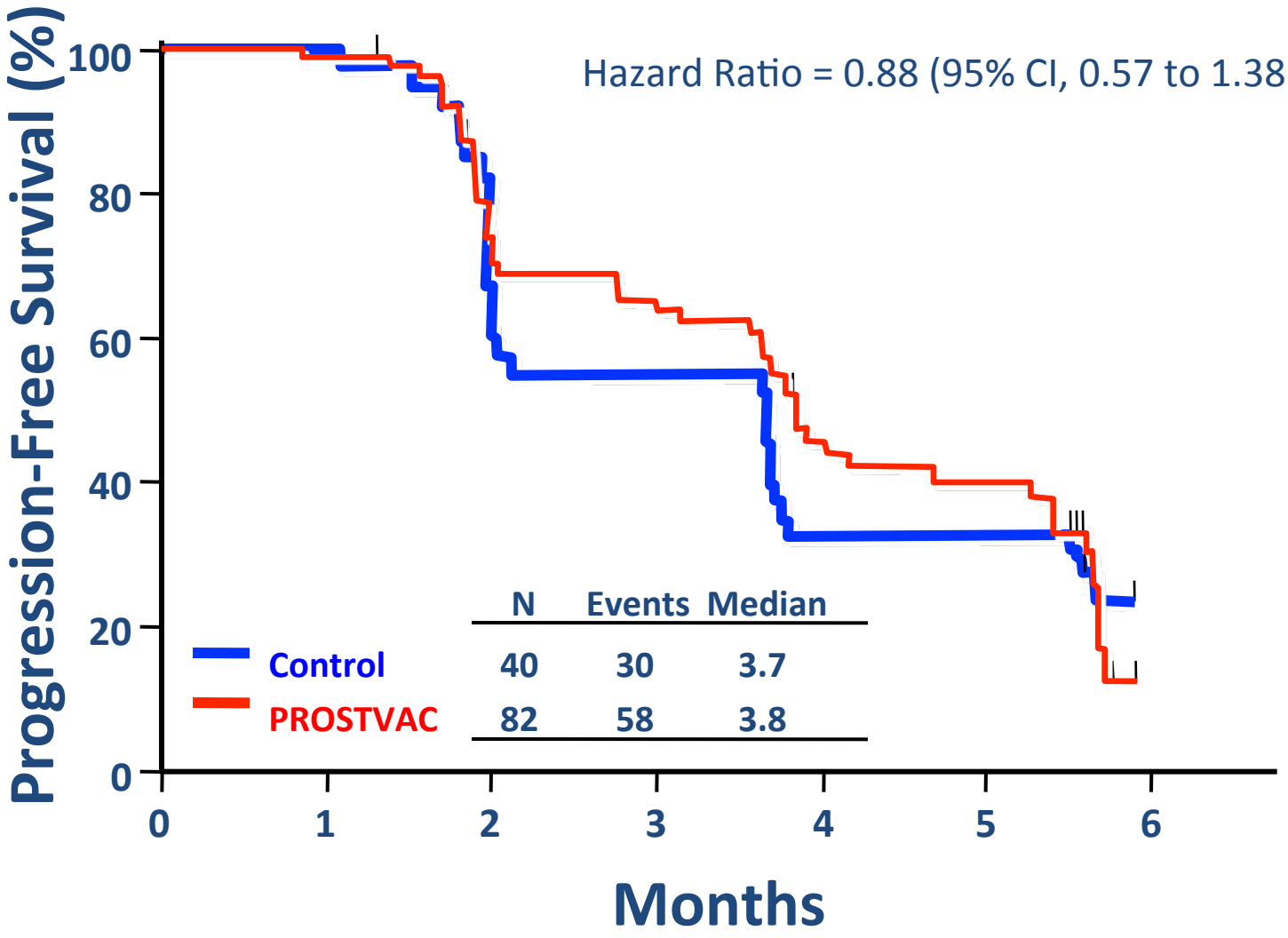
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral-Based PSA-Targeted Immunotherapy in Metastatic Castration-Resistant Prostate Cancer

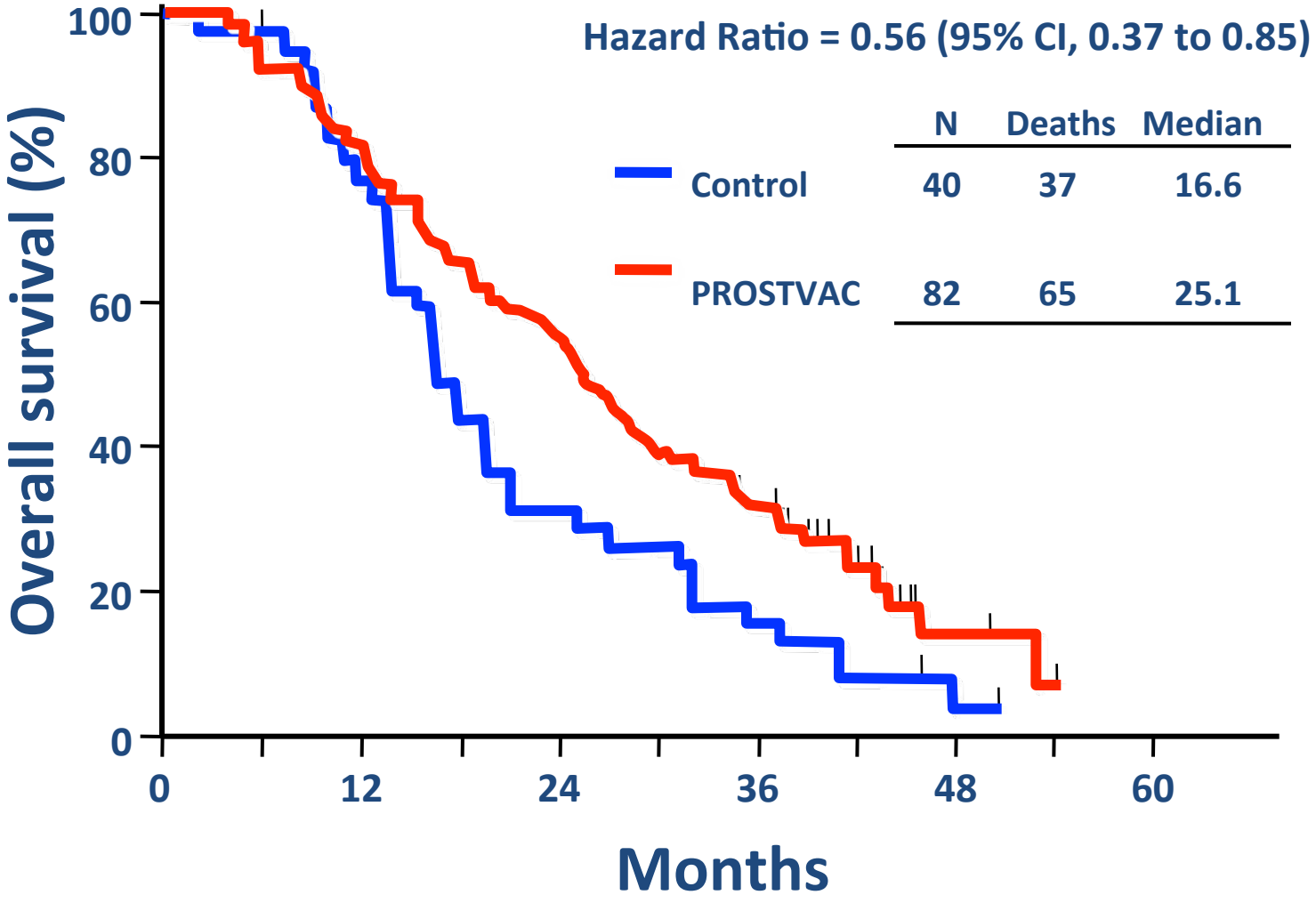
Philip W. Kantoff, Thomas J. Schuetz, Brent A. Blumenstein, L. Michael Glode, David L. Bilhartz, Michael Wyand, Kelledy Manson, Dennis L. Panicali, Reiner Laus, Jeffrey Schlom, William L. Dahut, Philip M. Arlen, James L. Gulley, and Wayne R. Godfrey

Progression-free survival



Kantoff PW, JCO 2010

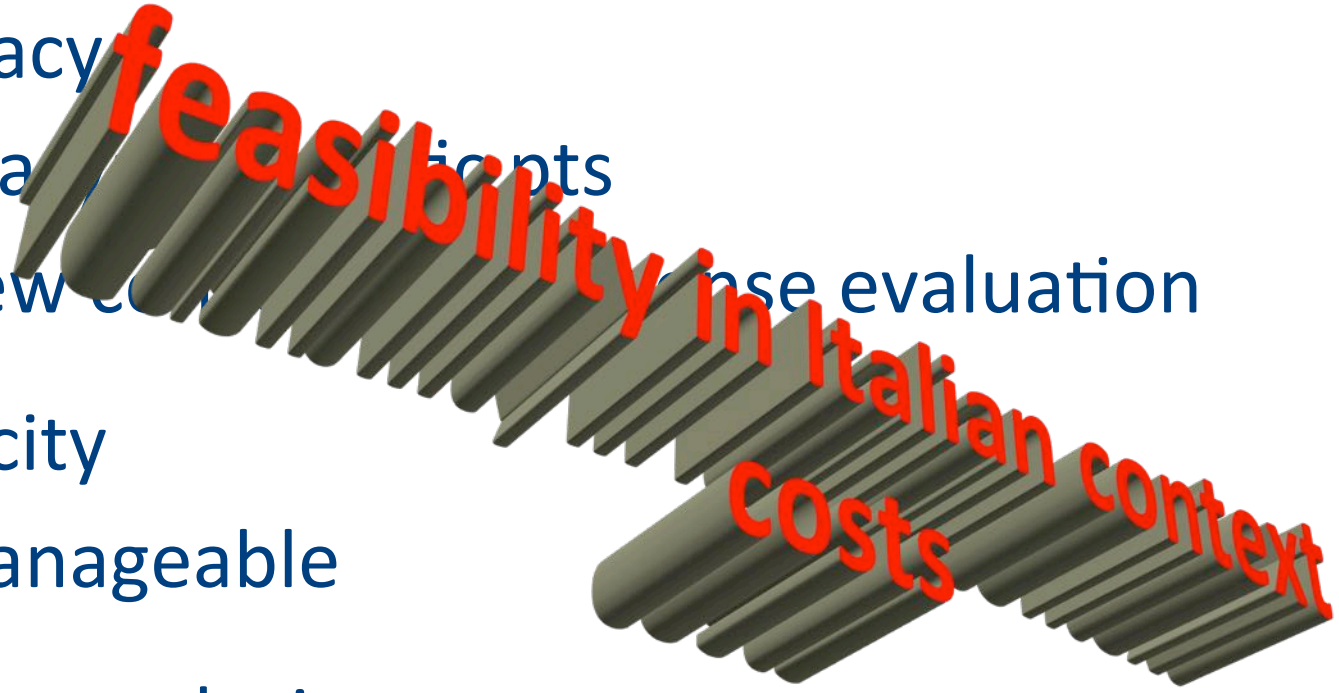
Overall Survival

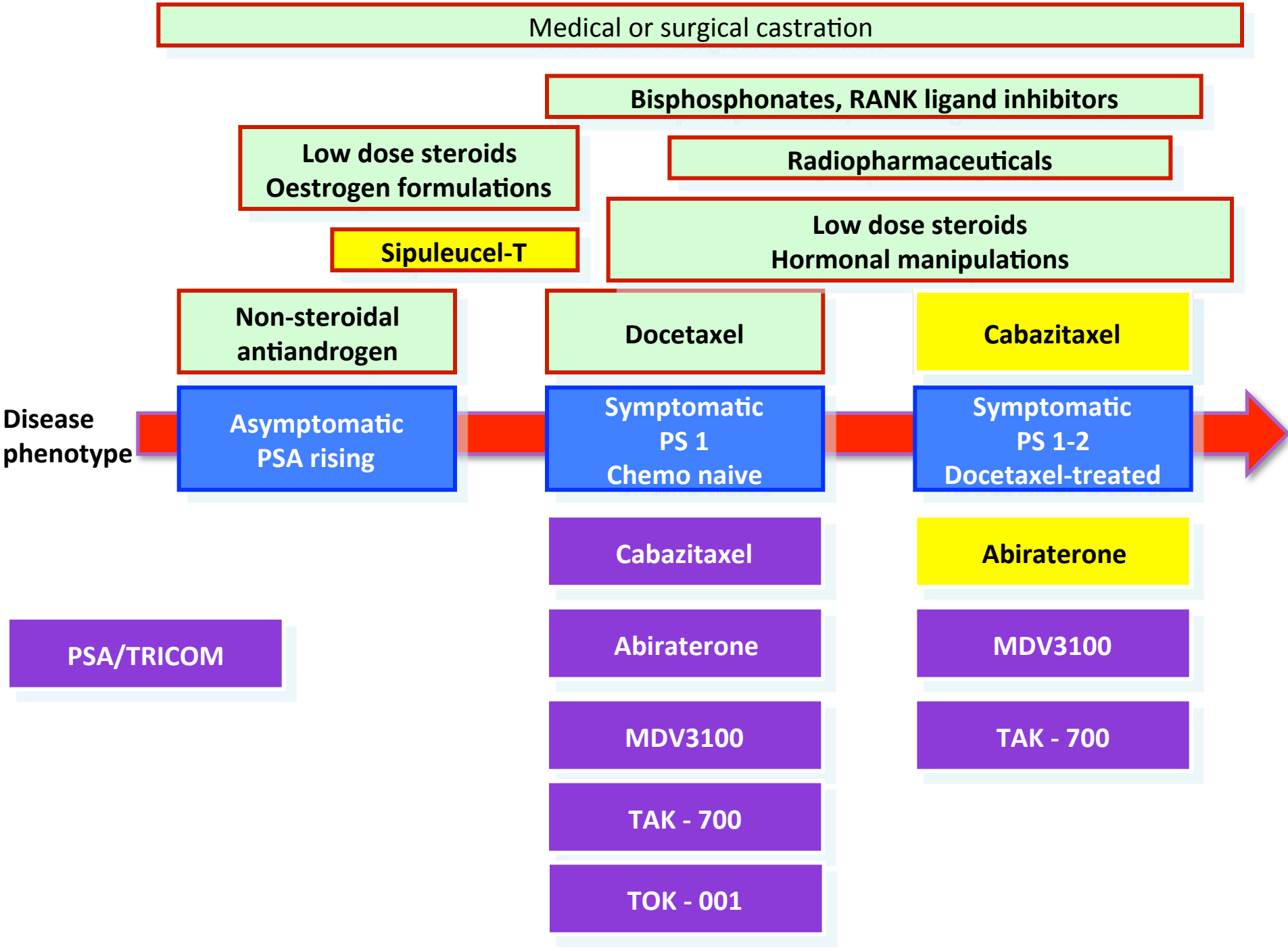


Kantoff PW, JCO 2010

Vaccines key issues

- Efficacy
  - In a[illegible]pts
  - New c[illegible]nse evaluation
- Toxicity
  - Manageable
- Strategy placing
  - Hormone-sensitive disease?
  - CRPC chemo-naive?




Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
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Docetaxel
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Disease phenotype
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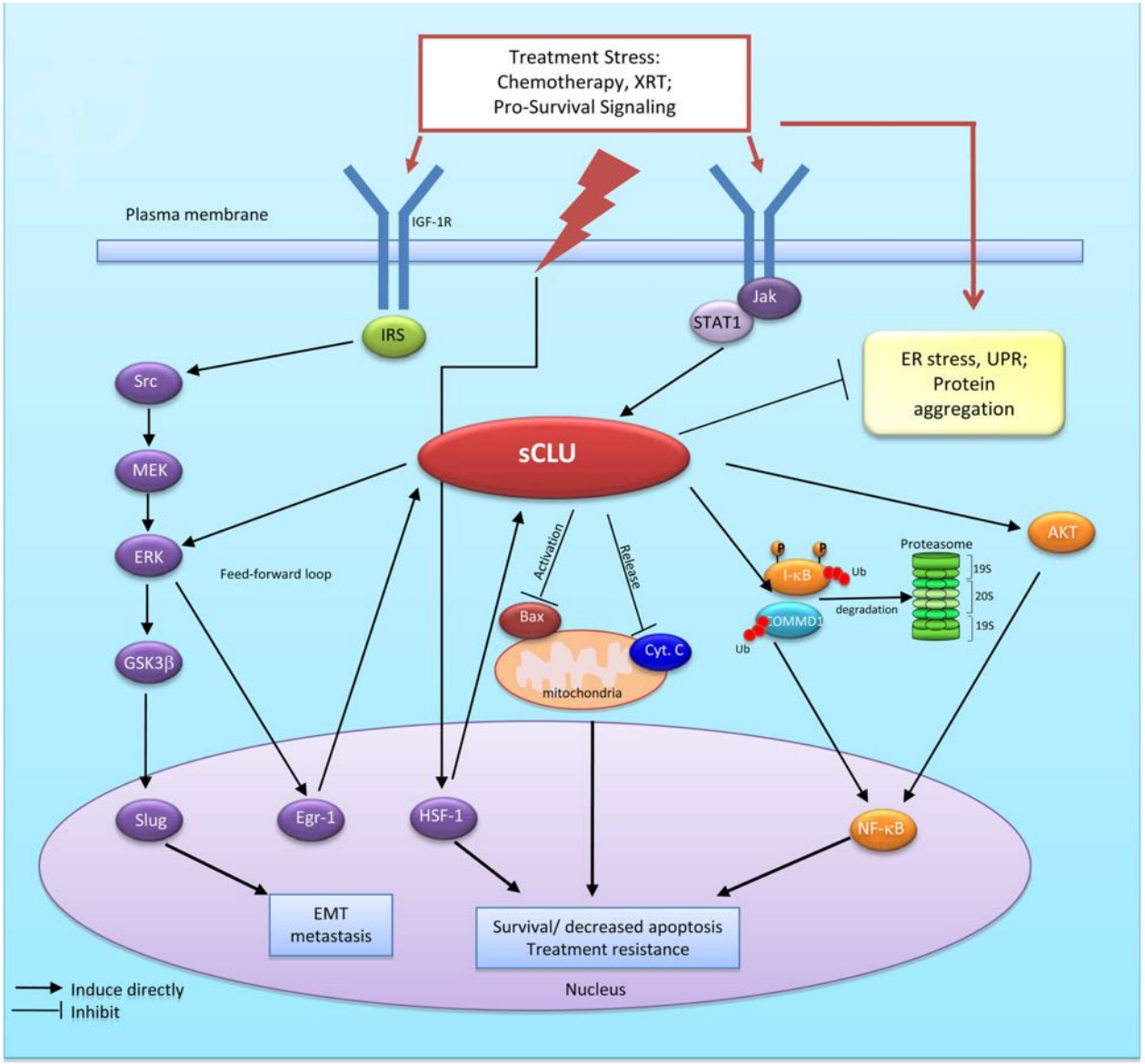
Cabazitaxel
Abiraterone
PSA/TRICOM
Abiraterone
MDV3100
MDV3100
TAK - 700
TAK - 700
TOK - 001

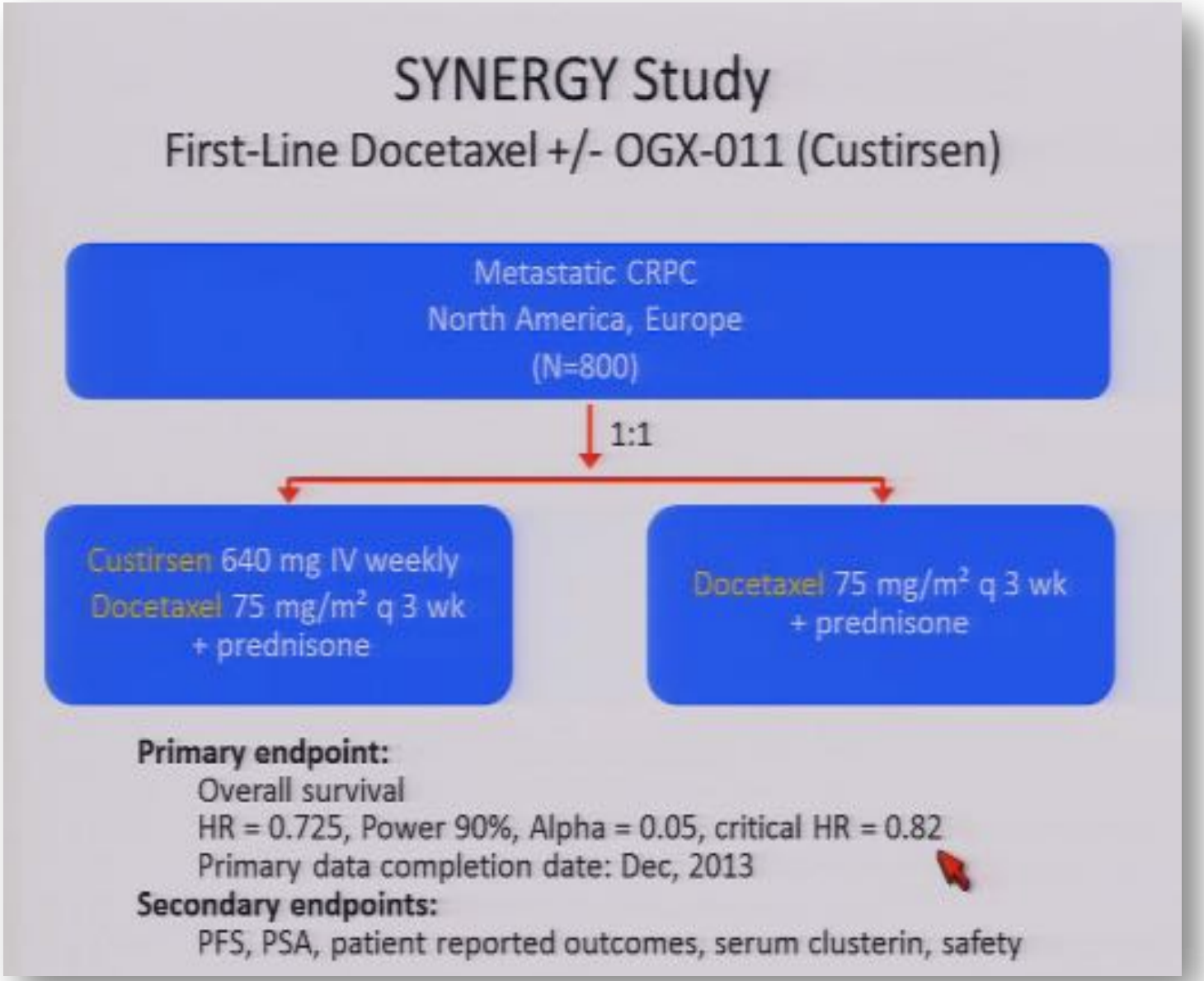
New Agents

Custirsen

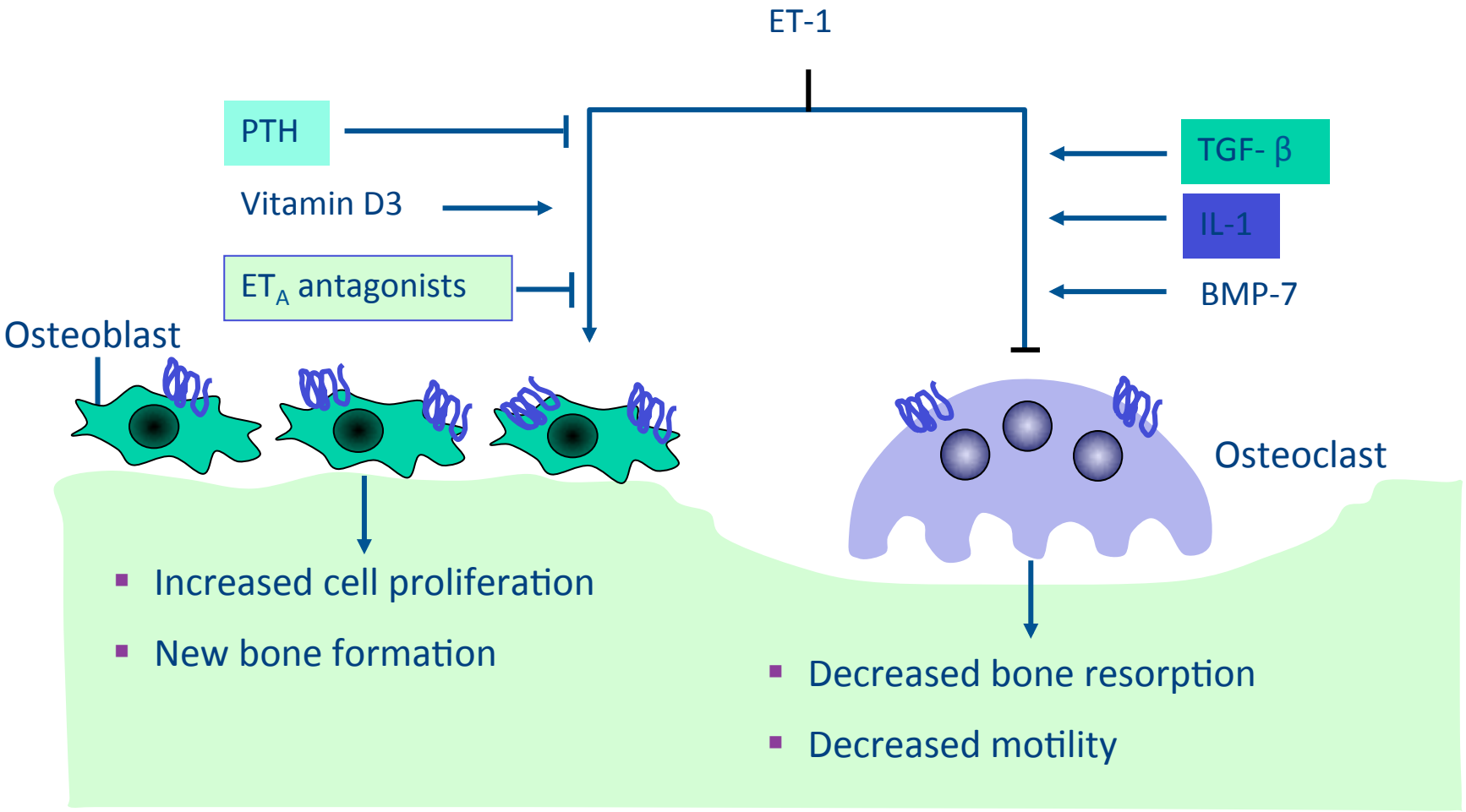


- CLU is a stress-activated cytoprotective chaperone
- It is upregulated by several cancer drugs and confers resistance when overexpressed
- OGX-011 targets CLU

Custirsen: studio di fase III

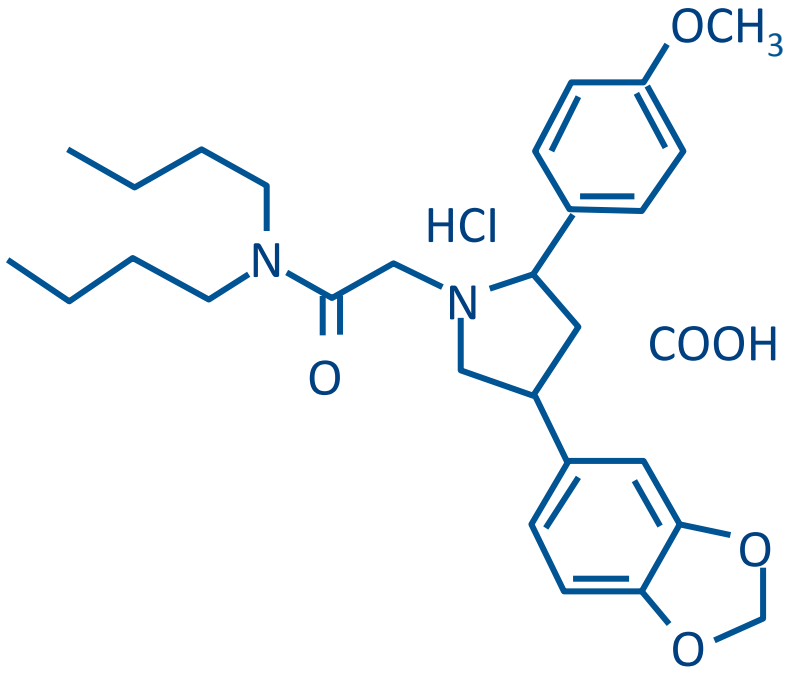


Endothelin Axis in Bone



Atrasentan

- A potent, selective ET_A receptor antagonist

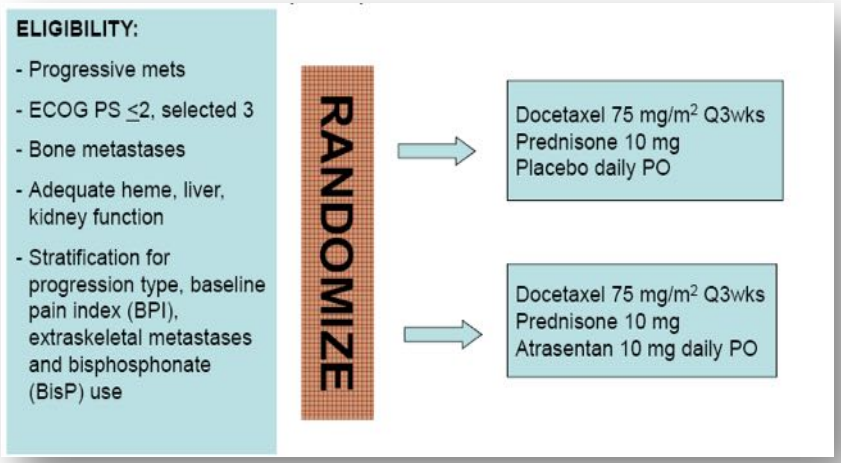


- ET_A K_i = 34 pM
- 1800-fold ET_A > ET_B
- Orally bioavailable
- Once-daily dosing, $t_{1/2}$ ≈ 24 hrs

Opgenorth TJ, et al. J Pharmacol Exp Ther. 1996;276:473-481. Verhaar MC, et al. Br J Clin Pharmacol. 2000;49:562-573.

SWOG S0421: Phase III study of docetaxel and atrasentan versus docetaxel and placebo in CRPC

991 eligible patients



Endpoint	D+A	D+P	Comparison
OS – median	18 mo	17 mo	HR=1.01 (95% CI 0.87,1.18) p=0.88
PFS – median	10 mo	10 mo	HR=1.03 (95% CI 0.90,1.19) p=0.64
RECIST confirmed response* + unconfirmed	14% 27%	14% 21%	p=1.0 p=0.23
PSA response confirmed**	40%	41%	p=0.88
Treatment-related death (possible, probable)	n=3	n=7	
Grade 3+ toxicity	48.4%	51.6%	p=0.19

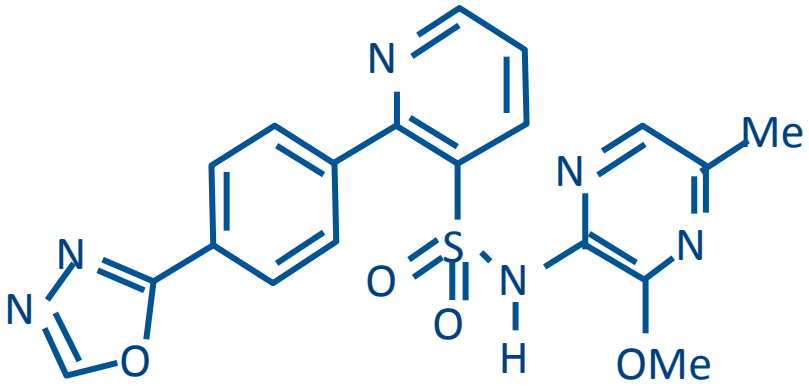
CONCLUSION

No benefit
for the addition of A to D
in CRPC

Quinn DI et al. J Clin Oncol 2012;30 (abstr 4511)

Zibotentan (ZD4054)

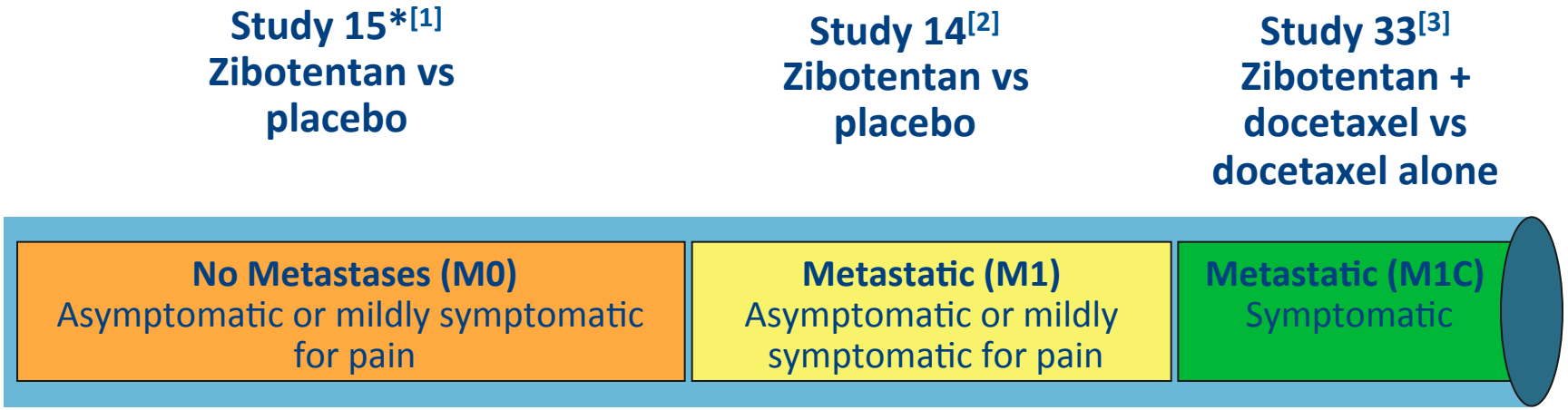
- A potent, *specific* ET_A receptor antagonist



- ET_A pIC_{50} = 8.27 nM
- No ET_B activity
- Orally bioavailable
- Once-daily dosing plasma $t_{1/2}$ = 9.1 hrs

Bradbury RH, et al. J Med Chem. 1997;40:996-1004. Morris CD, et al. Br J Cancer. 2005;92:2148-2151. Battistini B, et al. Exp Biol Med. 2006;231:653-695.

ENTHUSE (Endothelin A Use) Zibotentan Phase III Trial Program



*Study 15 terminated early based on independent data monitoring committee efficacy review indicating trial unlikely to meet primary efficacy endpoints.

1. ClinicalTrials.gov. NCT00626548. 2. ClinicalTrials.gov. NCT00554229. 3. ClinicalTrials.gov. NCT00617669.

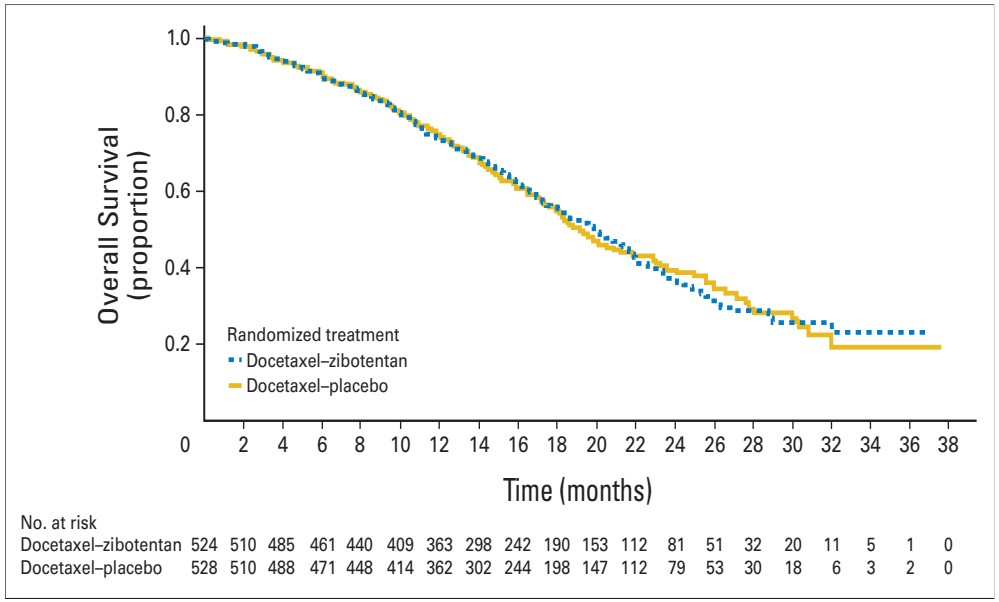
VOLUME 31 · NUMBER 14 · MAY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III, Randomized, Placebo-Controlled Study of Docetaxel in Combination With Zibotentan in Patients With Metastatic Castration-Resistant Prostate Cancer

Karim S. Fizazi, Celestia S. Higano, Joel B. Nelson, Martin Gleave, Kurt Miller, Thomas Morris, Faith E. Nathan, Stuart McIntosh, Kristine Pemberton, and Judd W. Moul



Docetaxel plus zibotentan 10 mg/d did not result in a significant improvement in OS compared with docetaxel plus placebo in patients with metastatic CRPC.

Fizazi Ket al. J Clin Oncol 2013;14, 1740-48

Multitargeted Tirosin Kinase Inhibitors

Sunitinib	VEGFR multikinase inhibitor	34	Phase II in CRPC Chemotherapy naïve (n = 17) Previously treated (n = 17)	PSA response rate: 6% in both groups	Dror Michaelson *et al.* [70]
Sunitinib		36	Phase II Previously treated with docetaxel	PSA response rate: 12% Median PFS: 4.5 months (19.4 weeks)	Sonpavde *et al.* [76]
Sorafenib	VEGFR multikinase inhibitor	22	Phase II mCRPC (59% pts had received prior chemotherapy)	No PSA response 2 pts had regression in bone lesions	Dahut *et al.* [68]
Sorafenib		28	Phase II Chemotherapy naïve CRPC	PSA response rate: 4%	Chi *et al.* [66]
Sorafenib		55	Phase II Chemotherapy naïve CRPC	PSA response rate: 4%	Steinbild *et al.* [77]
Aflibercept + docetaxel/ prednisone	VEGF Trap	1200	Randomized, phase III (VENICE) vs placebo + docetaxel/prednisone Chemotherapy naïve CRPC	Primary endpoint: OS	NIH NCT00519285 [62]

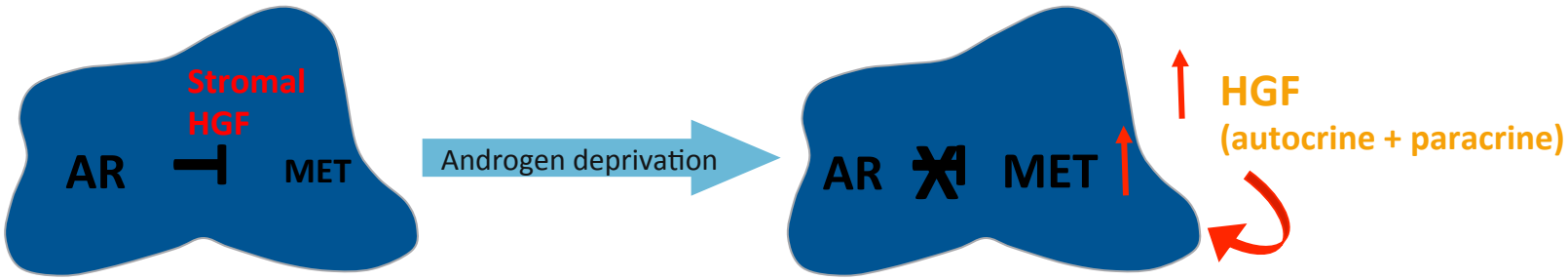
Fizazi, BJU, 2010

Antiangiogenic agents in randomized phase III trials against placebo

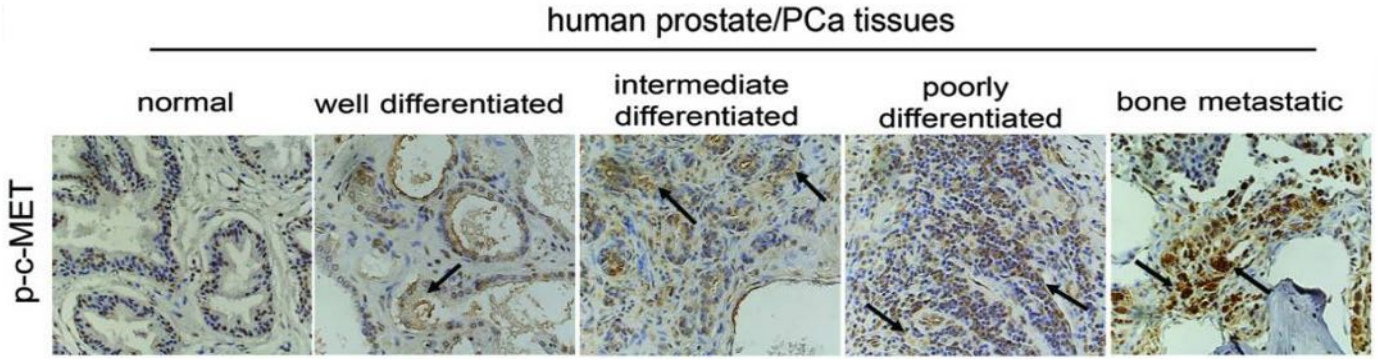
Study	N	Result
Docetaxel/Prednisone +/- Bevacizumab (CALGB) **1050 pts**		PFS improved but not OS (Kelly WK et al. J Clin Oncol. 2012; 30:1534-40.)
Prednisone +/- Sunitinib (post-Docetaxel)		PFS improved but not OS (Michaelson MD et al., ASCO 2011, Abstr 4515)
Docetaxel/Prednisone +/- Lenolidamide (MAINSAIL)		Stopped by Independent Monitoring Committee in Dec 2010 for futility
Docetaxel/Prednisone +/- Aflibercept (VENICE)		Announced no improvement in OS on April 5, 2012
Tasquinimod vs. Placebo (no/minimal symptom mCRPC, pre-chemo)	1200	Ongoing accrual with 2:1 randomization; Primary endpoint – PFS
Cabozantinib vs. Placebo (COMET 1)(post-Docetaxel)	960	Primary endpoint - OS

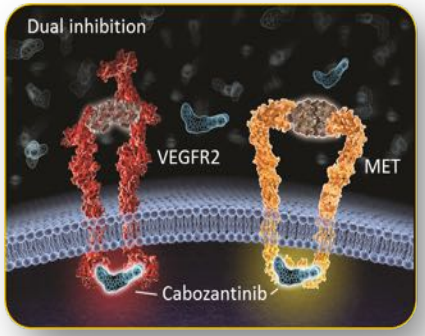
Role of MET in Prostate Cancer and Bone Metastases

Androgen deprivation activates MET signaling[1,2]



Activated MET is highly expressed in bone metastases[3]



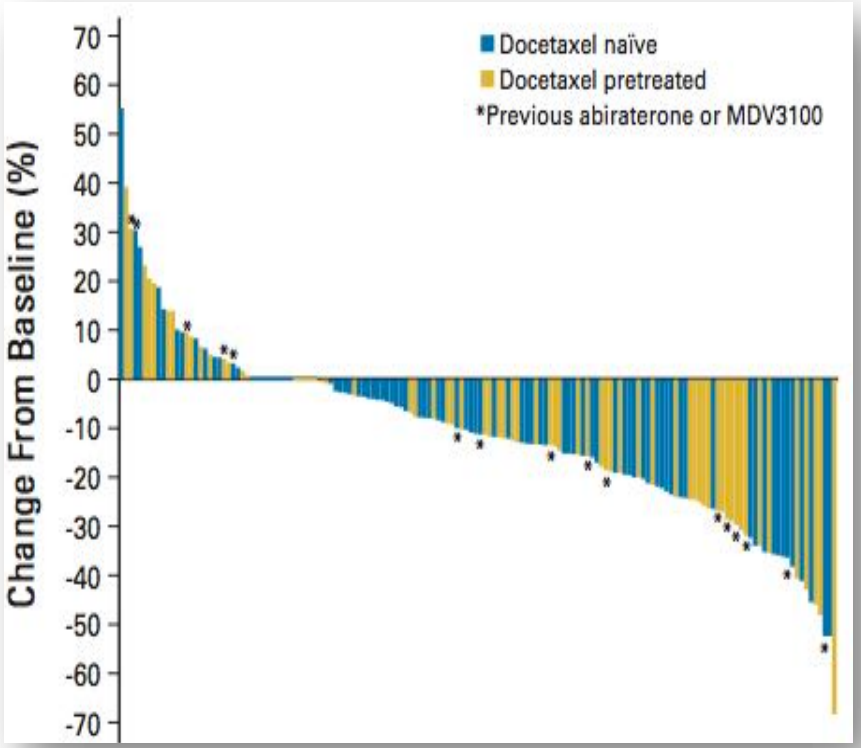


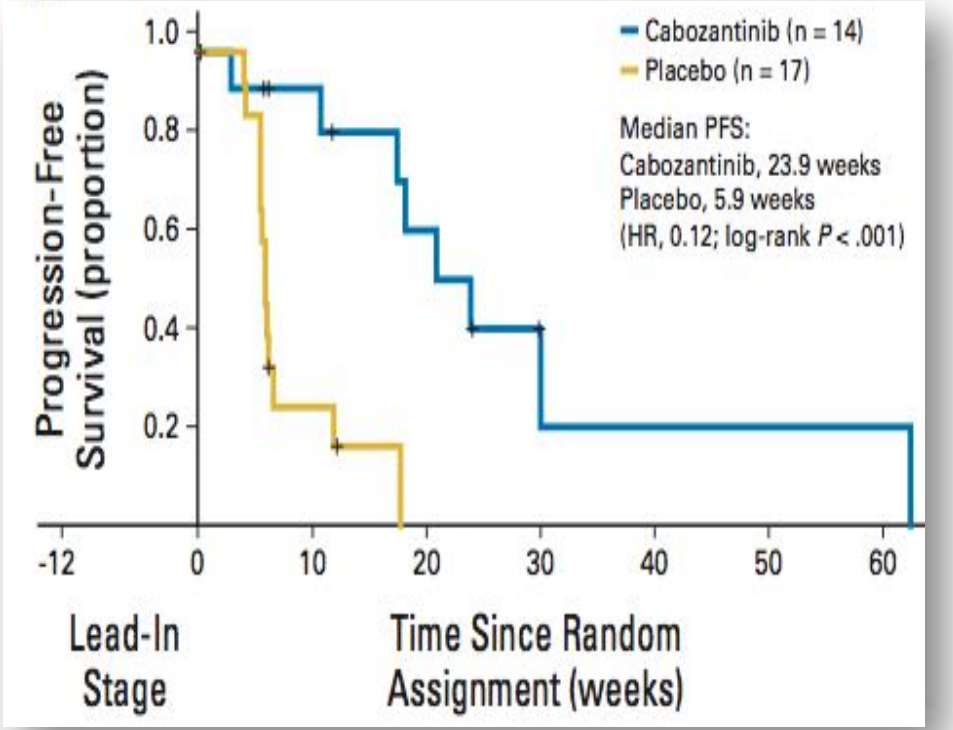
1. Humphrey PA, et al. Am J Pathol. 1995;147:386-396. 2. Verras M, et al. Cancer Res. 2007;67:967-975. 3. Zhang S, et al. Mol Cancer. 2010;9:9.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cabozantinib in Patients With Advanced Prostate Cancer: Results of a Phase II Randomized Discontinuation Trial

David C. Smith, Matthew R. Smith, Christopher Sweeney, Aymen A. Elfiky, Christopher Logothetis, Paul G. Corn, Nicholas J. Vogelzang, Eric J. Small, Andrea L. Harzstark, Michael S. Gordon, Ulka N. Vaishampayan, Naomi B. Haas, Alexander I. Spira, Primo N. Lara Jr, Chia-Chi Lin, Sandy Srinivas, Avishay Sella, Patrick Schöffski, Christian Scheffold, Aaron L. Weitzman, and Maha Hussain





Smith D. et al., JCO 2012

COMET-2: CabOzantinib MET Inhibition CRPC Efficacy Trial–2 Study Design

Patients with:
- Confirmed mCRPC with bone metastases
- Bone pain (BPI ≥ 4)
- Previously treated with docetaxel and either abiraterone or MDV3100

(N = 246)

Cabozantinib 60 mg QD + **Mitoxantrone Placebo** + **Prednisone Placebo** (n = 123)

Mitoxantrone + **Prednisone** + **Cabozantinib Placebo** (N = 123)

Primary endpoint: durable pain response

Secondary endpoint: bone scan response by IRF, OS

ClinicalTrials.gov. NCT01522443.

COMET-1: CabOzantinib MET Inhibition CRPC Efficacy Trial–1 (Planned Design)

Patients with:

- Confirmed mCRPC with bone metastases
- Previously treated with docetaxel
- Previously treated with either abiraterone or MDV3100
- No limit to prior treatments

Arm A
(n = 640)

Cabozantinib 60 mg QD +
Placebo

N = 960

Placebo +
Prednisone 5 mg BID

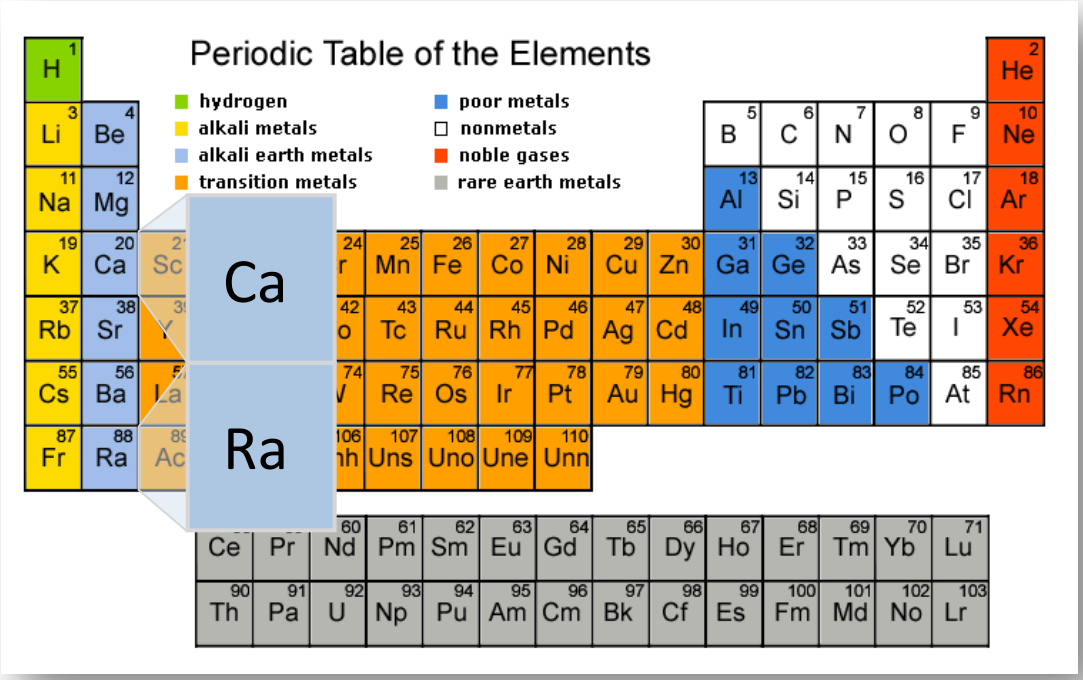
Arm B
(n = 320)

Primary endpoint: OS

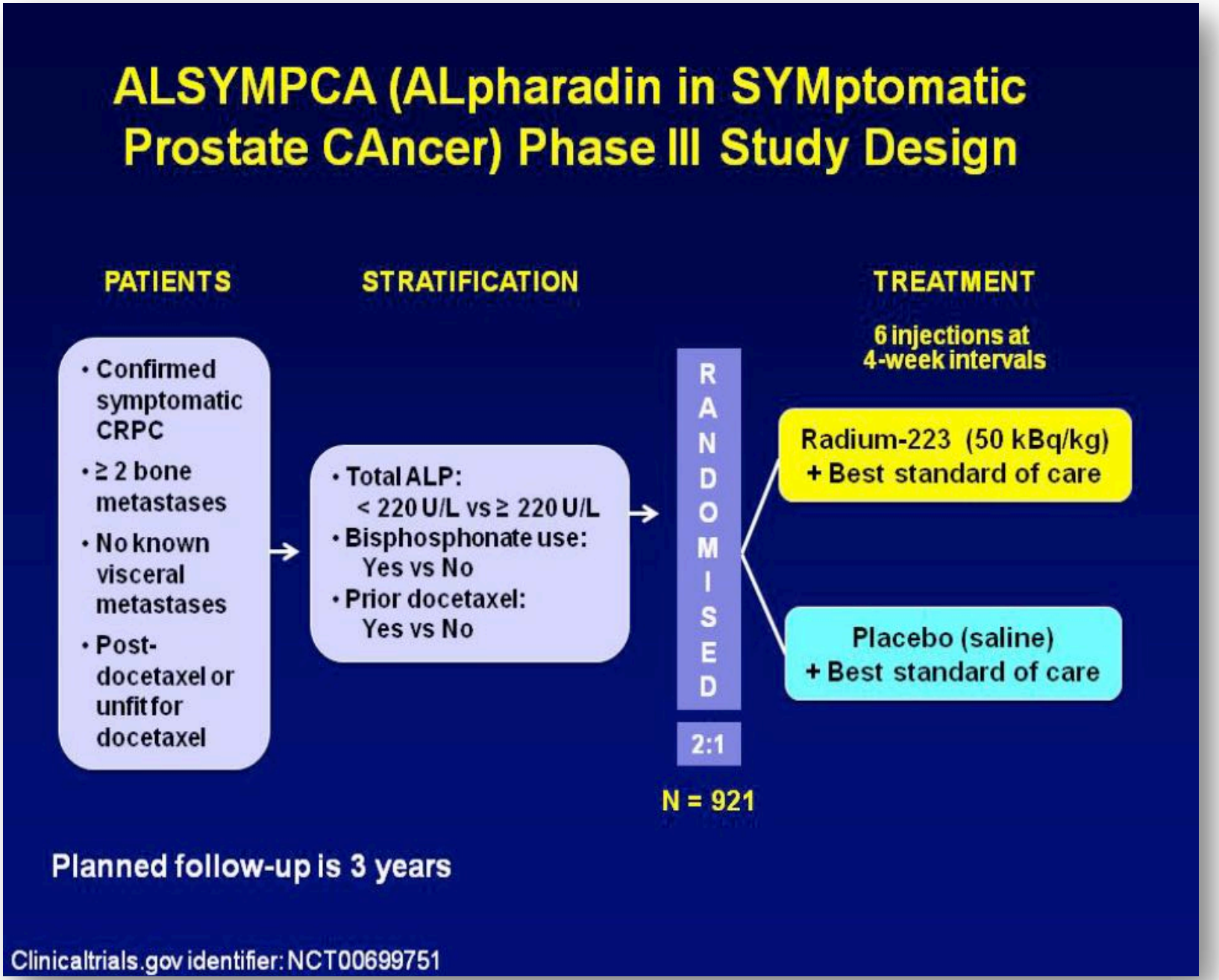
Secondary endpoint: bone scan response (IRF assessed)

Radium-223 Targets Bone Metastases

- Radium-223 functions as a calcium mimic
- Targets sites of new bone growth within and around bone metastases
- Excreted by the small intestine

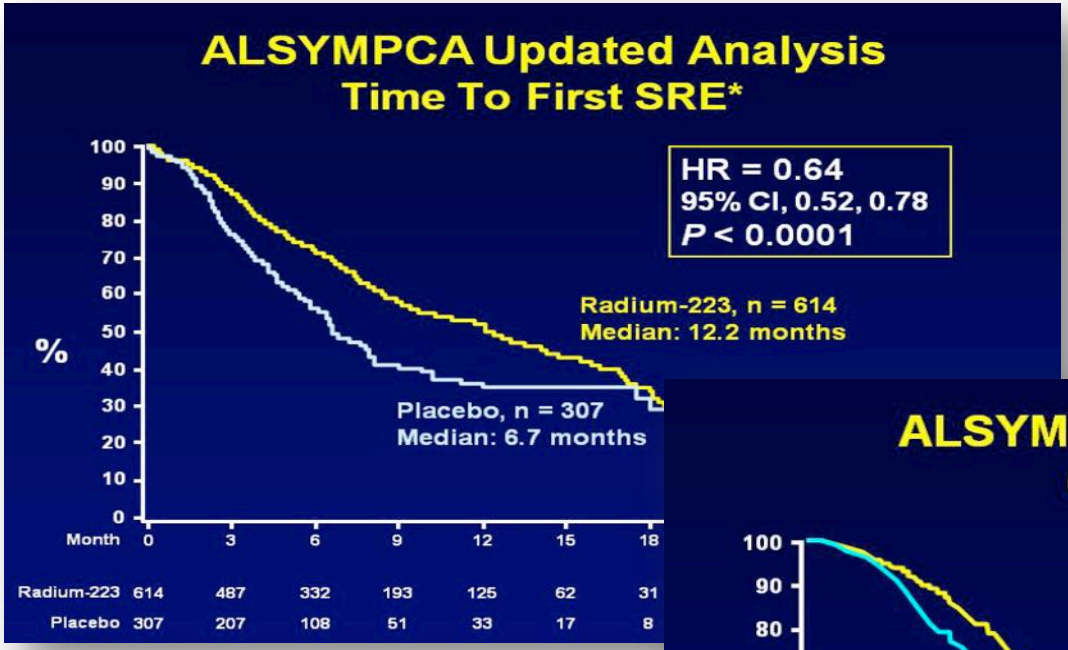


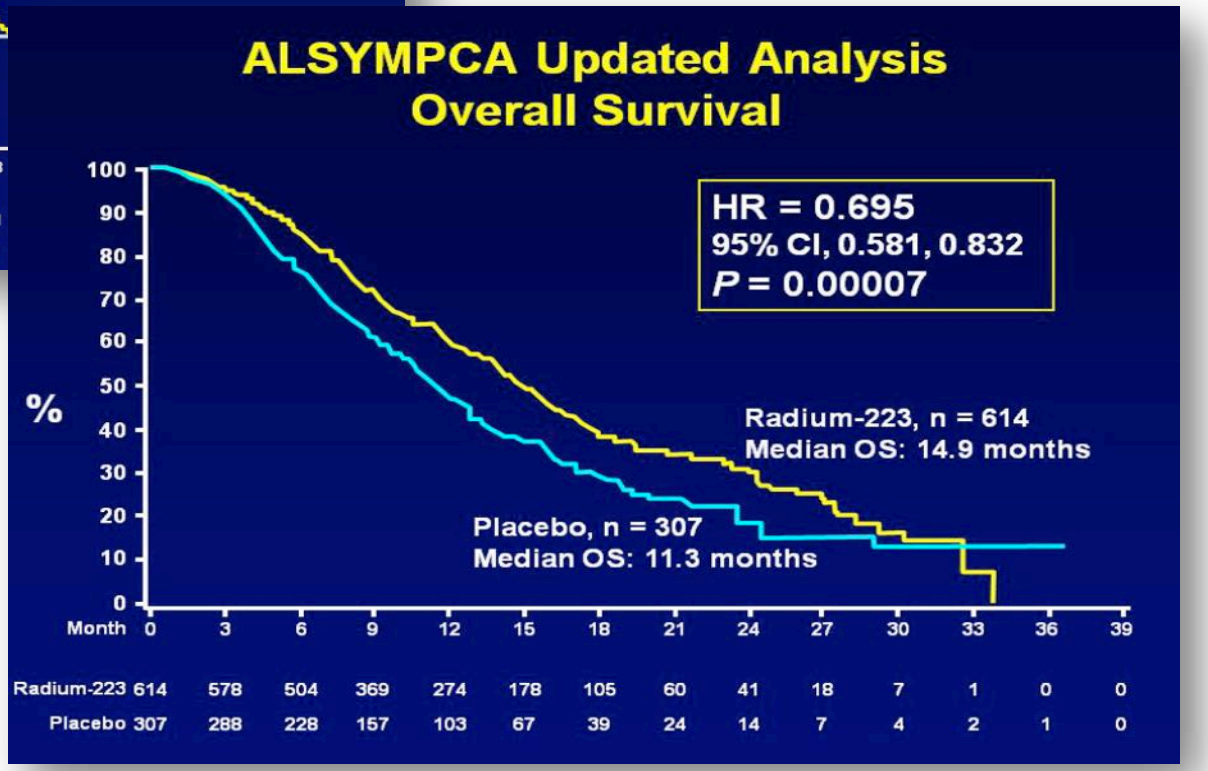
Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.



Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

The ‘ALSYMPCA’ trial





Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

How should we sequence therapy?

What is the optimal sequence?

- I am tired of the question…..no data!
  - Reasonable to use less toxic therapies first
  - Reasonable to involve patients in the decision making and respect patient preferences
- I believe….patients should have exposure to as many active drugs as possible
  - So long as the patient tolerates the drug well and does not "rapidly" progress, keep it going
  - Do not let the patient deteriorate too far, that limits future options….follow patients closely

From Oliver Sartor ASCO 2012 Educational Session

How to choose a sequential therapy?

Patients with visceral mets:

MDV3100 OS=18.4 + Cabazitaxel PFS=6.4 + Abirat rone PFS=10.2

Increase of O

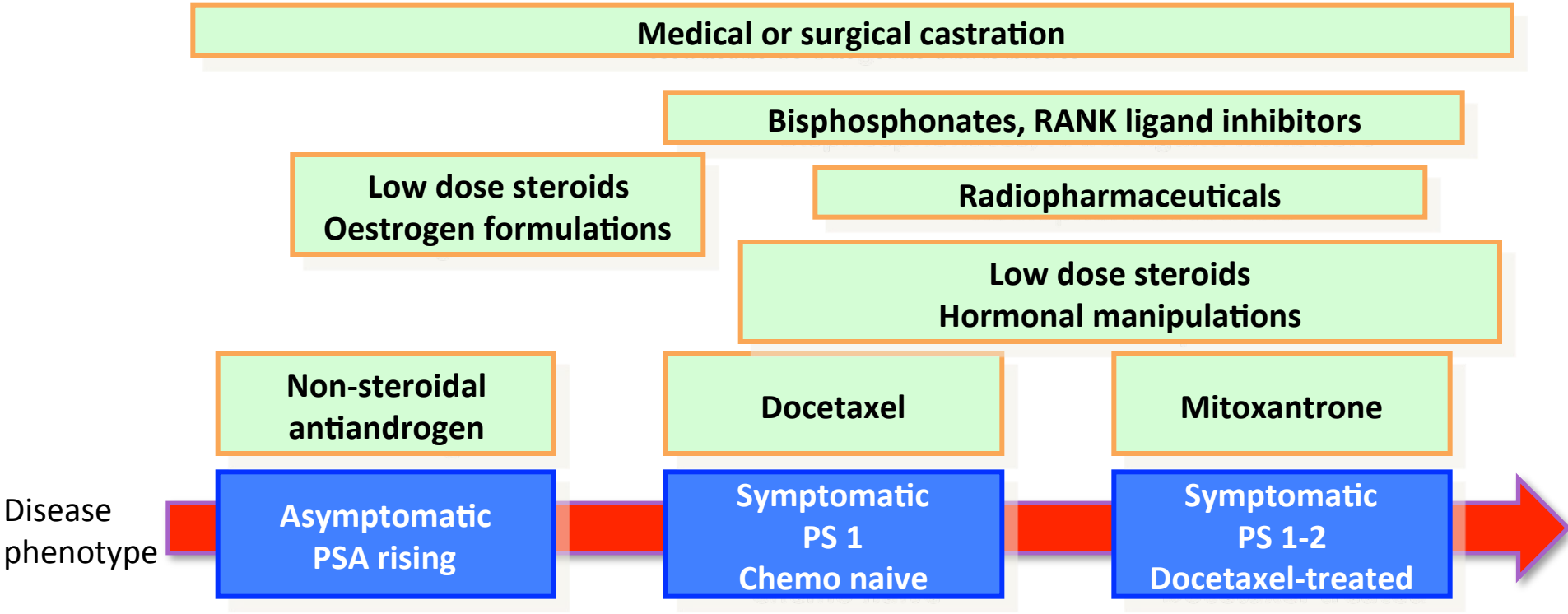
Patients with bone mets

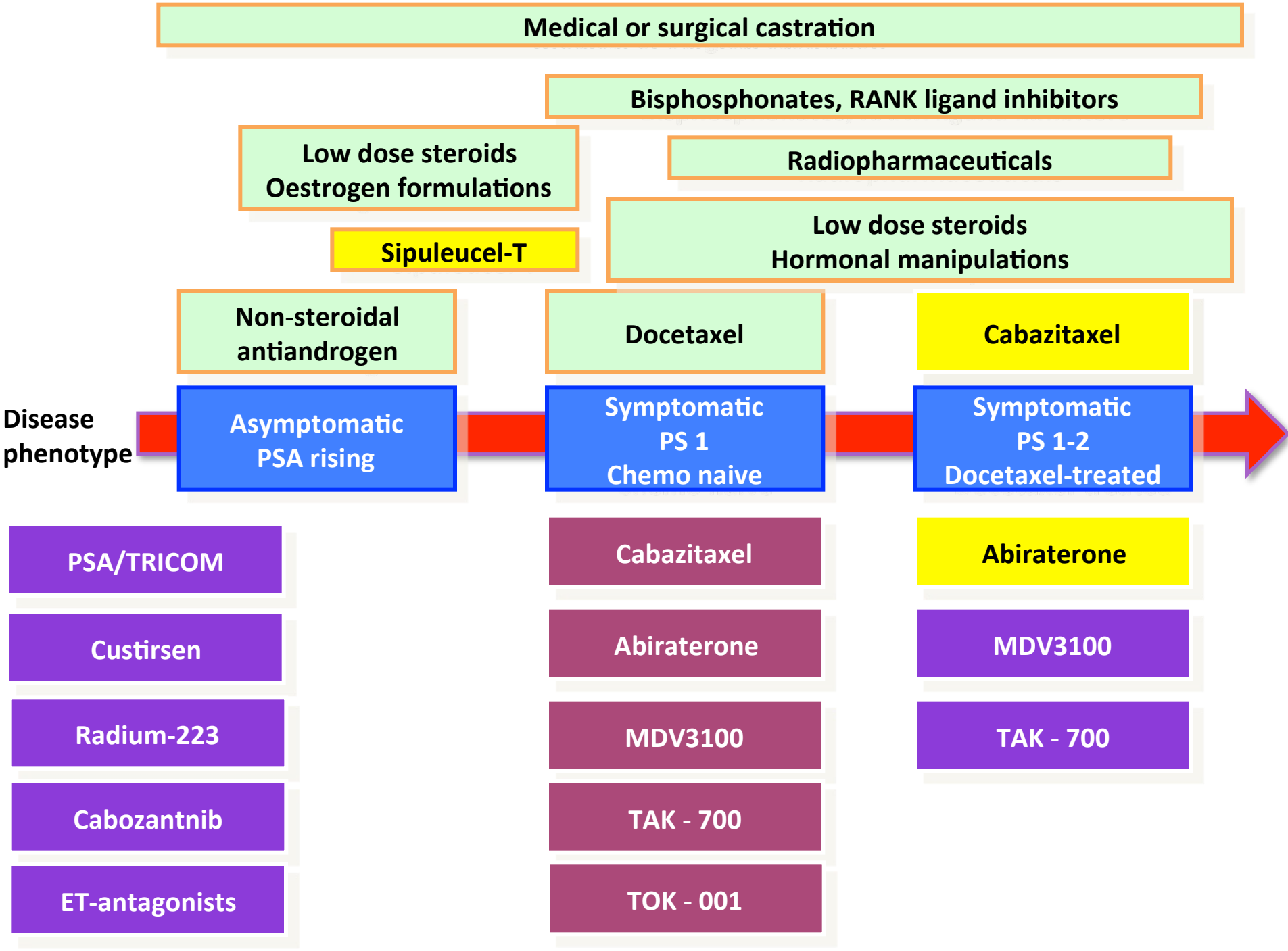
Alpharadin OS=14.(8.3 + Abiraterone PFS=10.2 + Cabazitaxel PFS=6.4

Increase of OS of 24 mos!!

This would be great but is not EBM!!!!

Take home message


Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
Oestrogen formulations
Radiopharmaceuticals
Low dose steroids
Hormonal manipulations
Non-steroidal antiandrogen
Docetaxel
Mitoxantrone
Disease phenotype
Asymptomatic PSA rising
Symptomatic PS 1 Chemo naive
Symptomatic PS 1-2 Docetaxel-treated


Medical or surgical castration
Bisphosphonates, RANK ligand inhibitors
Low dose steroids
Oestrogen formulations
Radiopharmaceuticals
Sipuleucel-T
Low dose steroids
Hormonal manipulations
Non-steroidal antiandrogen
Docetaxel
Cabazitaxel
Disease phenotype
Asymptomatic PSA rising
Symptomatic PS 1 Chemo naive
Symptomatic PS 1-2 Docetaxel-treated
PSA/TRICOM
Custirsen
Radium-223
Cabozantnib
ET-antagonists
Cabazitaxel
Abiraterone
MDV3100
TAK - 700
TOK - 001
Abiraterone
MDV3100
TAK - 700

- Management of CRPC is rapidly evolving
- Docetaxel is the standard in 1st-line mCRPC
- Progression after docetaxel is not an unmet need anymore:
  - Cabazitaxel shows a significant survival advantage vs mitoxantrone
  - Abiraterone also provides survival advantage vs placebo
  - The most appropriate sequencing of abiraterone and cabazitaxel remains to be determined

The right drug, at the right time, for the right patient

Possible Confusion in Names of New Treatments for Prostate Cancer

TO THE EDITOR: Several new drugs have been approved for the treatment of metastatic prostate cancer, and they are now in widespread use. Recent additions to the prostate-cancer armamentarium are listed in Table 1. Though each agent has a specific generic name, the unintended consequence of manufacturers' insatiable proclivity to include the letters X and Z in the marketed trade names will undoubtedly lead to confusion both by the physician prescribing and the pharmacy dispensing these agents.

Regulators and pharmaceutical manufacturers alike need to take heed of these areas of possible confusion. They should consider incorporation of the unique and distinguishing portions of the generic name in the creation and ultimate approval of the marketed trade name.

Table 1. New Drugs for the Treatment of Prostate Cancer.

Generic Name	Trade Name	Intended Use
Zoledronic acid	Zometa	Reduction of skeletal-related events due to metastatic prostate cancer
Denosumab	Xgeva	Reduction of skeletal-related events due to metastatic prostate cancer
Abiraterone	Zytiga	Treatment of metastatic castration-resistant prostate cancer
Enzalutamide	Xtandi	Treatment of metastatic castration-resistant prostate cancer
Cabazitaxel	Jevtana	Treatment of metastatic castration-resistant prostate cancer

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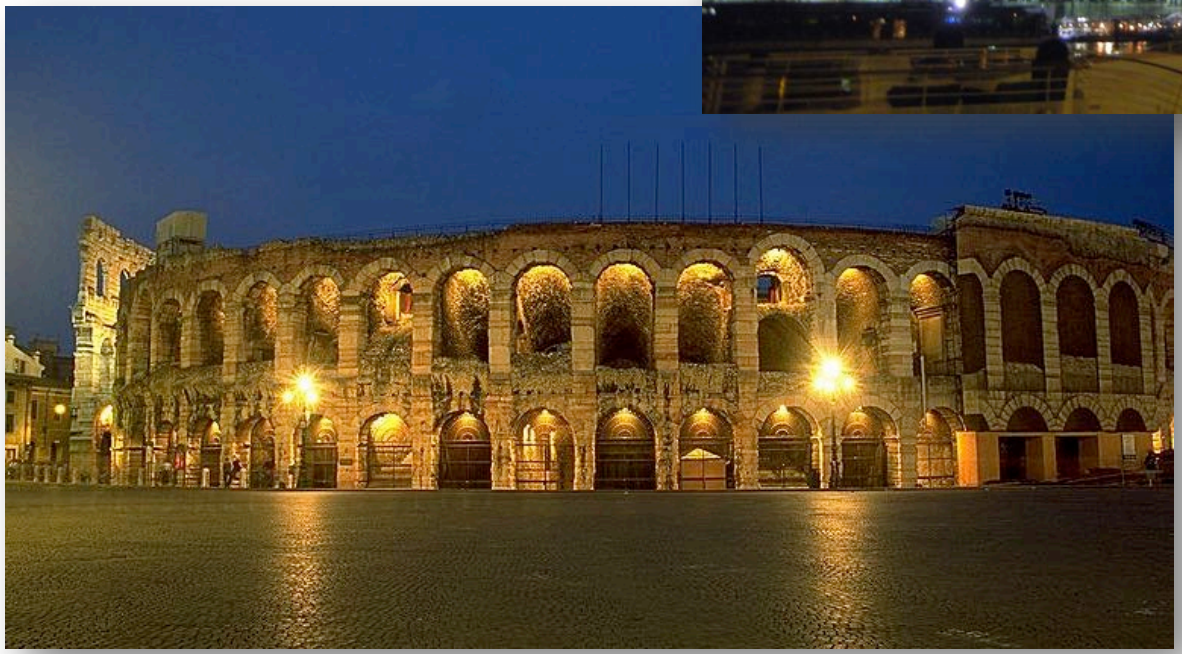
Disclosure forms provided by the author are available with the full text of this letter at NEJM.org.

DOI: 10.1056/NEJMc1213236

Garnick MB; NEJM 2013: 368;2



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