Προβληματισμοί στην αντιμετώπιση του μεταστατικού καρκίνου προστάτη

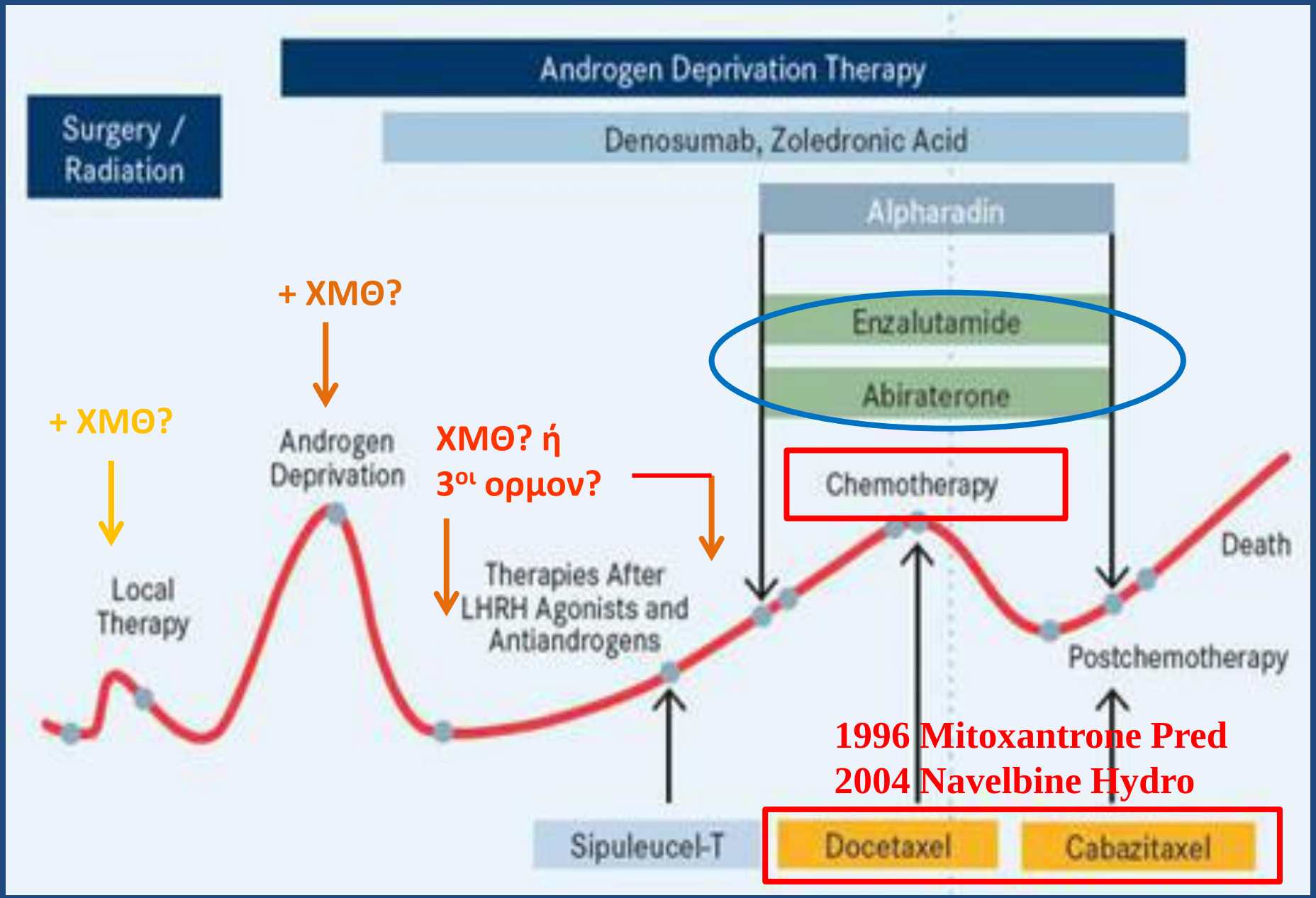
Δανάη Δαλιάνη, M.D.
Παθολόγος - Ογκολόγος
Διευθύντρια Ογκολογικής Κλινικής
Ευρωκλινική Αθηνών

Conflict of Interest

Consultant / Advisory Role: Astellas Pharma, Janssen Cilag, Sanofi-Aventis

Honoraria: Astellas Pharma, Janssen Cilag, Sanofi-Aventis

Research Funding: Sanofi-Aventis


Androgen Deprivation Therapy
Surgery / Radiation
Denosumab, Zoledronic Acid
Alpharadin
Enzalutamide
Abiraterone
+ ΧΜΘ?
+ ΧΜΘ?
Androgen Deprivation
ΧΜΘ? ή 3ου ορμον?
Chemotherapy
Death
Local Therapy
Therapies After LHRH Agonists and Antiandrogens
Postchemotherapy
1996 Mitoxantrone Pred
2004 Navelbine Hydro
Sipuleucel-T
Docetaxel
Cabazitaxel

ΧΜΘ σε «Μ» ορμονοευαίσθητο καρκίνο προστάτη ?

Ανάγκη βελτίωσης θεραπείας

Γνωστή **ετερογένεια** της νόσου

Μερική αντιανδρογονική δράση των ταξανών (αναστολή μετακίνησης /σηματοδότησης του AR)

Αποδεδειγμένο όφελος επιβίωσης δοσεταξέλης σε mCRPCa

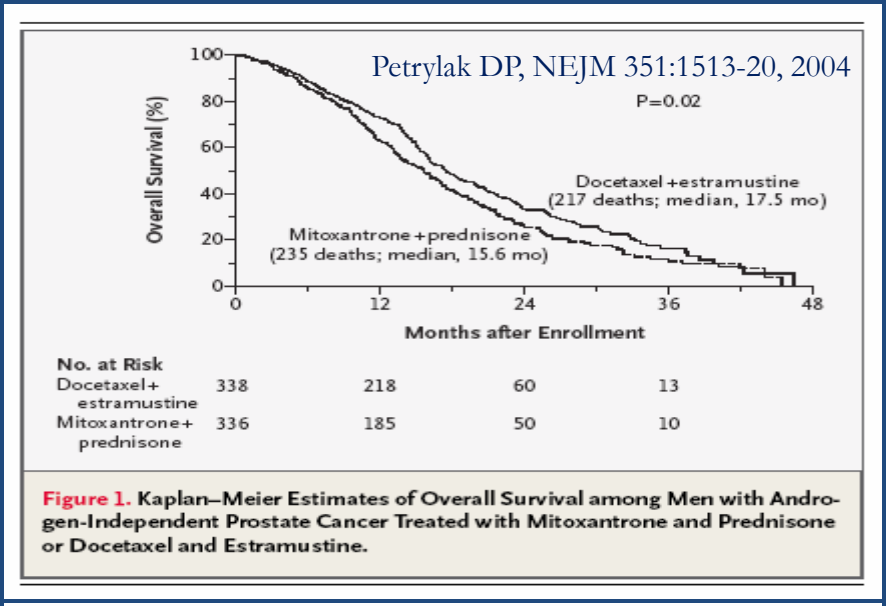


Figure 1. Kaplan–Meier Estimates of Overall Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

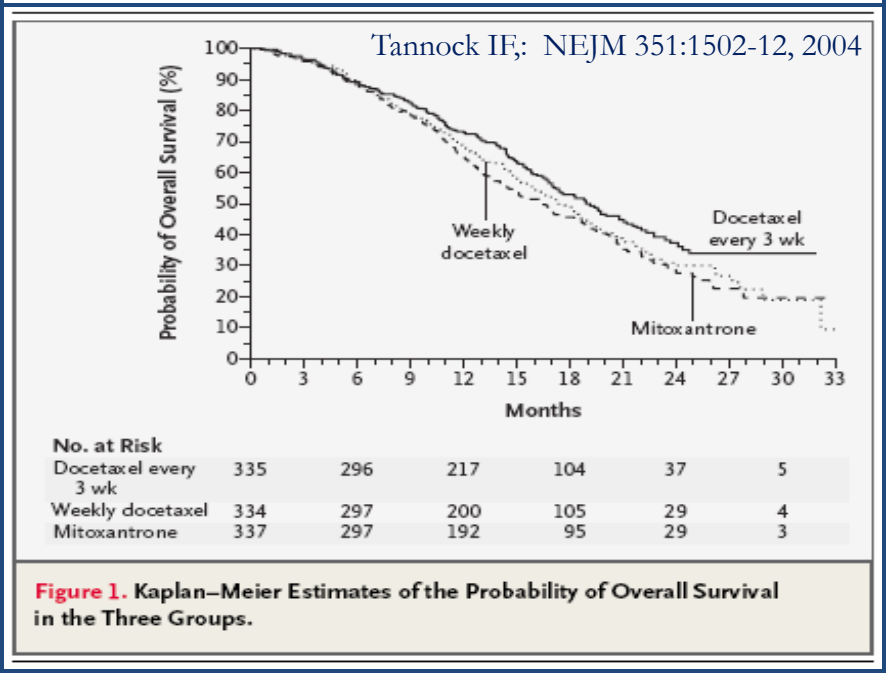


Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

The Concept of Testing Chemotherapy Early is Not New

First Author	No. of Pts	Treatment Arms	Median PFS (m)	Median OS(m)
Murphy, 1976-1980	246	A: DES/orch; B: DES+CTX; C: CTX+Estramustine	Not reported	23 months in all arms
Murphy 1980-1983	319	A: DES/orch B: CTX+5FU+DES C: Estramustine	15 months in all arms	33 months in all arms
Osborne 1982-1986	143	A: DES/orch B: DES/orch+CTX+Dox	A: 15 B: 18 (P=0.8)	A: 25.6 B: 22.0 (P=0.55)
Pummer 1988-1991	145	A: Flut/orch B: Flut/orch+epirubicin	A: 12 B: 22 (P=<0.02)	A: 18 B: 30 (P=0.12)
Janknegt 1989-1990	419	A: Orchiectomy B: Orch+estramustine	A: 17 B: 24 (P=0.3)	A: 24 B: 27 (NS)
Boel, 1988-1991	148	A: Orchiectomy B: Orch+Mitomycin C	A: 29 B: 26 (P=0.64)	A: 31 B: 31 (NS)
De Reijke 1990-1995	189	A: Orchiectomy B: Orch+Mitomycin C	A: 12 B: 12 (P=0.67)	A: 26 B: 22 (P=0.04)
Kuriyama 1990-1992	136	A: DES or Orchiectomy B: DES or Orch + UFT	A: 30 B: 72 (P=0.06)	A: 67 B: >96 (P=0.13)
Noguchi 1995-1998	51	A: LHRH + FLT; B: LHRH + estramustine	A: 14.6 B: 25.4(P=0.03)	A: 30 B: 30 (NS)
Millikan 1996-2003	286	A: LHRH or Orch B: LHRH/Orch + ketoc + Dox+vinb+estramustine	A: 24 B: 35 (P=0.39)	A: 64 B: 72(P=0.41)
Smith (SWOG) 2001-2005	35 (High risk)	CAD + Palcitaxel, VP-16 +Estramustine	13	38

Presented By Maha Hussain at 2015 ASCO Annual Meeting

Disease Extent is a Powerful Prognostic Factor for Overall Survival

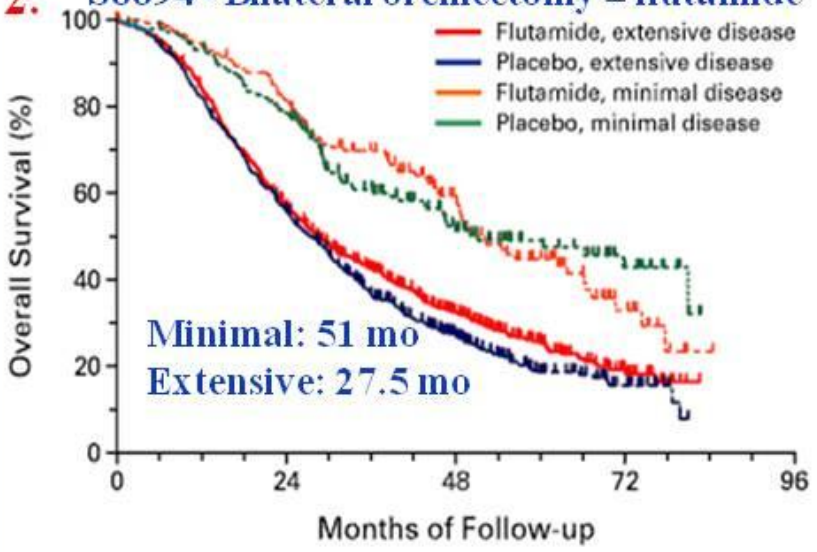
1. **First report on disease extent & OS**: *Crawford, NEJM,1989*

- Minimal: Spine, pelvis &/or Lymph nodes

vs.

-Extensive: Ribs, long bones and / or visceral organs (Liver, lung)

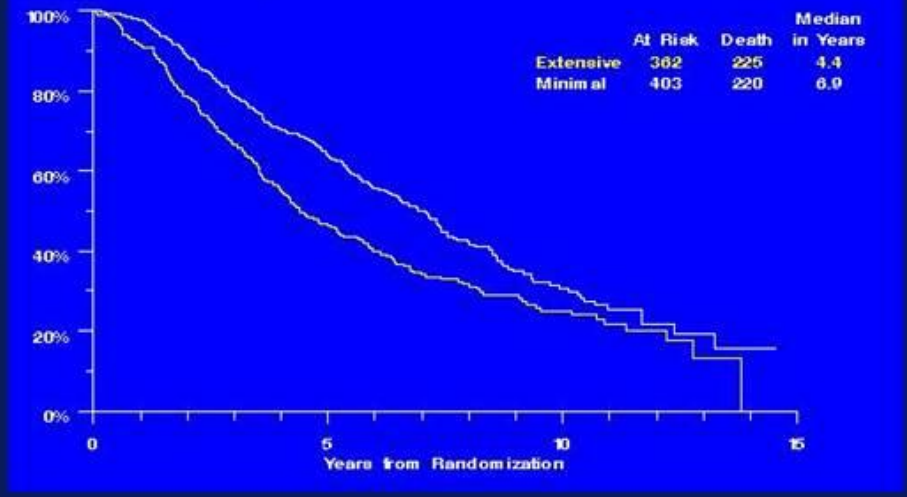
2. S8894 - Bilateral orchiectomy ± flutamide



Eisenberger et al. NEJM,1998

3. S9346

Survival by Disease Extent for CAD Arm Only



4. MDACC

High volume: at least 3 bone mets or visceral disease:

Low": 7.8 yr

"High": 3.1 yr

GETUG-AFU 15 Phase III Trial: ADT + Docetaxel vs ADT Alone for Hormone-Naïve Metastatic PCa
Long-term Analysis: Median F/U ***82.9 months***

2004-2008
N= 385

Stratification :
- Prior systemic TT
- Glass[1] risk group

RANDOMIZATION

Arm A — **ADT + Docetaxel** **N= 192**

D: 75 mg/m^2 q3 up to 9 cycles

Arm B — **ADT alone** **N= 193**

OS

ADT:
- LHRH agonist
- or maximum androgen blockade
- or orchiectomy

Retrospective assessment of tumor volume

High Volume Disease (HVD):
-≥ 4 bone lesions and ≥ 1 lesion in any bony structure beyond the spine/pelvis.
-Or visceral metastasis

Gravis et al: 2015 ASCO GU Symposium
K. Fizazi

Patients Metastasis Characteristics

	ADT (N=193)	ADT + D (N = 192)
Visceral metastasis	23 (12%)	28 (15%)
≥ 4 bone mets with ≥ 1 beyond pelvis or spine	95 (49%)	82 (43%)
Volume mets (%) -Low -High	102 (53%) 91 (47%)	100 (52%) 92 (48%)
Docetaxel beyond PSA progression (%)	127/158 (80%)	64/143 (45%)

> 65% "M" at diagnosis

KPS: 100%

Gravis G et al: The Lancet Oncol 2013; 14: 149-158

Gravis et al: 2015 ASCO GU Symposium

Without GCSF

Neutropenia Gr 3-4 41%
Feb Neutropenia 8%
2/192 deaths
(+ 1 MOF, 1 PE)

With GCSF

Neutropenia Gr 3-4 15%
Feb Neutropenia 6%
No deaths

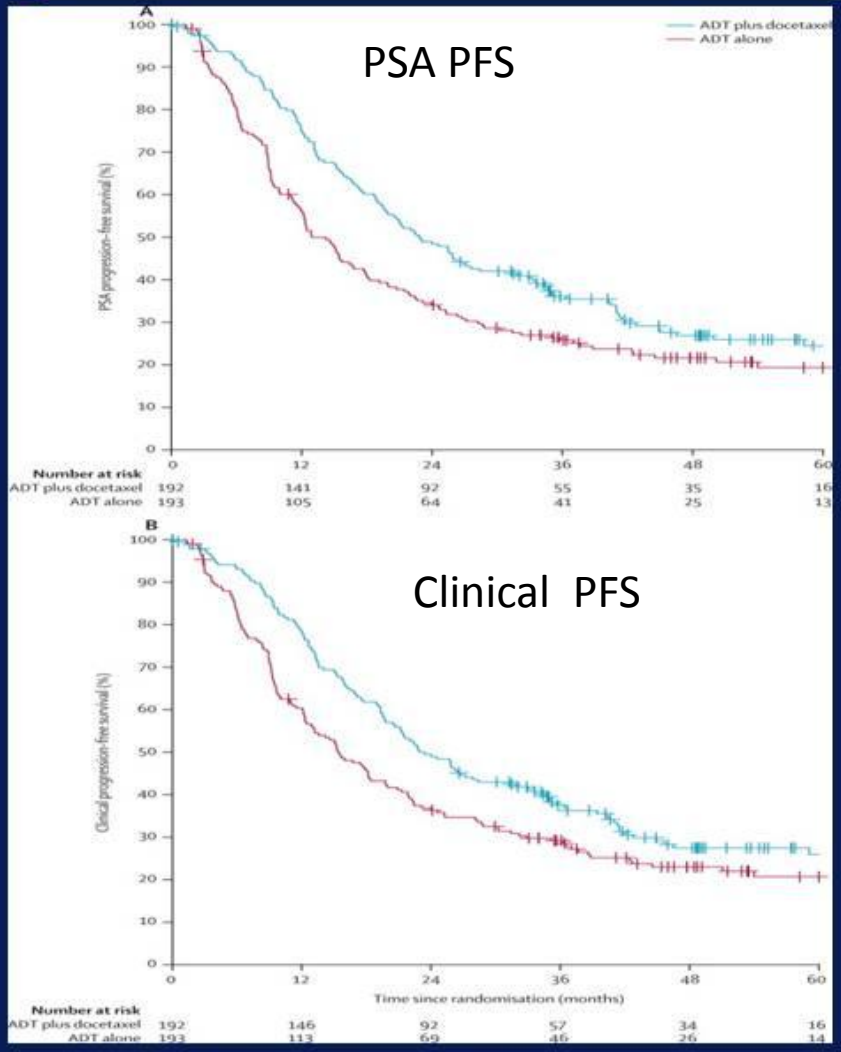
Docetaxel Clearance ???

	Androgen-deprivation therapy plus docetaxel (n=189)			Androgen-deprivation therapy alone (n=186)		
	Grade 1–5	Grade 3–4	Grade 5	Grade 1–5	Grade 3–5	Grade 5
Neutropenia	94 (50%)	61 (32%)	0	5 (3%)	0	0
Febrile neutroperia	15 (8%)	14 (7%)	1 (<1%)	0	0	0
Infections with neutropenia	5 (3%)	4 (2%)	1 (<1%)	0	0	0
Anaemia	136 (72%)	4 (2%)	0	41 (22%)	2 (1%)	0
Thrombocytopenia	20 (11%)	1 (<1%)	0	9 (5%)	0	0
Fatigue	140 (74%)	13 (7%)	0	37 (20%)	2 (1%)	0
Nausea	55 (29%)	0	0	4 (2%)	0	0
Vomiting	16 (8%)	0 (0%)	0	0	0	0
Diarrhoea	58 (31%)	1 (<1%)	0	4 (2%)	0	0
Constipation	42 (22%)	0	0	9 (5%)	0	0
Alopecia	102 (54%)	5 (3%)	0	1 (<1%)	0	0
Sensory neuropathy	54 (29%)	3 (2%)	0	7 (4%)	0	0
Nail changes	74 (39%)	5 (3%)	0	0	0	0
Peripheral oedema	55 (29%)	2 (1%)	0	10	0	0
Dyspnoea	36 (19%)	4 (2%)	0	6 (3%)	0	0
Stomatitis	15 (8%)	1 (<1%)	0	0	0	0
Mucositis	40 (21%)	1 (<1%)	0	0	0	0
Hot flushes	70 (37%)	8 (4%)	0	118 (63%)	3 (2%)	0
Erectile dysfunction	21 (11%)	16 (8%)	0	23 (12%)	14 (8%)	0
Decreased libido	21 (11%)	12 (6%)	0	28 (15%)	9 (5%)	0
Gynaecomastia	8 (4%)	0 (0%)	0	10 (5%)	1 (<1%)	0
Increased concentrations of alanine aminotransferase	43 (23%)	3 (2%)	0	22 (12%)	1 (<1%)	0
Increased concentrations of aspartate aminotransferase	38 (20%)	3 (2%)	0	17 (9%)	1 (<1%)	0
Other	131 (69%)	13 (7%)	2 (1%)	56 (30%)	1 (<1%)	0

Table 3: Toxic effects reported in the first 6 months of treatment

Gravis G et al: The Lancet Oncol 2013; 14: 149-158

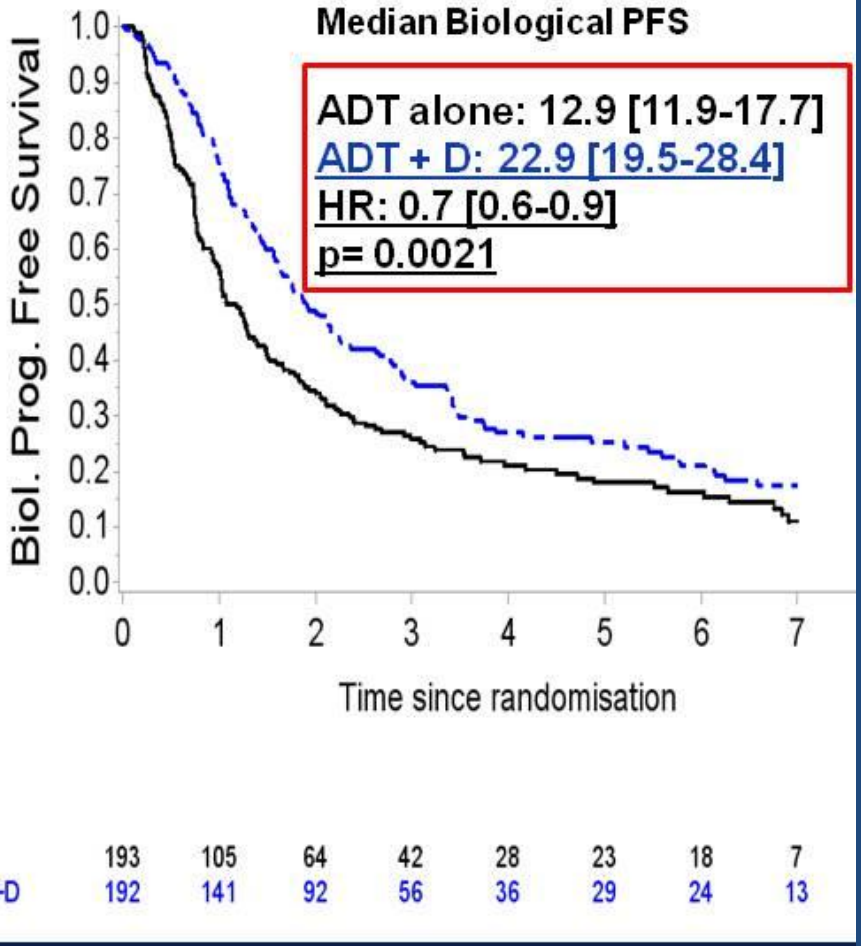
BIOLOGICAL PROGRESSION FREE SURVIVAL



PSA PFS

Clinical PFS

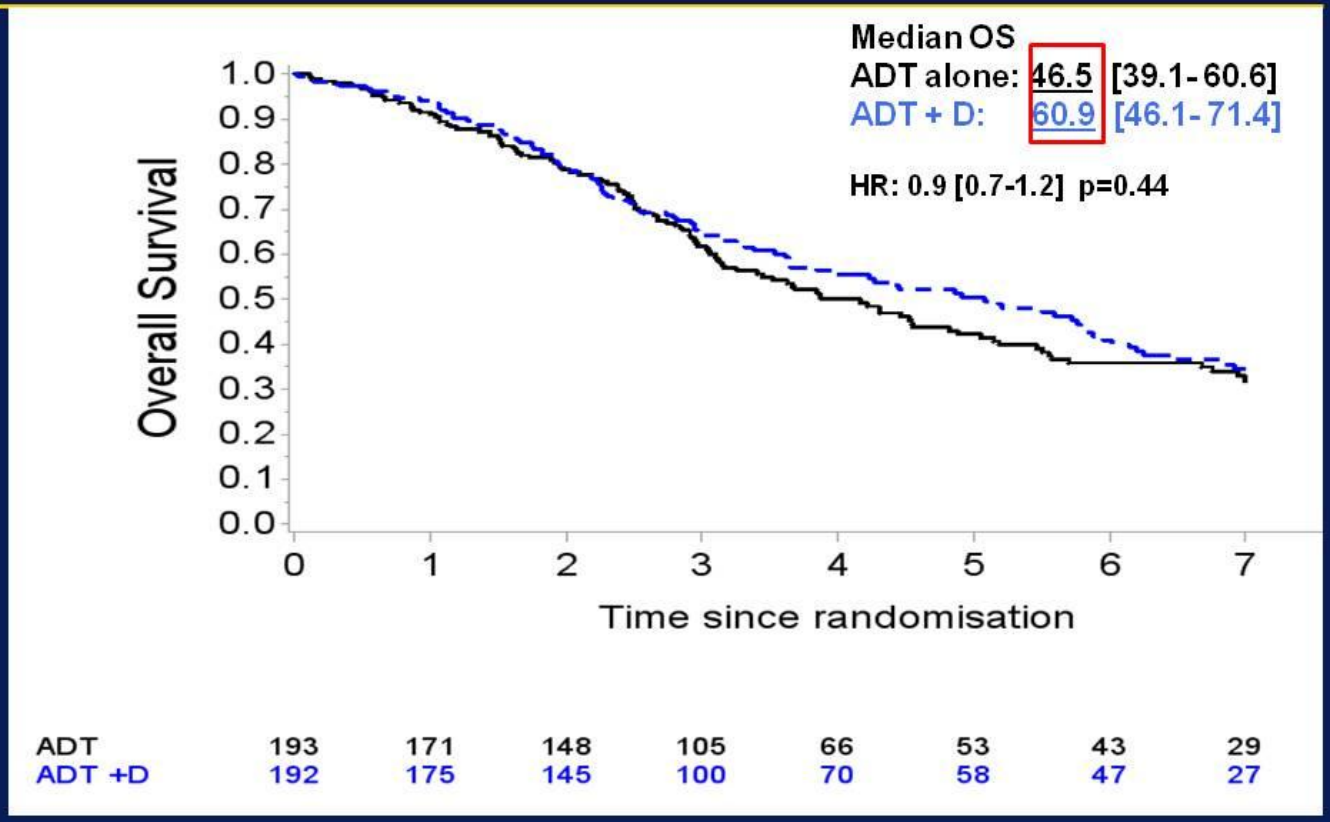
Gravis et al, Lancet Oncology,, 2013



Gravis et al: 2015 ASCO GU Symposium

UPDATED ANALYSIS: OVERALL SURVIVAL

N=385 (2004-2008)



Gravis et al: 2015 ASCO GU Symposium

Less effect of Doc etaxel in HSPCa?
Sample size ?
Crossover ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevrin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

E3805 – CHAARTED Treatment

2006-2012

High volume: visceral metastases and/or ≥4 bone metastases (at least 1 beyond pelvis and vertebral column)

N=790

STRATIFICATION

Extent of Mets
High vs Low
Age
≥70 vs < 70yo
ECOG PS
- 0-1 vs 2
CAB> 30 days
-Yes vs No
SRE Prevention
-Yes vs No
Prior Adjuvant ADT
≤12 vs > 12 months

RANDOMIZE

N=397

ARM A:
ADT + Docetaxel
75mg/m2 every 21 days for up to 6 cycles

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

N=393

ARM B:
ADT (androgen deprivation therapy alone)

Evaluate every 12 weeks

Follow for
TTP
OS

Chemotherapy at investigator's discretion at progression

- **ADT allowed up to 120 days prior to randomization.**
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but **no daily prednisone**

Presented by: Christopher J. Sweeney, MBBS, ASCO 2014

N Engl J Med 2015;373:737-46.

Table 1. Baseline Characteristics of the Patients.*

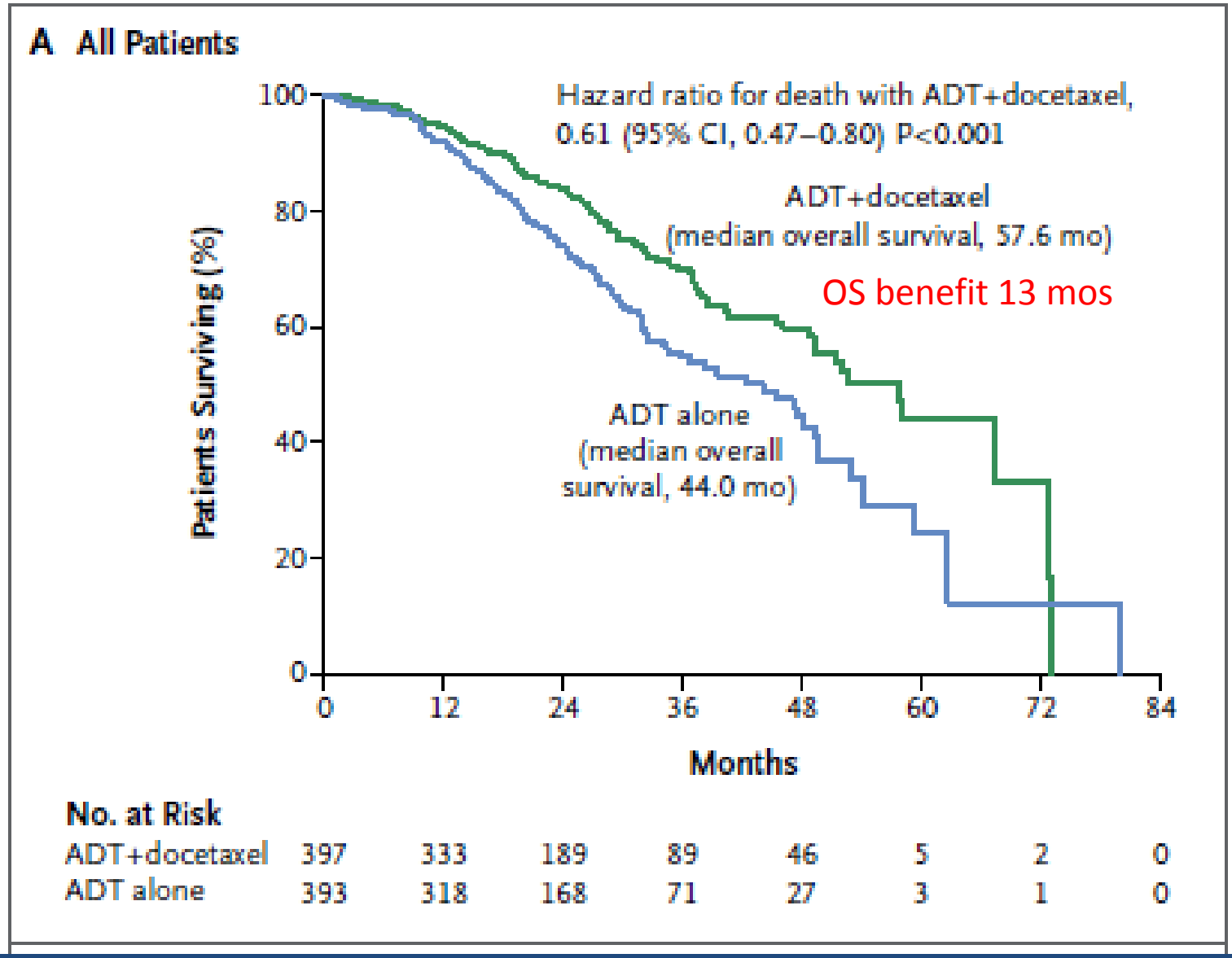
Characteristic	ADT plus Docetaxel (N=397)	ADT Alone (N=393)
Age — yr		
Median	64	63
Range	36–88	39–91
Race — no. (%)†		
White	344 (86.6)	330 (84.0)
Black	39 (9.8)	37 (9.4)
Other	4 (1.0)	6 (1.5)
Unknown	10 (2.5)	20 (5.1)
ECOG performance status — no. (%)‡		
0	277 (69.8)	272 (69.2)
1	114 (28.7)	115 (29.3)
2	6 (1.5)	6 (1.5)
Volume of metastases — no. (%)§		
Low	134 (33.8)	143 (36.4)
High	263 (66.2)	250 (63.6)
Visceral metastases — no. (%)	57 (14.4)	66 (16.8)
Gleason score — no. (%)¶		
4–6	21 (5.3)	21 (5.3)
7	96 (24.2)	83 (21.1)
8–10	241 (60.7)	243 (61.8)
Unknown	39 (9.8)	46 (11.7)
PSA level at start of ADT — ng/ml		
Median	50.9	52.1
Range	0.2–8540.1	0.1–8056.0
Prior treatment for prostate cancer — no. (%)		
No local therapy	289 (72.8)	286 (72.8)
Primary radiation	27 (6.8)	33 (8.4)
Prostatectomy	81 (20.4)	73 (18.6)
Missing data	0	1 (0.3)
Adjuvant ADT — no. (%)	18 (4.5)	16 (4.1)
Time from start of ADT to randomization — mo		
Median	1.2	1.3
Range	0.03–3.9	0.03–3.9
No ADT before randomization — no. (%)	51 (12.8)	52 (13.2)

N Engl J Med 2015;373:737-46.

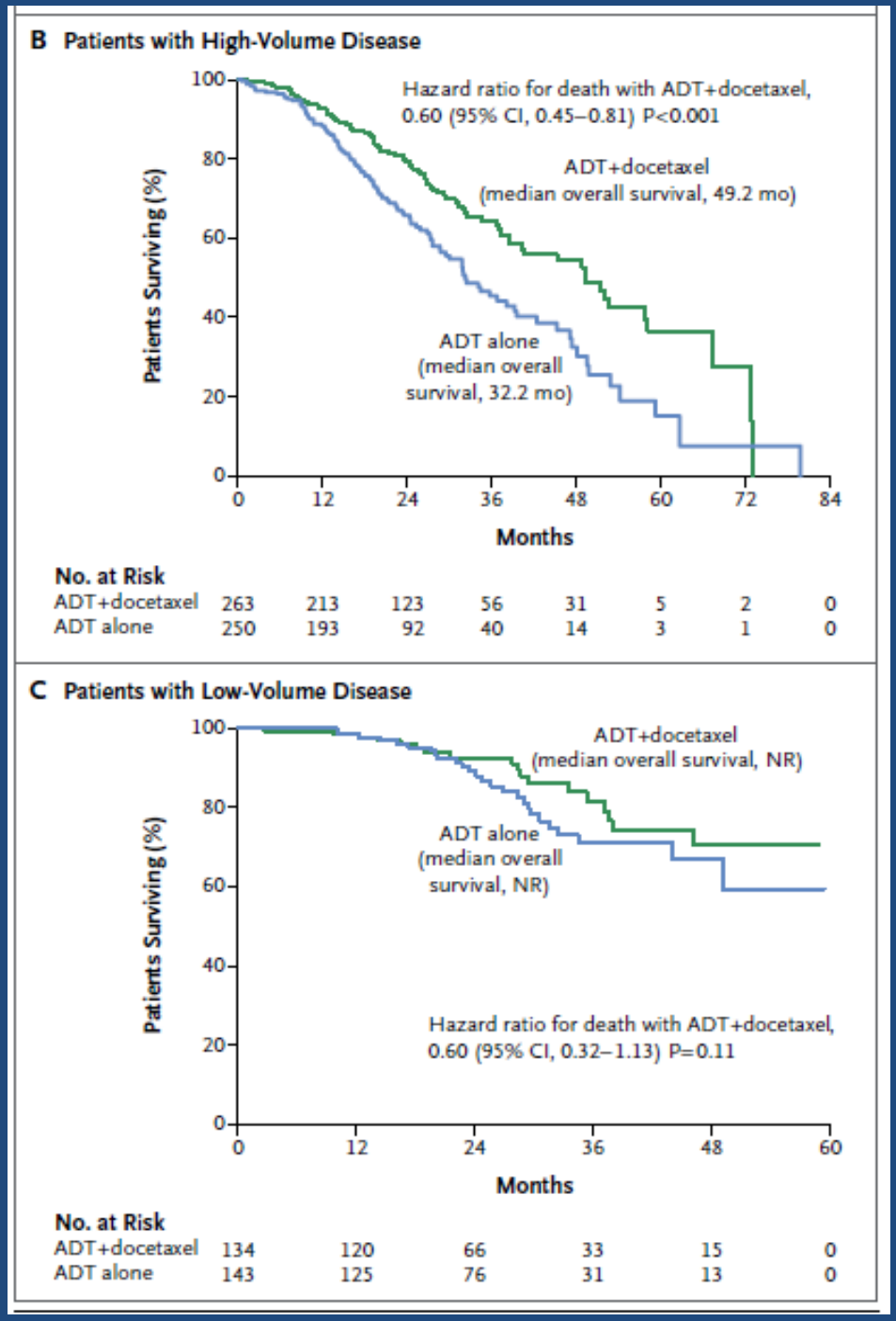
Table 3. Adverse Events of Grade 3 or Higher among the 390 Patients Who Received the Docetaxel-Containing Regimen and Had Follow-up Data Available.*

Event	Grade 3	Grade 4	Grade 5
		no. of patients (%)	
Allergic reaction	7 (1.8)	1 (0.3)	0
Fatigue	16 (4.1)	0	0
Diarrhea	4 (1.0)	0	0
Stomatitis	2 (0.5)	0	0
Neuropathy, motor	2 (0.5)	0	0
Neuropathy, sensory	2 (0.5)	0	0
Thromboembolism	1 (0.3)	2 (0.5)	0
Sudden death	0	0	1 (0.3)
Anemia	4 (1.0)	1 (0.3)	0
Thrombocytopenia	0	1 (0.3)	0
Neutropenia	12 (3.1)	35 (9.0)	0
Febrile neutropenia	15 (3.8)	9 (2.3)	0
Infection with neutropenia	5 (1.3)	4 (1.0)	0
Any event	65 (16.7)	49 (12.6)	1 (0.3)

OS



N Engl J Med 2015;373:737-46.



OS benefit 17 mos

N Engl J Med 2015;373:737-46.

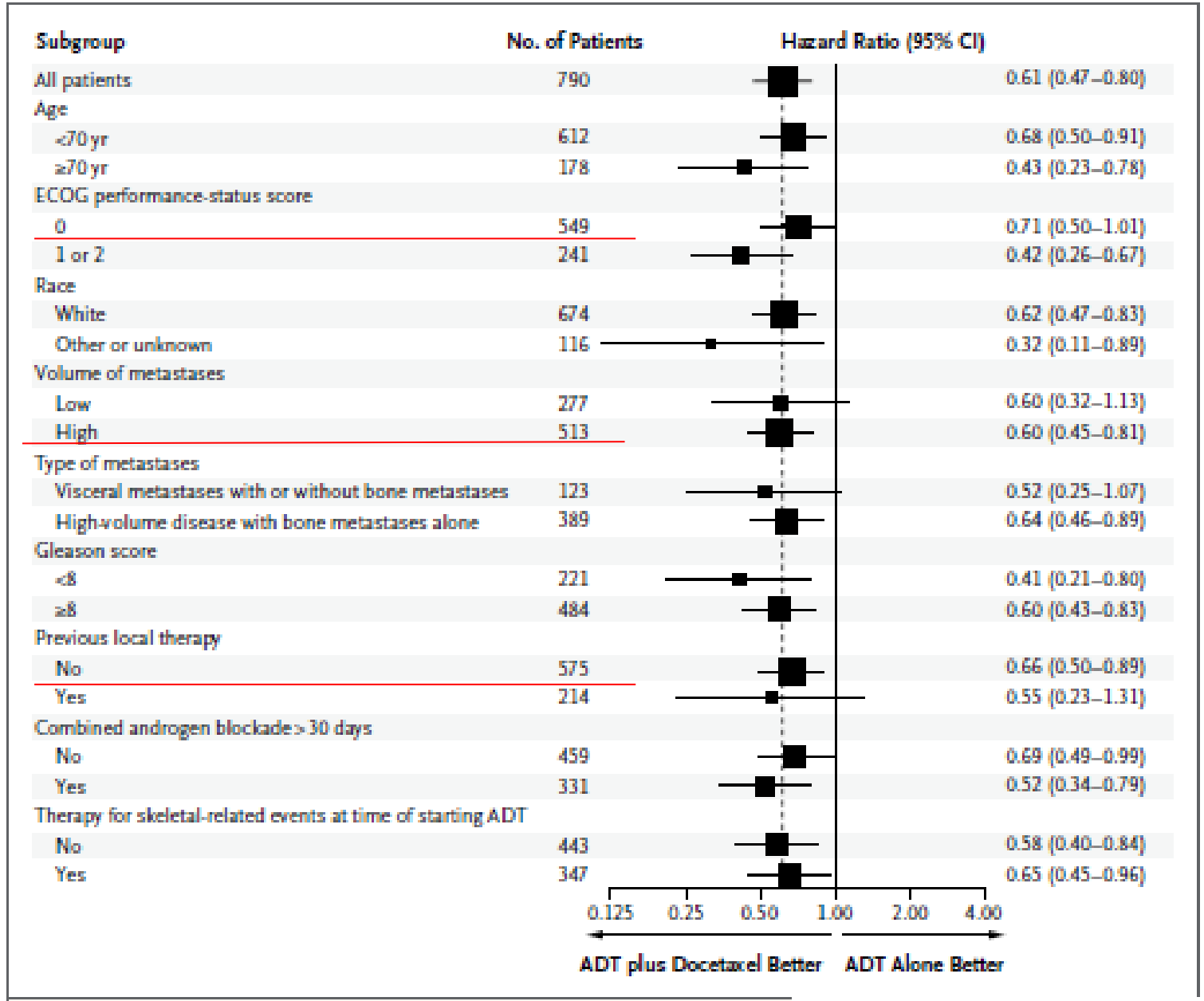


Figure 2. Hazard Ratios for Death in Subgroups.

N Engl J Med 2015;373:737-46.

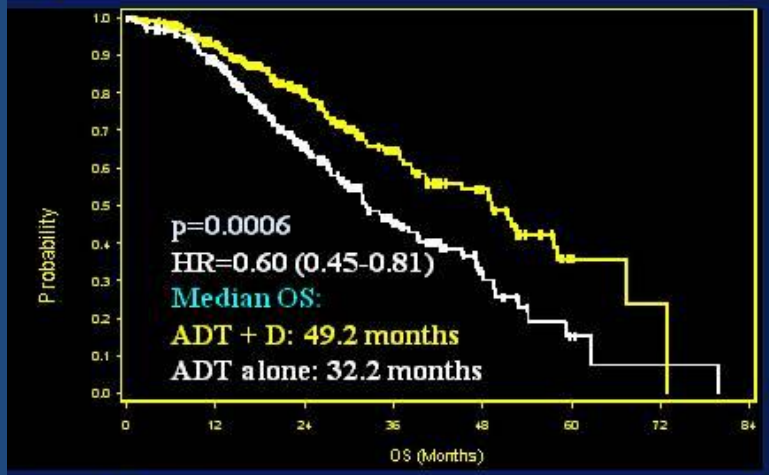
Table 2. Secondary End Points.

End Point	ADT plus Docetaxel (N=397)	ADT Alone (N=393)	P Value	Hazard Ratio (95% CI)
PSA level <0.2 ng/ml at 6 mo — no. (%)	127 (32.0)	77 (19.6)	<0.001	
PSA level <0.2 ng/ml at 12 mo — no. (%)	110 (27.7)	66 (16.8)	<0.001	
Time to castration-resistant prostate cancer — mo*				
Median	20.2	11.7	<0.001	0.61 (0.51–0.72)
95% CI	17.2–23.6	10.8–14.7		
Time to clinical progression — mo†				
Median	33.0	19.8	<0.001	0.61 (0.50–0.75)
95% CI	27.3–41.2	17.9–22.8		

F/up
29 mo

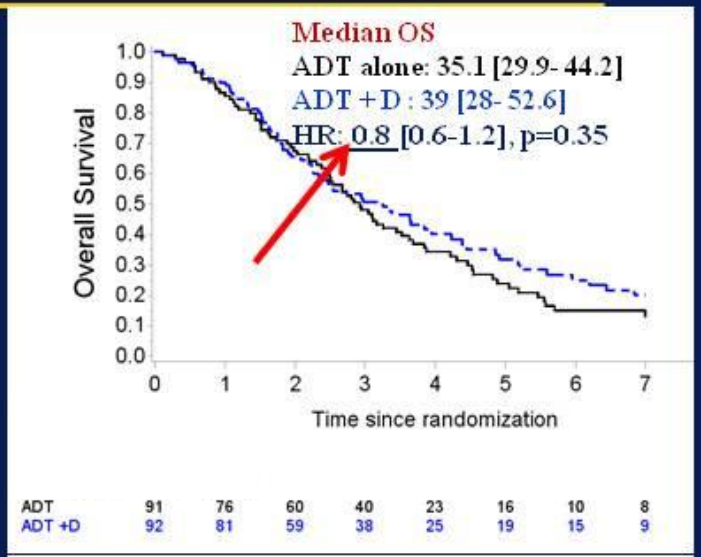
E3805: N= 790 pts
GETUG15: N= 385 pts

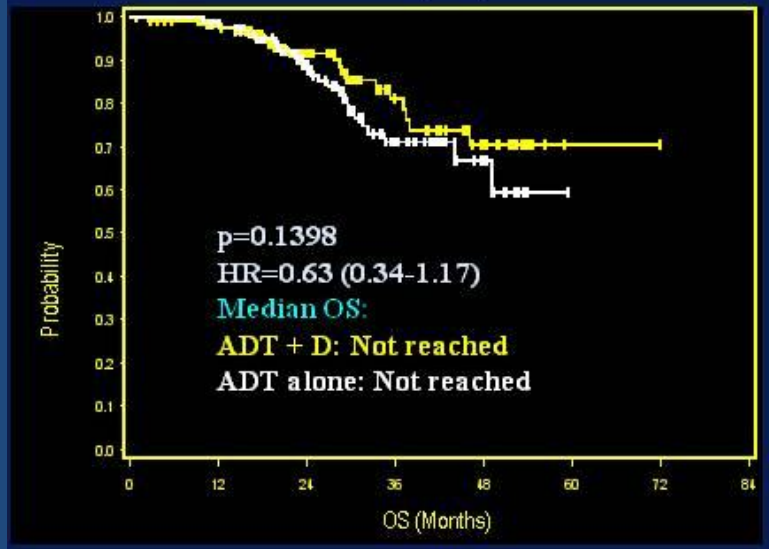
F/up
83mo



 # Patients
High volume

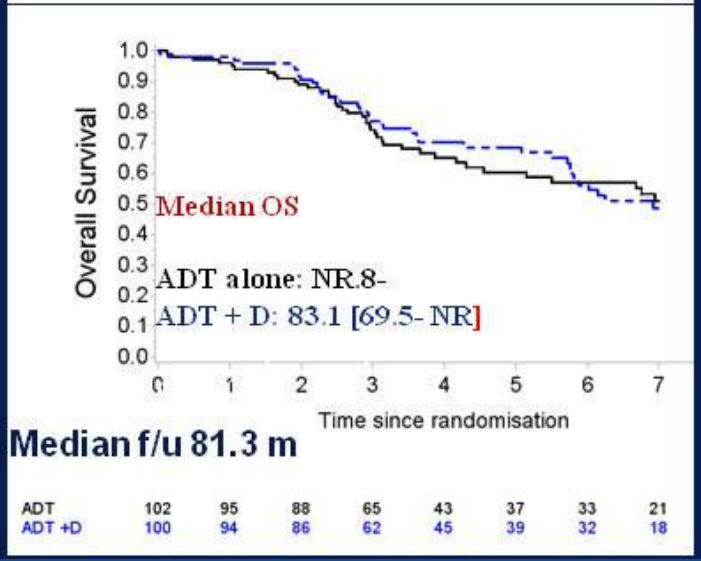
514 vs 183





Low Volume

276 vs 202



Adapted from Sweeney C

CHAARTED and GETUG-15: similarities

Presenting features	CHAARTED	GETUG-15
Age	64yrs	64yrs
Metastases at presentation	73%	71%
Docetaxel: Courses (% dose reductions)	6 (26%)	8 (11%)
Outcomes		
Deaths	237	176
Median OS ADT+Docetaxel group	57.6m	58.9m
Improved PSA/clinical PFS	20.7m vs 14.7m H.R 0.56 (0.44-0.70)	22.9m vs 12.9m HR 0.72 (0.57-0.91)

CHAARTED and GETUG-15: differences

Presenting features	CHAARTED	GETUG-15
Geography	N.America	France/Belgium
Recruitment period	2006-2012	2004-2008
Number	790	385
Follow-up	29 months	50 months → **83 months**
Risk groups: High	66%	22%
PSA at entry	53ng/ml	26ng/ml
Outcomes		
OS ADT+D vs ADT	58m vs 44m HR 0.61	59m vs 54m HR 1.01
(Time to PSA/clinical failure	21m vs 15m HR 0.56	23m vs 13m HR 0.72)
Time from failure to death	***37m vs 34m***	***36m vs 41m***

Total Treatment given to patients in each arm of the study : Intent to Treat

	GETUG-15		CHAARTED	
	ADT + D	ADT	**ADT + D**	ADT
Total Enrolled	192	193	397	393
Total Failed	142 (74%)	146 (81%)	145 (36%)	174 (44%)
Post-Prot. Docetaxel	54 (28%)	**120 (62%)**	49 (12%)	**129 (32%)**
Post-Prot. Cabazitaxel	3 (2%)	2 (1%)	43 (11%)	29 (7%)
Post-Prot. Abi or Placebo	19 (10%)	21 (11%)	**92 (23%)**	**79 (20%)**
Post-Prot. Enza or Placebo	9 (5%)	7 (4%)	0	0
Post-Prot. Sipuleucel-T	0	0	20 (8%)	20 (8%)
Non-life Prolonging	106 (55%)	131 (69%)	49 (12%)	129 (32%)
Courses Life Prolonging Rx.	277 (144%)	150 (78%)	603 (151%)	255 (65%)
Taxane Only	249 (130%)	122 (63%)	489 (123%)	158 (40%)

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

Lancet 2016; 387: 1163–77

Accrual

Comparison

Open: Oct-2005

Closed: Mar-2013

Accrual: 2962

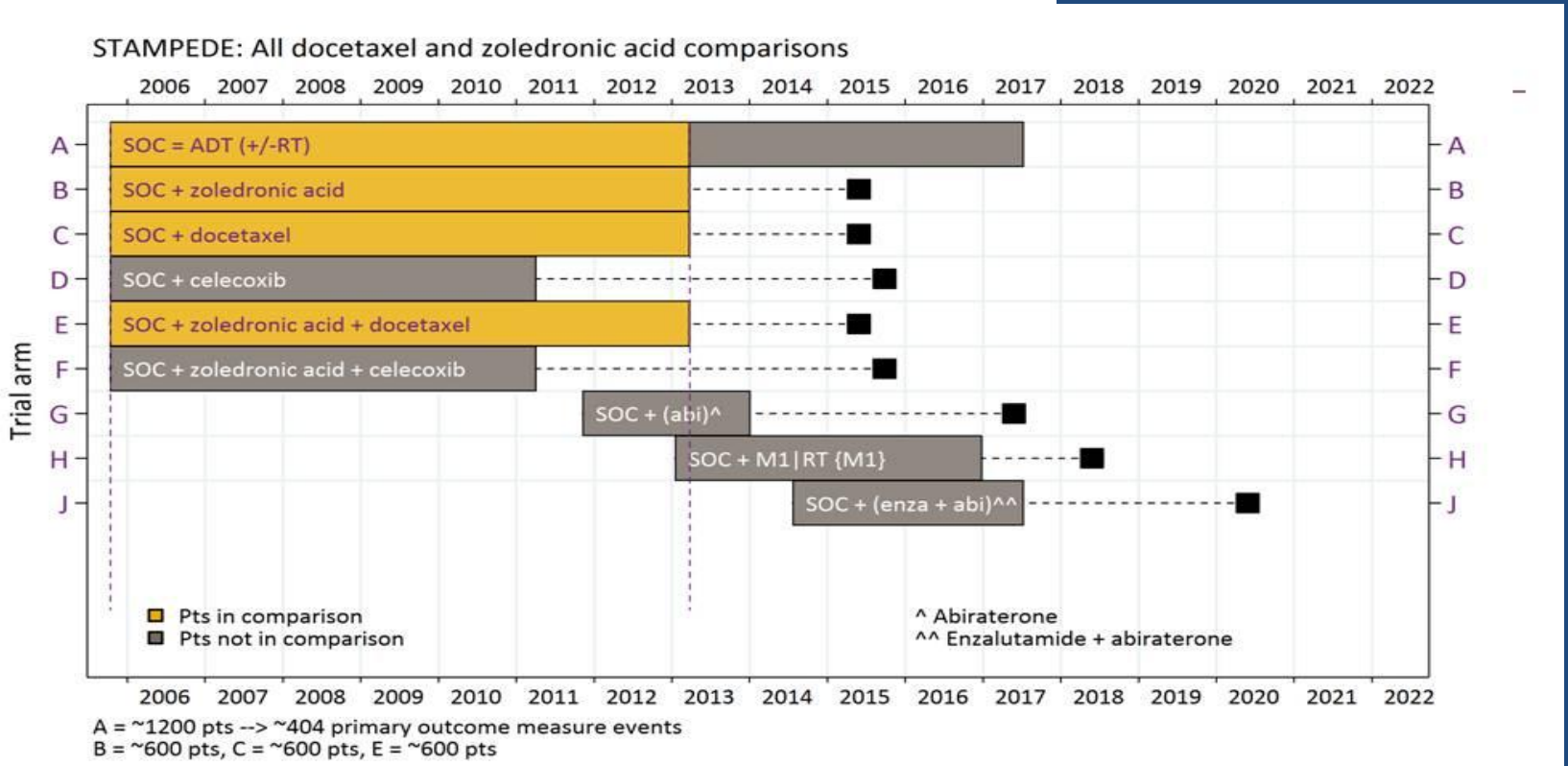
Number of patients

1184 **A** Standard-of-care (SOC)

593 **B** SOC + zoledronic acid

592 **C** SOC + docetaxel

593 **E** SOC + zoledronic acid + docetaxel



Patient characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
65yr	Median age (min 40, max 84)	[s]
61%	Metastatic (85% Bony mets)	[s]
15%	N+M0	
24%	N0M0	
98%	LHRH analogues	[s]
29%	Planned for RT (72% of N0M0 pts)	[s]
6%	Previous local therapy	

Balanced by arm
[s] Stratification factors + hospital + NSAID/aspirin

78% PS: 0

GS≤7: 20-25%

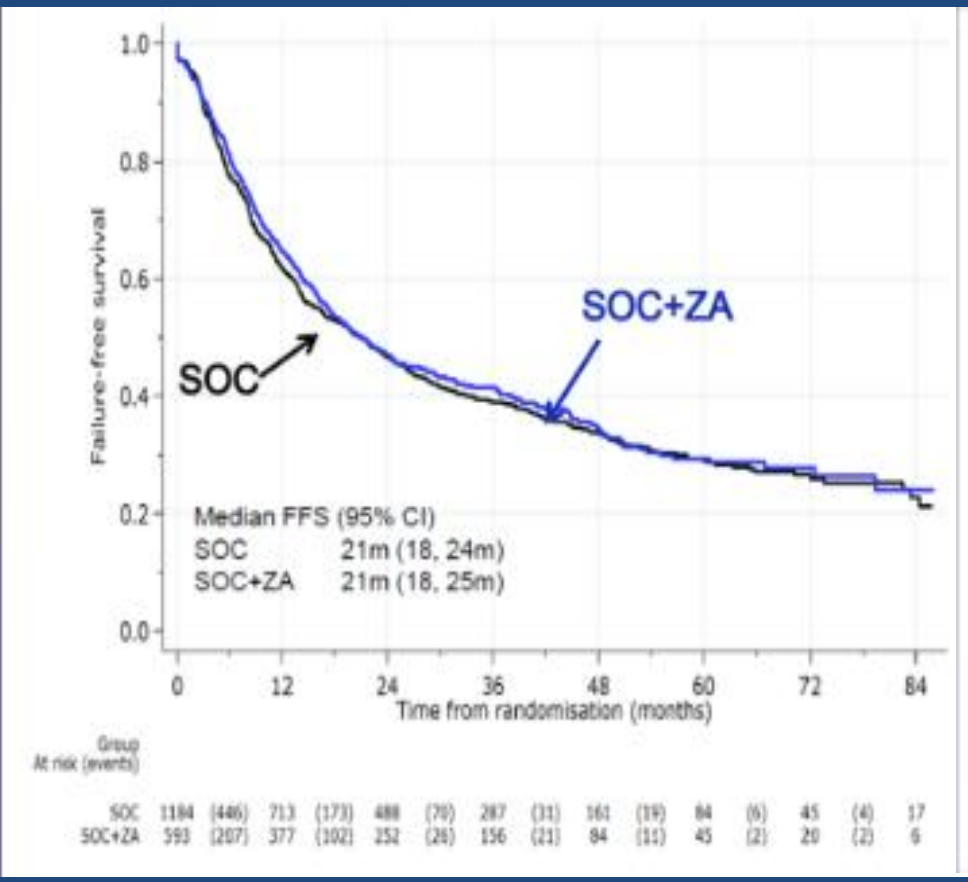
61% Metastatic
NO stratification for volume of metastases

85% non-smokers
90% non-diabetic
98% no MI
99% no CVD
100% no CHF
97% no H/o angina
65% no HTN

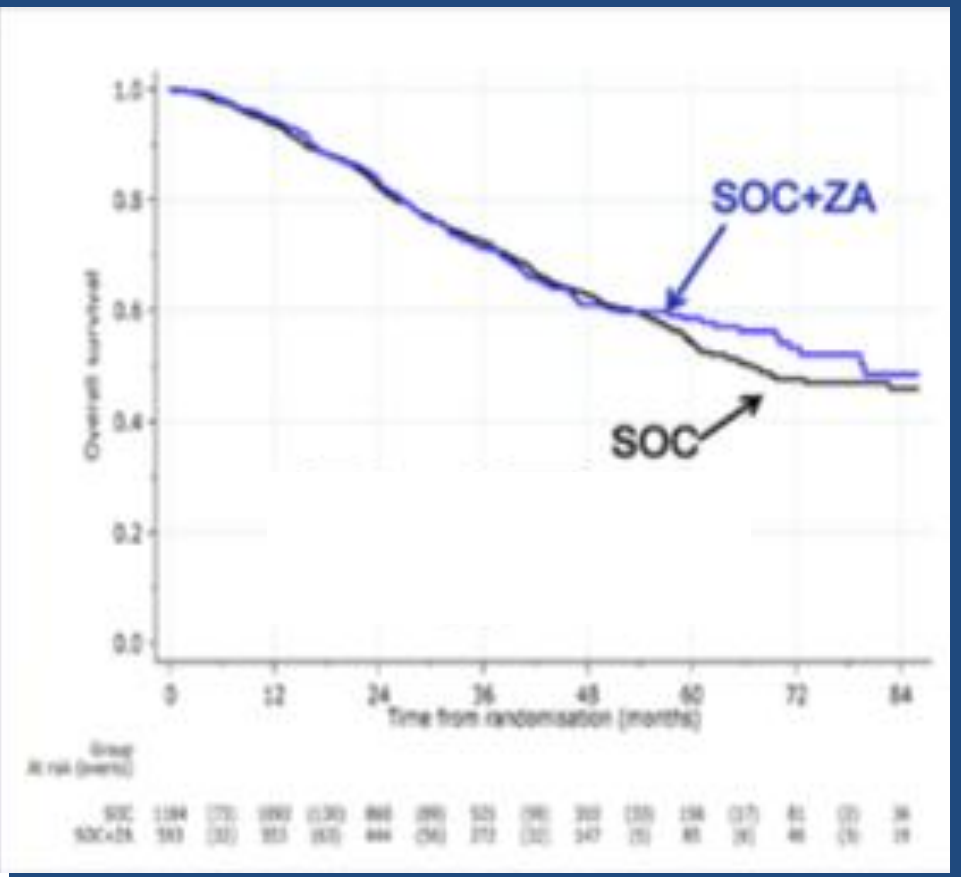
Zoledronic Acid

f/up:43 mos

Failure – Free Survival



Overall Survival

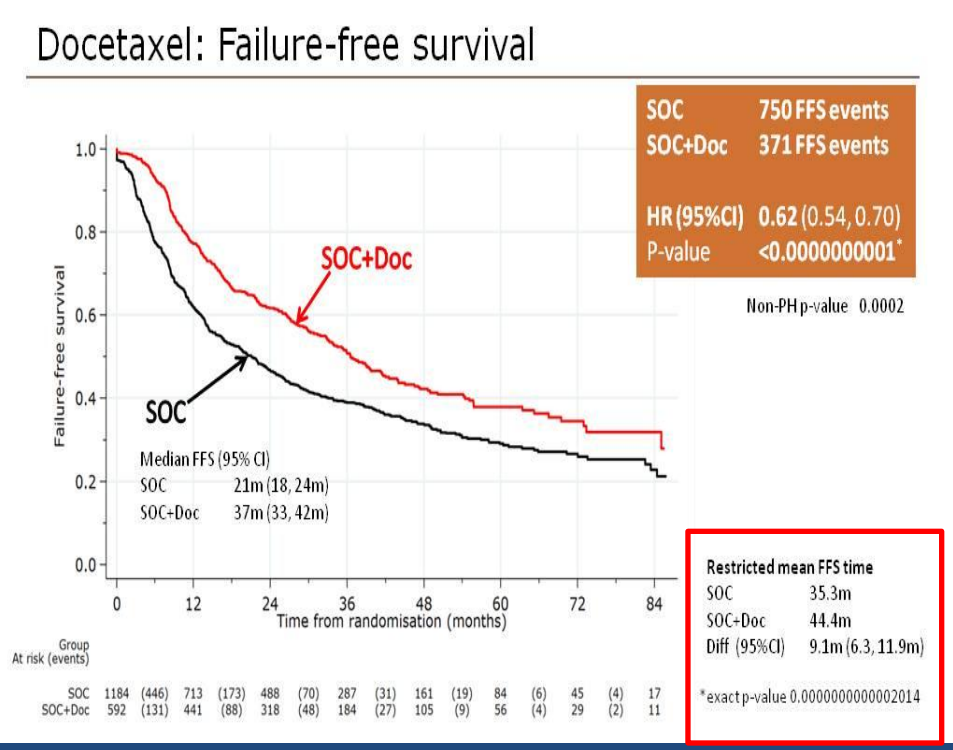


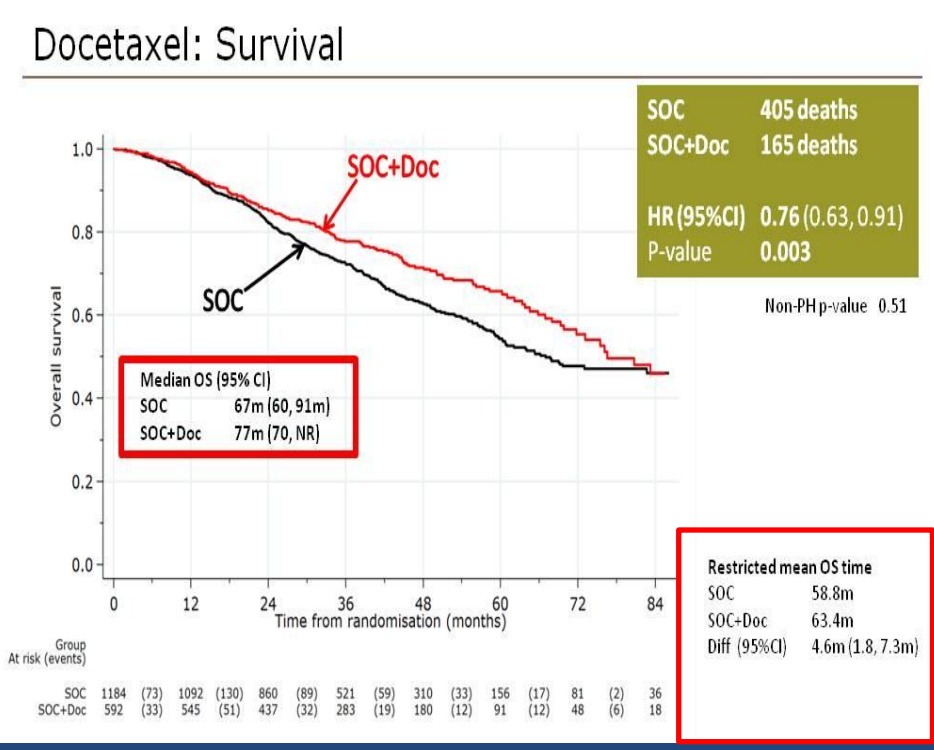
Docetaxel

f/up:43 mos

FFS benefit: 16 mos

OS benefit: 10 mos





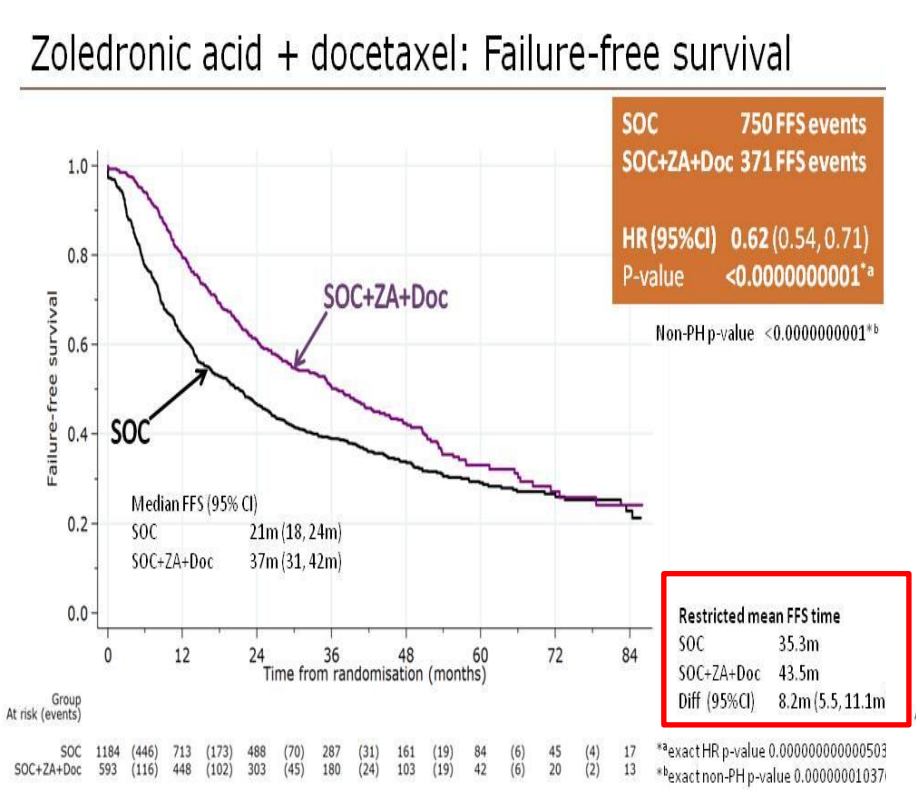
Restricted FFS benefit: 9.1 mos

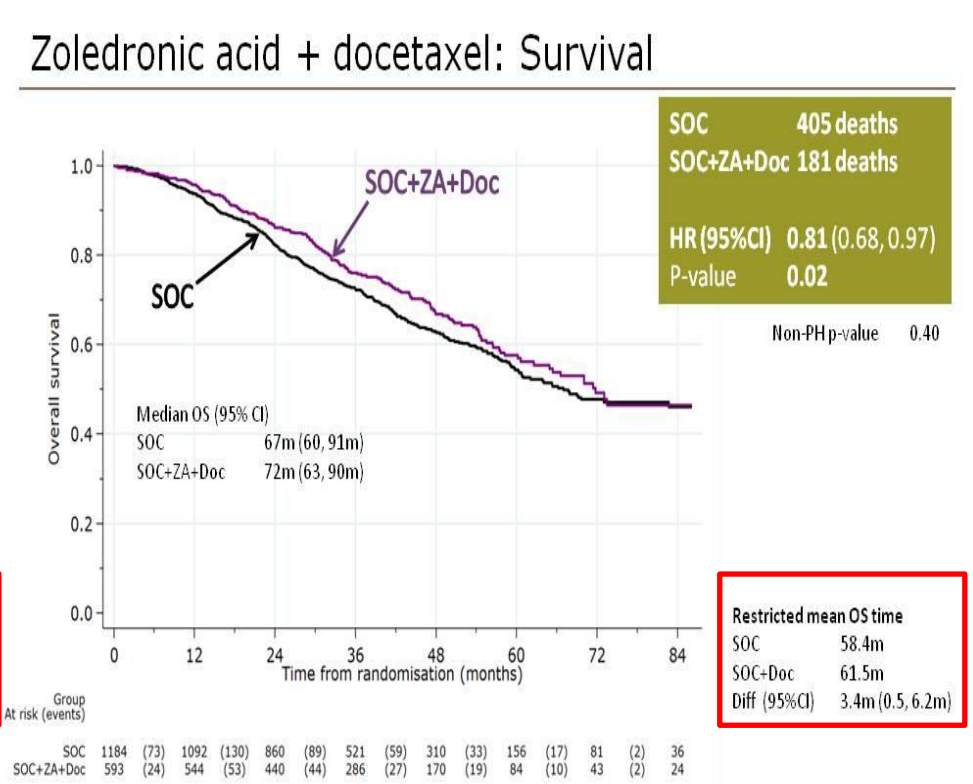
Restricted OS benefit: 4.6 mos

Zoledronic Acid + Docetaxel f/up:43 mos

FFS benefit: 16 mos

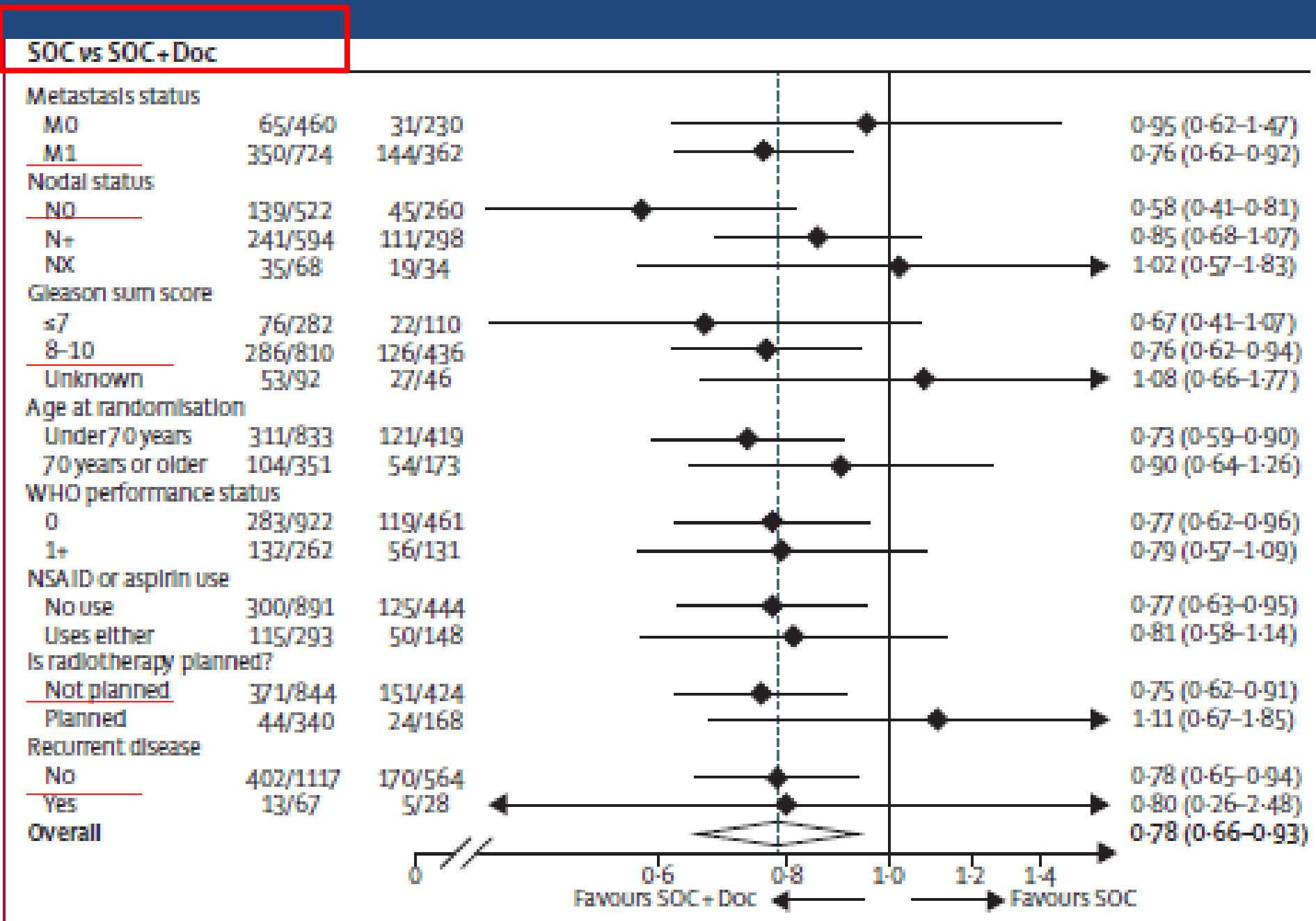
OS benefit: 5mos , NS





Restricted FFS benefit: 8.2 mos

Restricted OS benefit: 3.4 mos


SOC vs SOC+Doc
Metastasis status
M0 65/460 31/230 0·95 (0·62–1·47)
M1 350/724 144/362 0·76 (0·62–0·92)
Nodal status
N0 139/522 45/260 0·58 (0·41–0·81)
N+ 241/594 111/298 0·85 (0·68–1·07)
NX 35/68 19/34 1·02 (0·57–1·83)
Gleason sum score
≤7 76/282 22/110 0·67 (0·41–1·07)
8–10 286/810 126/436 0·76 (0·62–0·94)
Unknown 53/92 27/46 1·08 (0·66–1·77)
Age at randomisation
Under 70 years 311/833 121/419 0·73 (0·59–0·90)
70 years or older 104/351 54/173 0·90 (0·64–1·26)
WHO performance status
0 283/922 119/461 0·77 (0·62–0·96)
1+ 132/262 56/131 0·79 (0·57–1·09)
NSAID or aspirin use
No use 300/891 125/444 0·77 (0·63–0·95)
Uses either 115/293 50/148 0·81 (0·58–1·14)
Is radiotherapy planned?
Not planned 371/844 151/424 0·75 (0·62–0·91)
Planned 44/340 24/168 1·11 (0·67–1·85)
Recurrent disease
No 402/1117 170/564 0·78 (0·65–0·94)
Yes 13/67 5/28 0·80 (0·26–2·48)
Overall 0·78 (0·66–0·93)
0
0·6
0·8
1·0
1·2
1·4
Favours SOC + Doc
Favours SOC

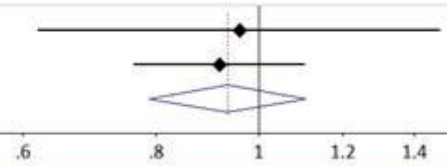
f/up:43 mos

Treatment effect by metastatic status: Overall survival

Pre-planned analysis

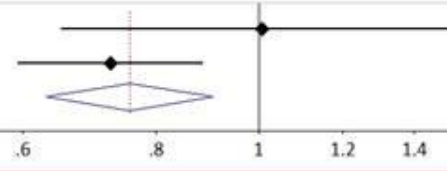
+ZA

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	93	686	0.96 (0.62, 1.48)
M1	509	1091	0.92 (0.76, 1.11)
Overall	602	1777	0.93 (0.79, 1.11)



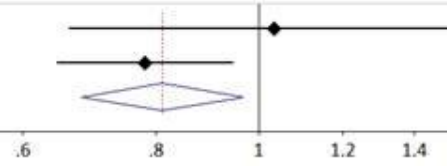
+Doc

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	93	689	1.01 (0.65, 1.56)
M1	477	1087	0.73 (0.59, 0.89)
Overall	570	1776	0.76 (0.63, 0.91)



+ZA+Doc

Mets status	OS events	No. pts	Haz. Ratio (95% CI)
M0	91	687	1.03 (0.66, 1.61)
M1	495	1090	0.78 (0.65, 0.95)
Overall	586	1777	0.81 (0.68, 0.97)



~ 60% never got chemo

	Standard of care	Standard of care plus zoledronic acid	Standard of care plus docetaxel	Standard of care plus zoledronic acid and docetaxel
Patients with progression	761	374	315	318
Reported new treatment	671 (88%)	303 (81%)	260 (83%)	257 (81%)
Reported (new) life-extending treatment	383 (50%)	172 (46%)	139 (44%)	136 (43%)
Life-extending treatment				
Docetaxel	313 (41%)	136 (36%)	44 (14%)	49 (15%)
Abiraterone	177 (23%)	72 (19%)	89 (28%)	88 (28%)
Enzalutamide	66 (9%)	18 (5%)	25 (8%)	26 (8%)
Cabazitaxel	26 (3%)	14 (4%)	22 (7%)	30 (9%)
Radium-223	6 (1%)	1 (0%)	6 (2%)	3 (1%)
Other treatments				
Anti-androgens	512 (67%)	234 (63%)	181 (57%)	174 (55%)
Zoledronic acid	128 (17%)	50 (13%)	35 (11%)	36 (11%)
Dexamethasone	104 (14%)	42 (11%)	39 (12%)	29 (9%)
Diethylstilbestrol (also known as stilboestrol)	84 (11%)	43 (11%)	38 (12%)	41 (13%)
Prednisolone	72 (9%)	22 (6%)	28 (9%)	23 (7%)
Other chemotherapy*	26 (3%)	17 (5%)	21 (7%)	15 (5%)
Other bisphosphonate†	22 (3%)	3 (1%)	8 (3%)	5 (2%)
Strontium	12 (2%)	3 (1%)	2 (1%)	4 (1%)
Cox-2 inhibition	0 (0%)	1 (0%)	0 (0%)	0 (0%)

*Not docetaxel or cabazitaxel. †Not zoledronic acid

Table 4: Treatments ever used at relapse, at the discretion of the treating clinician

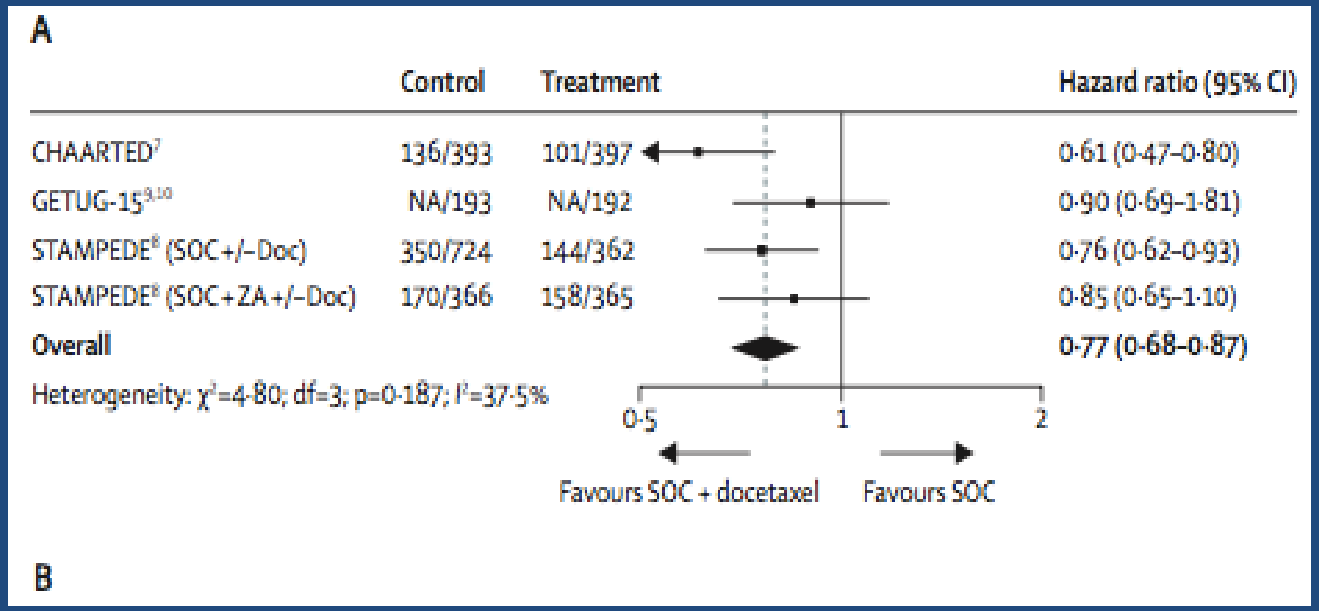
STOpCaP meta-analysis

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

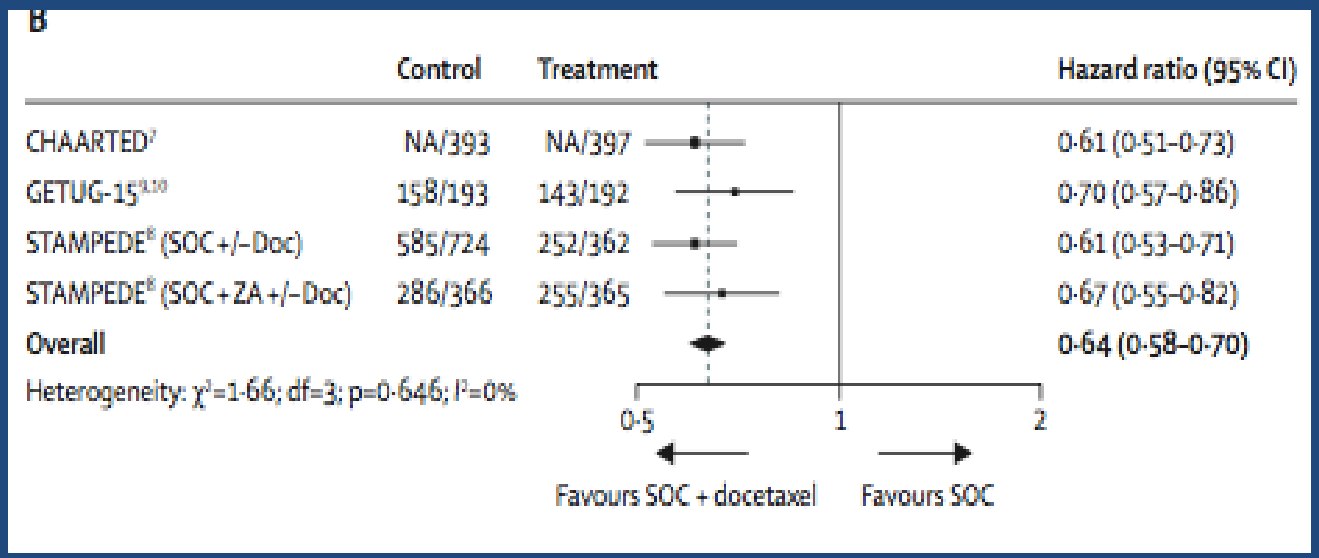
Claire L Vale, Sarah Burdett*, Larysa H M Rydzewska, Laurence Albiges, Noel W Clarke, David Fisher, Karim Fizazi, Gwenaelle Gravis, Nicholas D James, Malcolm D Mason, Mahesh K B Parmar, Christopher J Sweeney, Matthew R Sydes, Bertrand Tombal, Jayne F Tierney, for the STOpCaP Steering Group*

Lancet Oncol 2016; 17: 243–56

Docetaxel – M1 patients



9% absolute improvement in OS (40% → 49%) at 4 yrs



16% absolute improvement in FFS (64% → 80%) at 4 yrs

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v69–v77, 2015
doi:10.1093/annonc/mdv222
Published online 22 July 2015

Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker[1], S. Gillessen[2], A. Heidenreich[3] & A. Horwich[4], on behalf of the ESMO Guidelines Committee*

[1]Royal Marsden Hospital, Sutton, UK; [2]Department of Oncology/Hematology, Kantonsspital St Gallen, St Gallen, Switzerland; [3]Department of Urology, Uniklinik RWTH Aachen, Aachen, Germany; [4]Institute of Cancer Research, Sutton, UK

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

The Concept of Testing Chemotherapy Early is Not New

First Author	No. of Pts	Treatment Arms	Median PFS (m)	Median OS(m)
Murphy, 1976-1980	246	A: DES/orch; B: DES+CTX; C: CTX+Estramustine	Not reported	23 months in all arms
Murphy 1980-1983	319	A: DES/orch B: CTX+5FU+DES C: Estramustine	15 months in all arms	33 months in all arms
Osborne 1982-1986	143	A: DES/orch B: DES/orch+CTX+Dox	A: 15 B: 18 (P=0.8)	A: 25.6 B: 22.0 (P=0.55)
Pummer 1988-1991	145	A: Flut/orch B: Flut/orch+epirubicin	A: 12 B: 22 (P=<0.02)	A: 18 B: 30 (P=0.12)
Janknegt 1989-1990	419	A: Orchiectomy B: Orch+estramustine	A: 17 B: 24 (P=0.3)	A: 24 B: 27 (NS)
Boel, 1988-1991	148	A: Orchiectomy B: Orch+Mitomycin C	A: 29 B: 26 (P=0.64)	A: 31 B: 31 (NS)
De Reijke 1990-1995	189	A: Orchiectomy B: Orch+Mitomycin C	A: 12 B: 12 (P=0.67)	A: 26 B: 22 (P=0.04)
Kuriyama 1990-1992	136	A: DES or Orchiectomy B: DES or Orch + UFT	A: 30 B: 72 (P=0.06)	A: 67 B: >96 (P=0.13)
Noguchi 1995-1998	51	A: LHRH + FLT; B: LHRH + estramustine	A: 14.6 B: 25.4(P=0.03)	A: 30 B: 30 (NS)
Millikan 1996-2003	286	A: LHRH or Orch B: LHRH/Orch + ketoc + Dox+vinb+estramustine	A: 24 B: 35 (P=0.39)	A: 64 B: 72(P=0.41)
Smith (SWOG) 2001-2005	35 (High risk)	CAD + Palcitaxel, VP-16 +Estramustine	13	38

VOLUME 26 · NUMBER 36 · DECEMBER 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Androgen Ablation With or Without Three Cycles of Systemic Chemotherapy for Advanced Prostate Cancer

Randall E. Millikan, Sijin Wen, Lance C. Pagliaro, Melissa A. Brown, Brenda Moomey, Kim-Anh Do, and Christopher J. Logothetis

1996-2003

Results

Three hundred six patients were registered; 286 are reported. Median time to progression was 24 months (95% CI, 18 to 39 months) in the standard therapy arm, and 35 months (95% CI, 26 to 44 months) in the chemohormonal group ($P = .39$). At median follow-up of 6.4 years, overall survival was 5.4 years (95% CI, 4.7 to 7.8 years) in the standard therapy arm versus 6.1 years (95% CI, 5.1 to 10.1 years; $P = .41$). Prostate-specific antigen kinetics at the time of androgen ablation and the nadir after hormone treatment were strongly correlated with survival. Chemotherapy significantly increased the burden of therapy, with 51% of patients experiencing an adverse event of grade 3 or worse, especially thromboembolic events.

Conclusion

There is no role for ketoconazole and doxorubicin alternating with vinblastine and estramustine before emergence of a castrate-resistant phenotype.

J Clin Oncol 26:5936-5942. © 2008 by American Society of Clinical Oncology

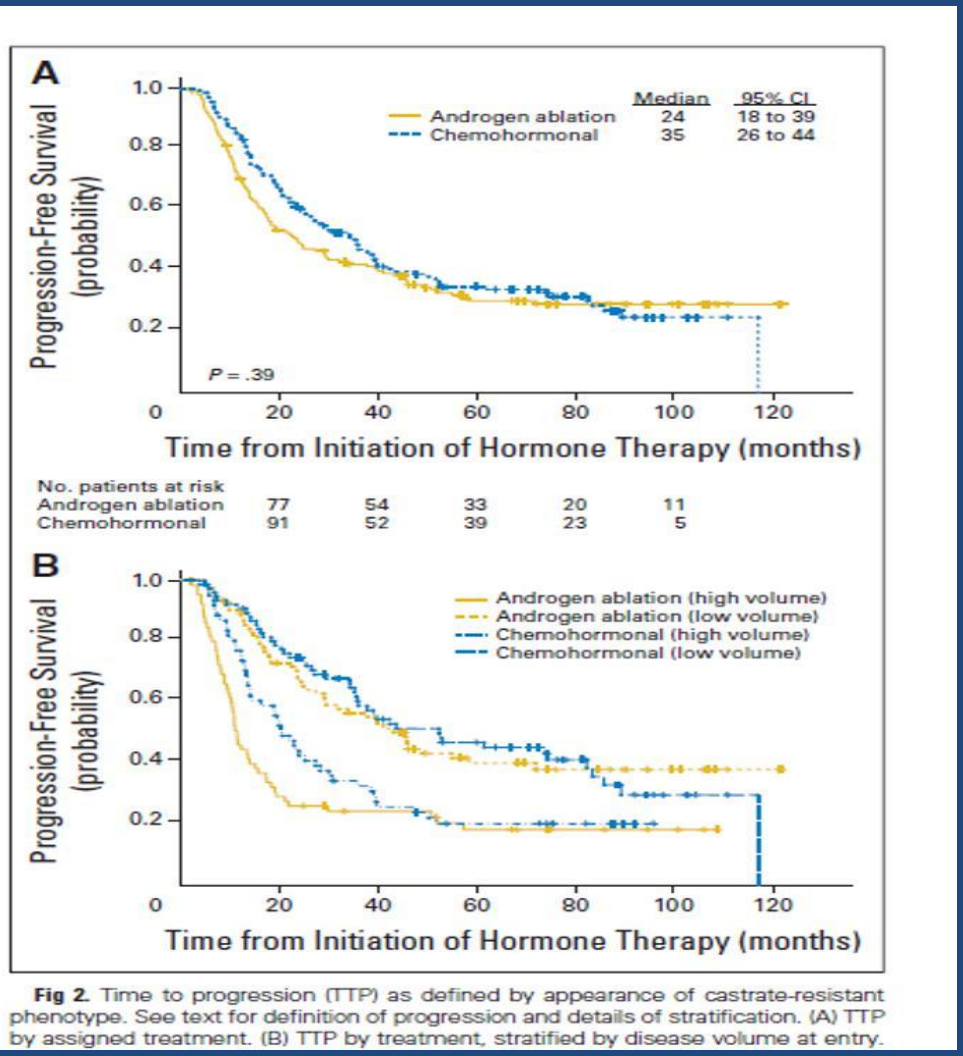


Fig 2. Time to progression (TTP) as defined by appearance of castrate-resistant phenotype. See text for definition of progression and details of stratification. (A) TTP by assigned treatment. (B) TTP by treatment, stratified by disease volume at entry.

Millikan et al, High volume: 126 pts

f/up: 76,8 mos

PFS: 11,2 vs 20,5 mos (ns)

Sweeney et al, High volume : 514 pts
f/up: 29 mos

	ADT + Doc (N=397)	ADT alone (N=393)	P-value	Hazard Ratio (95%CI*)
Median time to CRPC - biochemical, symptoms, or radiographic (months)	20.7	14.7	<0.0001	0.56 (0.44, 0.70)

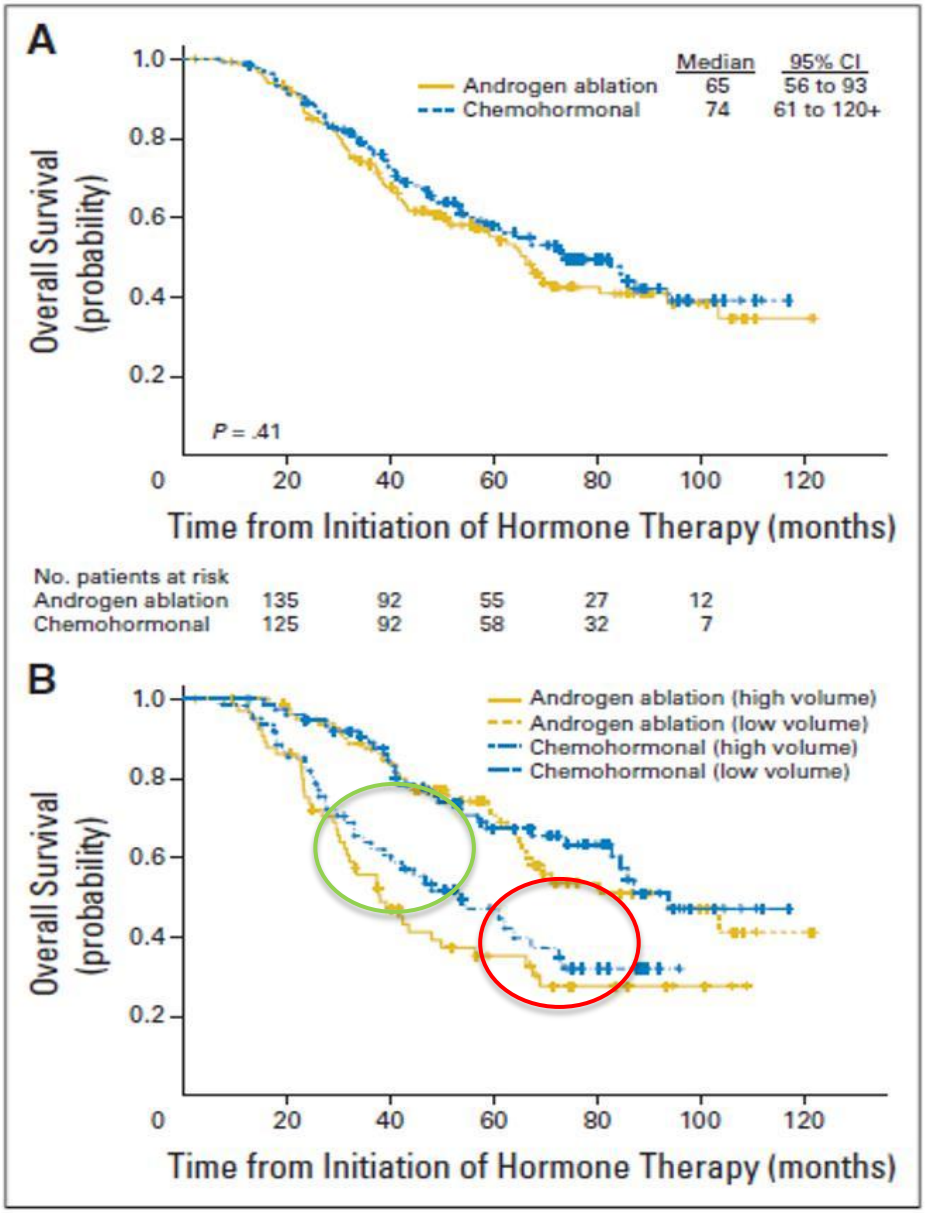


Fig 3. Overall survival. See text for details of stratification. (A) Survival by assigned treatment. (B) Survival by treatment, stratified by disease volume at entry.

Millikan et al,
High volume: 126 pts

OS: 3,1 vs 4,4 yrs (ns)
37,2 vs 52,8 mos

Sweeney et al:
p=0.0006
HR=0.60 (0.45-0.81)
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months

	N	x Age	% M at presentation	High risk / Strata ?	Chemo at PD Control arm	F/ up	Diffence of PFS / OS
GETUG-15	385	64	71%	47% / NO	63%	83 mos	YES / NO
CHAARTED	790	63	75%	65% / YES	40%	29 mos	YES / YES
STAMPEDE	2962	65	Most (94%)	?? / NO	40%	43 mos	YES / YES
MDACC	306 (286)	58	60% (LN,B,Visc)	41% / YES	Nearly all (Taxane)	73 mos	NO / NO

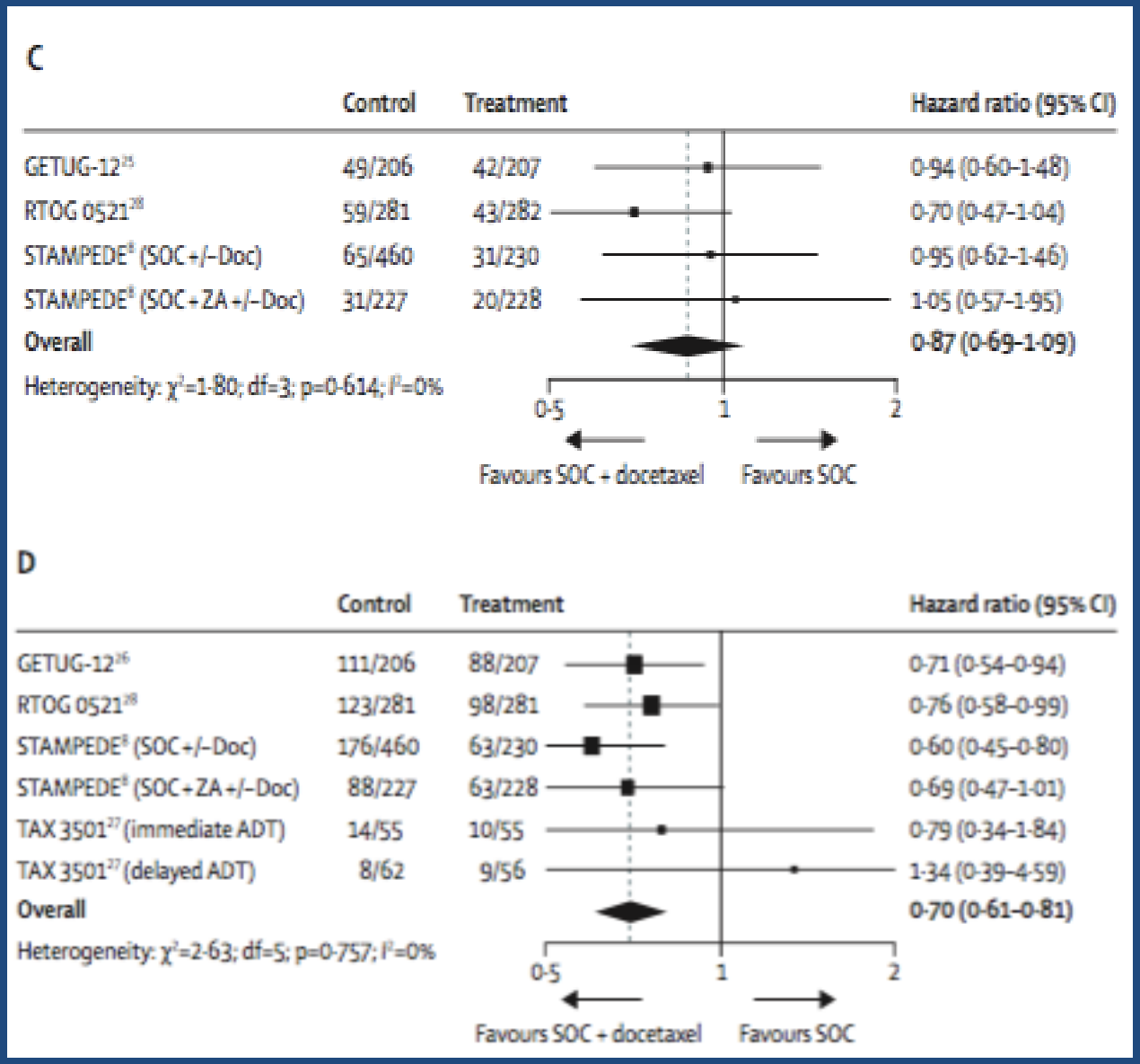
? N of pts
? Stratification (upfront metastatic vs slow progressors – volume of M)
? F/up
? PS (fit for Treatment)
? Early vs Late or vs NO Chemo
? PFS vs OS

Chemo in M0 high risk disease ?

	Accrual period	Number of patients	Control	Treatment	Metastatic status	Median age (range)	Gleason score of 8–10 (%)	Performance status of 0–1 (%)	Median follow-up (survival)	Treatment on progression (control group only)
Docetaxel trials										
GETUG-12[25,26]	November, 2002–December, 2006	413	ADT (goserelin 10·8 mg every 3 months for 3 years)	ADT plus docetaxel (70 mg/m² for four cycles) plus estramustine	M0	63 (46–77)	42%	Unknown	7 years, 6 months	Not reported
TAX 3501[27]	December, 2005–September, 2007	228	ADT (leuprolide 22·5 mg every 3 months for 18 months)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0	61·9*	52%	Unknown	3 years, 3 months	Not reported
RTOG 0521[28]	December, 2005–August, 2009	612	ADT (LHRH agonist plus oral anti-androgen plus RT)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus prednisone	M0	66 (unknown)	84%	Unknown	6 years	Not reported
STAMPEDE (standard of care with or without docetaxel)[8]	September, 2005–March, 2013	1776	ADT (plus radiotherapy for M0 patients)	ADT plus docetaxel (75 mg/m² every 3 weeks for six cycles) plus predisone	M0 and M1	65 (40–82)	70%	99%	3 years, 6 months	40% received docetaxel (49% received life-extending treatments)
STAMPEDE (standard of care plus zoledronic acid with or without docetaxel)[8]	September, 2005–March, 2013	1186	ADT (plus radiotherapy for M0 patients) plus zoledronic acid (4 mg every 3–4 weeks for 2 years)	ADT (plus radiotherapy for M0 patients) + zoledronic acid (4 mg for 3–4 weeks for 2 years) plus docetaxel (75 mg/m² every 3 weeks for six cycles)	M0 and M1	66 (42–84)	71%	99%	3 years, 6 months	36% received docetaxel (45% received life-extending treatments)

Adapted from: Vale CL, et al: Lacet Oncol 2016; 17:243-256

Docetaxel – M0 patients



No statistically significant difference OS between the groups in non-metastatic men

The smaller number of deaths in M0 men makes the analysis underpowered to detect differences

8% absolute improvement in FFS (22% → 30 %) at 4 yrs

My take home mesage

- ADT + D early may benefit some metastatic HSPCa pts
  - Upfront metastatic, High volume bone (lytic?), visceral, high GS (? Anaplastic phenotype ?),
  - No comorbidities
- Toxicity is manageable but real
  - PS 0 in most pts in trials
- PFS benefit =≠ OS benefit
- Post-protocol therapy effect ?
  - Early vs No chemo ?
  - If not given chemo upfront, I would follow high risk pts very closely not to miss the opportunity for chemo

mCRPCa - Treatment options

- Abiraterone + prezolon
- Enzalutamide
- Docetaxel rechallenge
- Cabazitaxel
- Ra-223 dichloride
- (Sipuleucel-T)

Docetaxel in the treatment of metastatic hormone-sensitive and castration-resistant prostate cancer: A meta-analysis.

Eleven RCTs involving 12,468 patients included in the analysis.

-Three studies (4,137 pts) compared the addition of docetaxel to androgen deprivation therapy (ADT) vs. ADT alone in pts with mHSPC

- 8 studies (8,331 pts) compared docetaxel-based combination with another agent (custirsen, lenalidomide, dasatinib, atrasentan, aflibercept, zibotentan, bevacizumab, or GVAX) to docetaxel alone in pts with mCRPC.

-Adding docetaxel to ADT improved OS (HR 0.75; 95% CI 0.62-0.90, P = 0.002) and PFS/FFS (HR 0.62; 95% CI 0.56-0.69, P < 0.001) compared to ADT alone in pts with mHSPC
- However, it also increased the risks of grade 3-5 AEs, particularly febrile neutropenia

- Docetaxel combined with another agent did not improve OS or PFS as compared to docetaxel alone in mCRPC pts who were taxane-naïve for metastatic disease. As expected, the combination therapy increased the risks of grade 3-5 AEs

Presented by Shijia Zhang at 2016 ASCO Annual Meeting

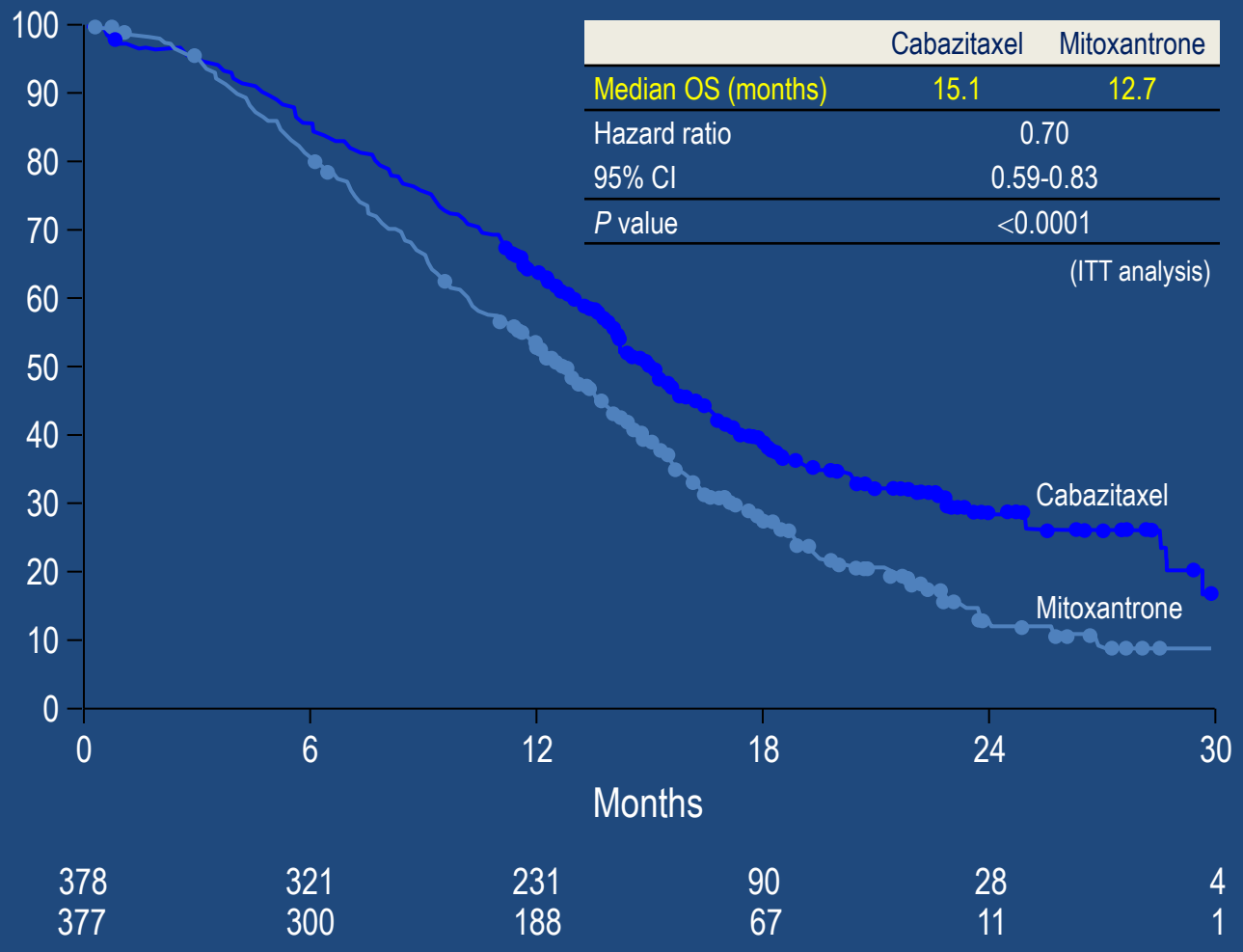
TROPIC Overall Survival (ITT analysis)

N=755

Pain 45%

Measurable 54%

During / <3 mos >70%



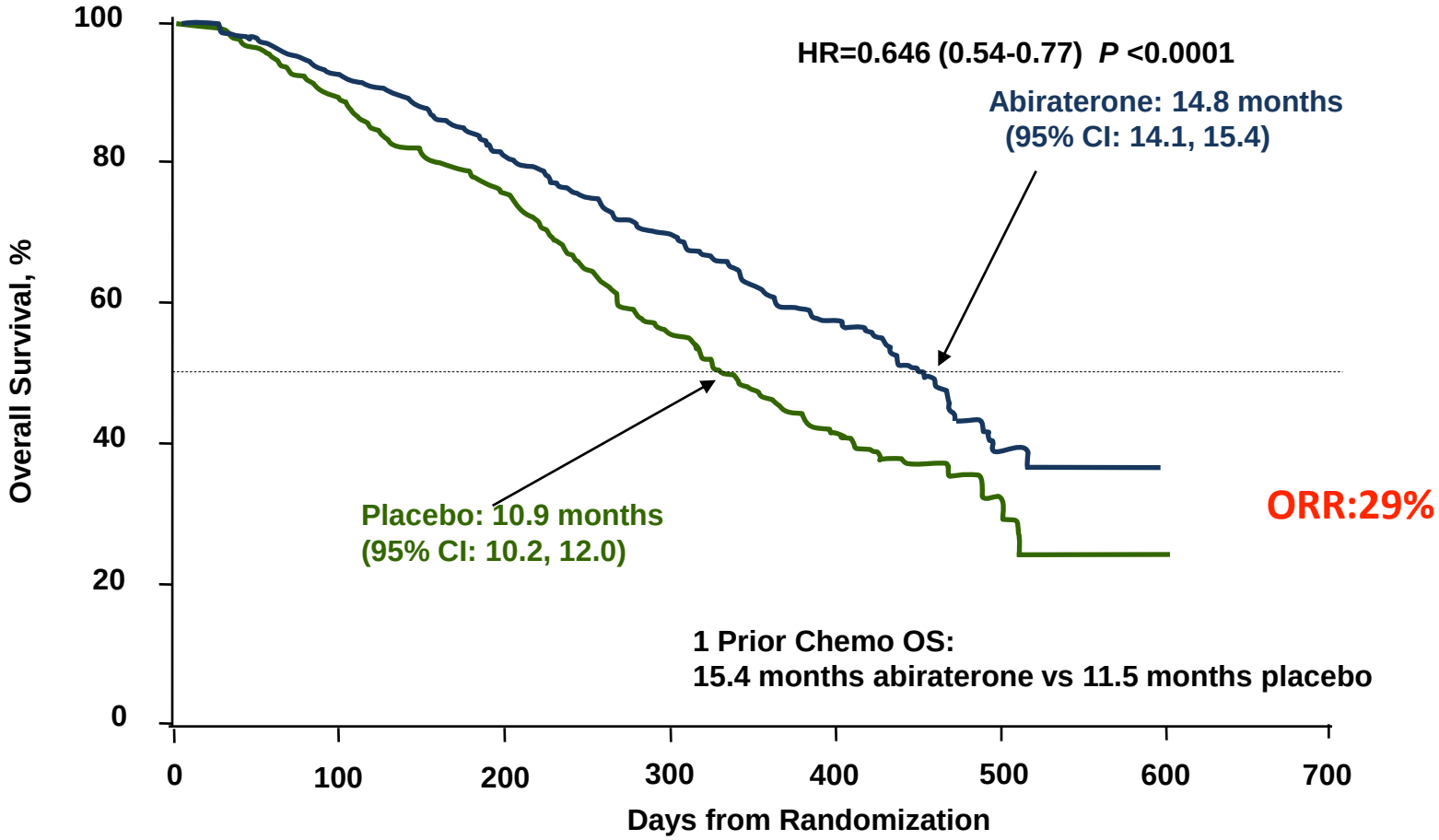
	Cabazitaxel	Mitoxantrone
Median OS (months)	15.1	12.7
Hazard ratio	0.70	
95% CI	0.59-0.83	
P value	<0.0001	

(ITT analysis)

Number at risk						
Cabazitaxel	378	321	231	90	28	4
Mitoxantrone	377	300	188	67	11	1

De Bono JS et al. *Lancet.* 2010;376:1147-154.

COU-AA-301: Abiraterone Acetate Improves OS in mCRPC post Docetaxel



Abiraterone	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

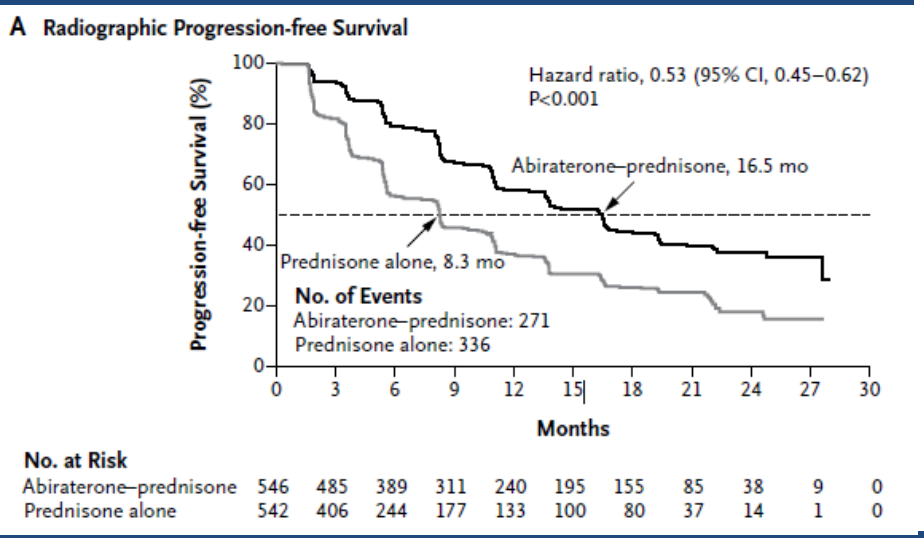
deBono N Engl J Med. 2011 May 26;364(21):1995-2005

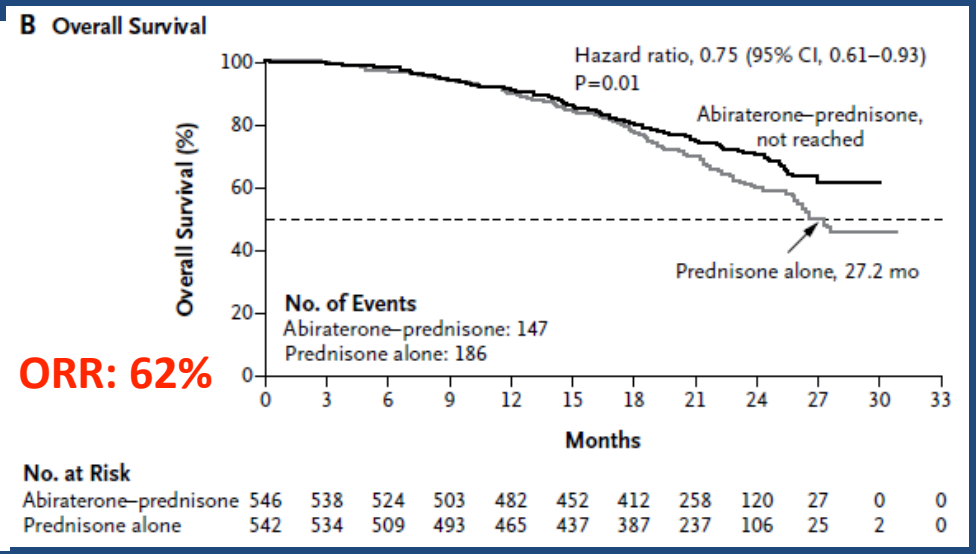
The NEW ENGLAND JOURNAL of MEDICINE

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.,

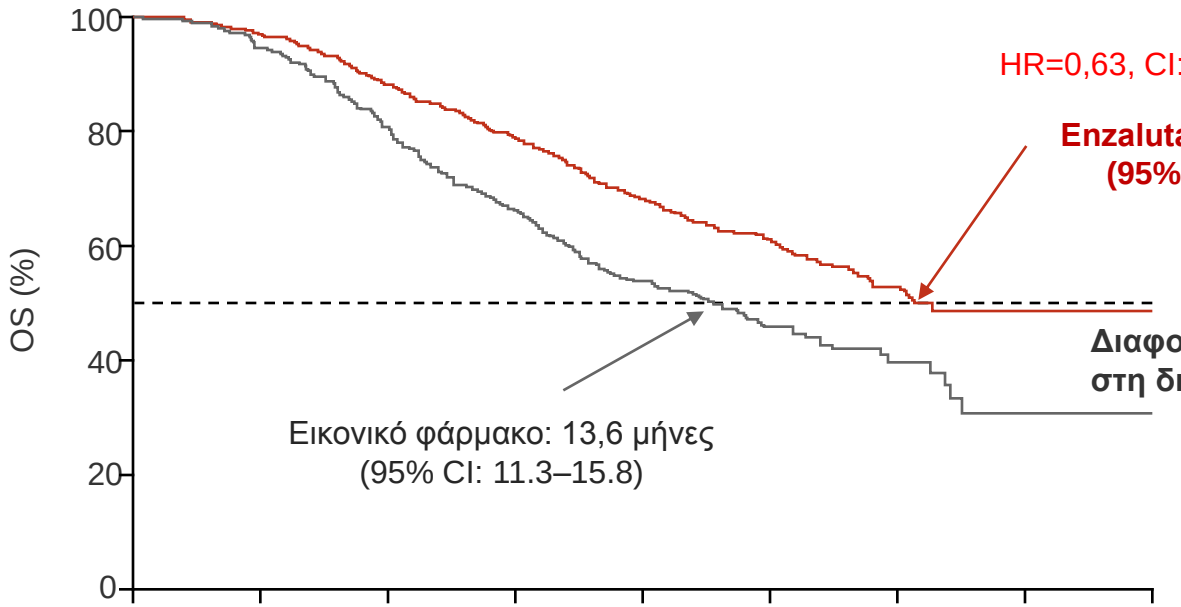




ORR: 62%

AFFIRM

Enzalutamide improves OS in mCRPCa post Docetaxel



Αριθμός ασθ. σε κίνδυνο									
Enzalutamide, n=	800	775	701	627	400	211	72	7	0
Εικονικό φάρμακο, n=	399	376	317	263	167	81	33	3	0

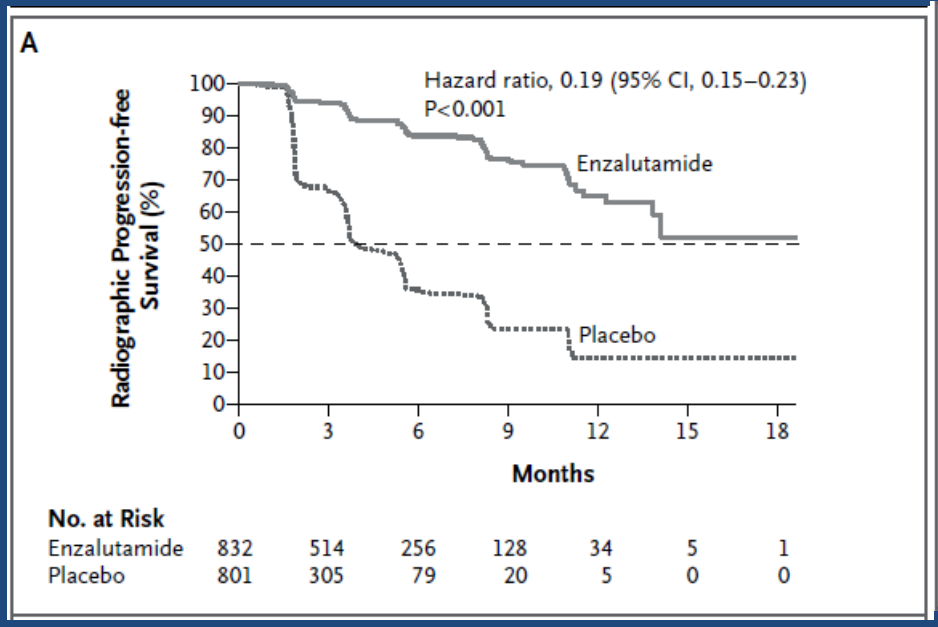
Η OS μετρήθηκε ως το χρονικό διάστημα από την τυχαιοποίηση έως τον θάνατο από οποιαδήποτε αιτία.
CI=διάστημα εμπιστοσύνης. HR=λόγος κινδύνου. OS=συνολική επιβίωση. NYR=δεν έχει επιτευχθεί ακόμα.
Scher HI, *et al*. *N Eng J Med* 2012;367:1187–97.

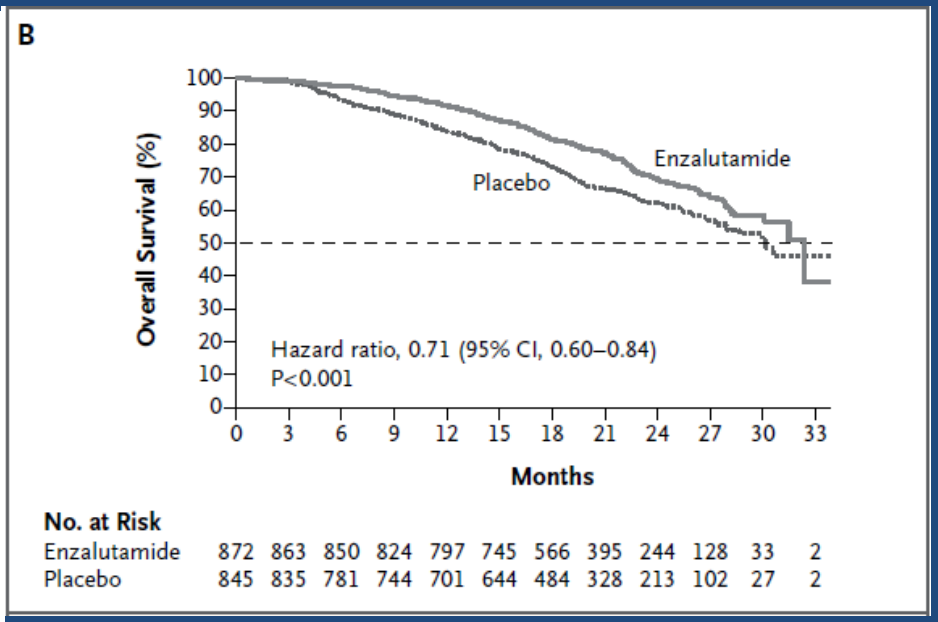
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

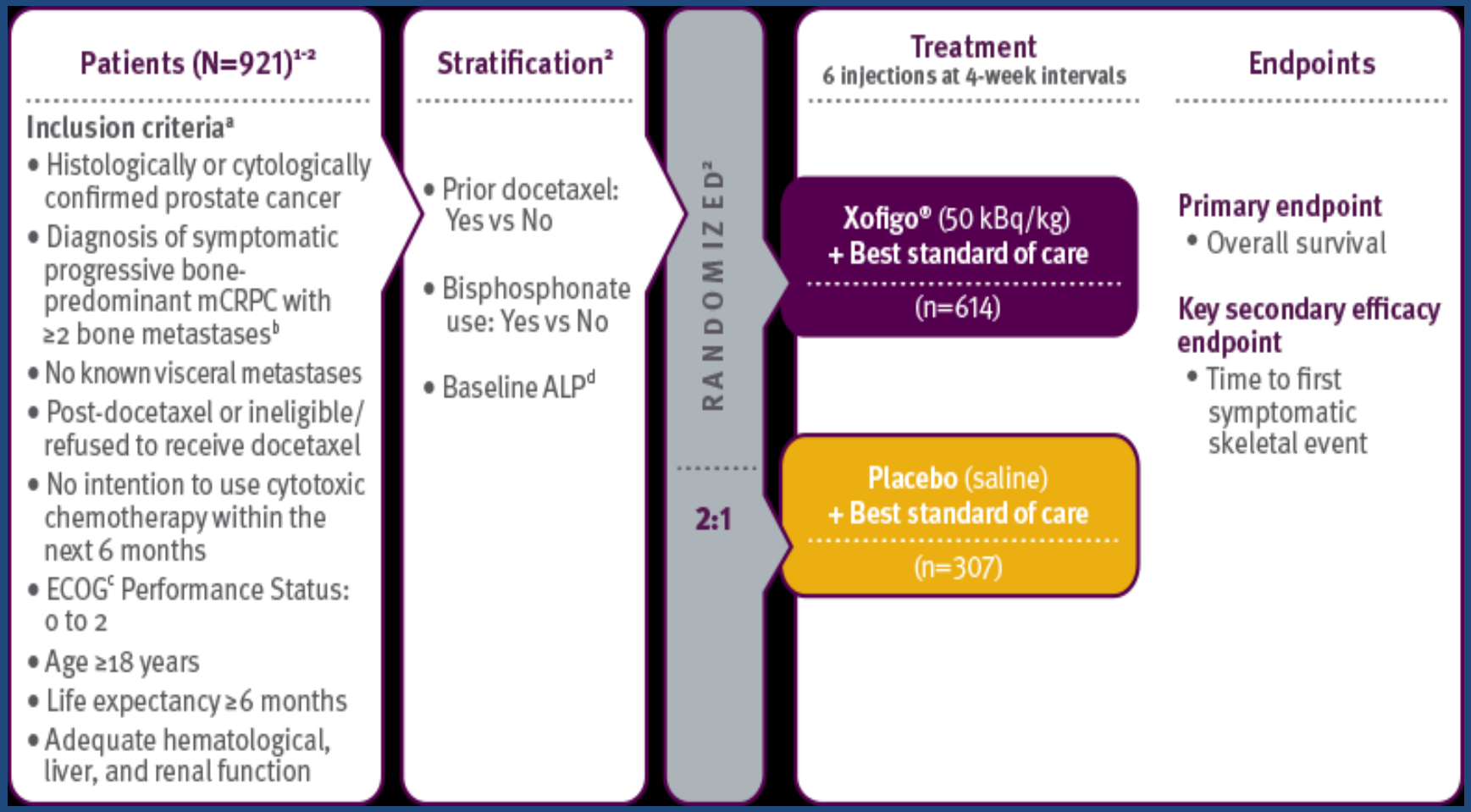
Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

DOI: 10.1056/NEJMoa1405095

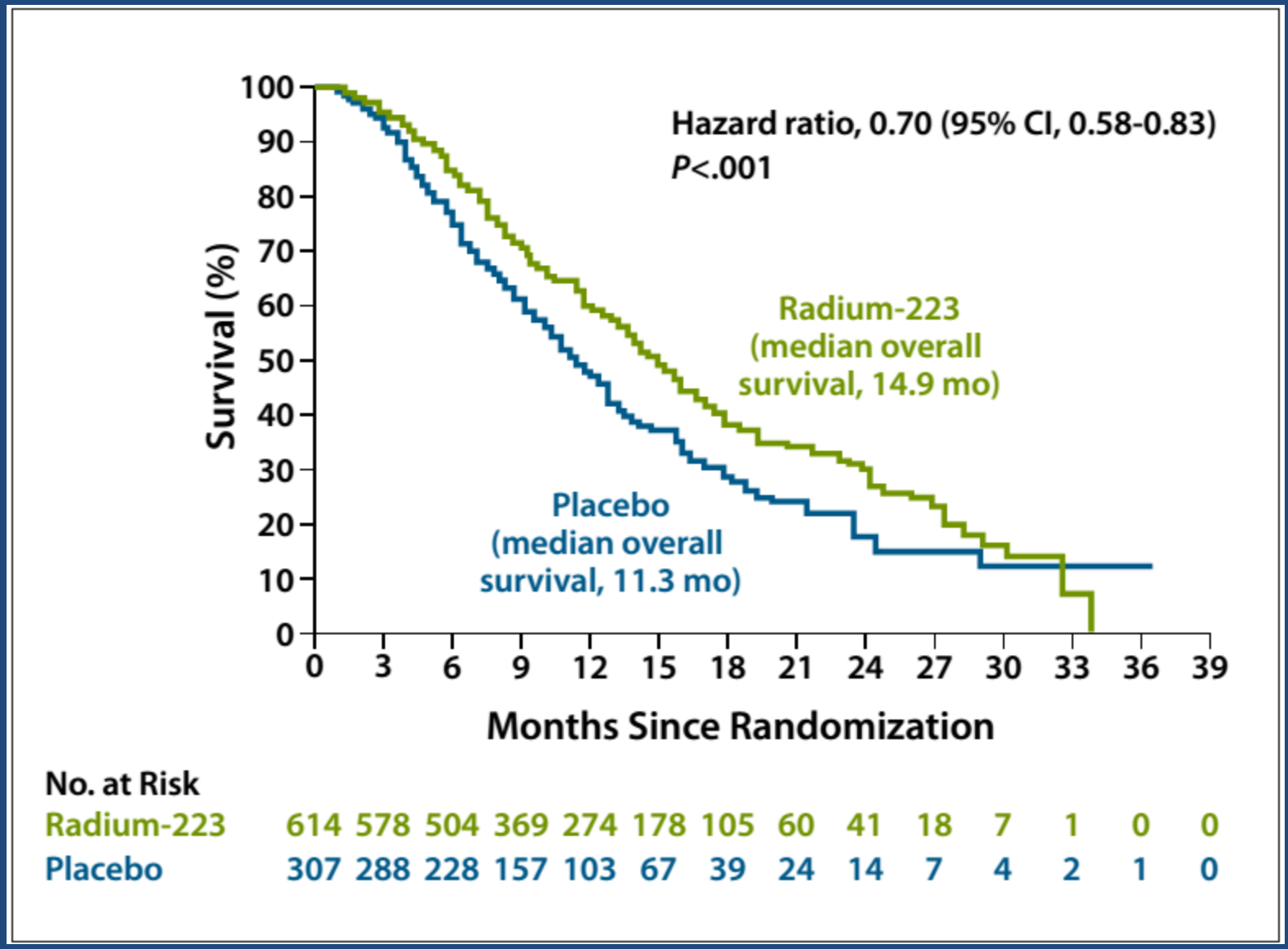




RA-223 DICHLORIDE STUDY DESIGN

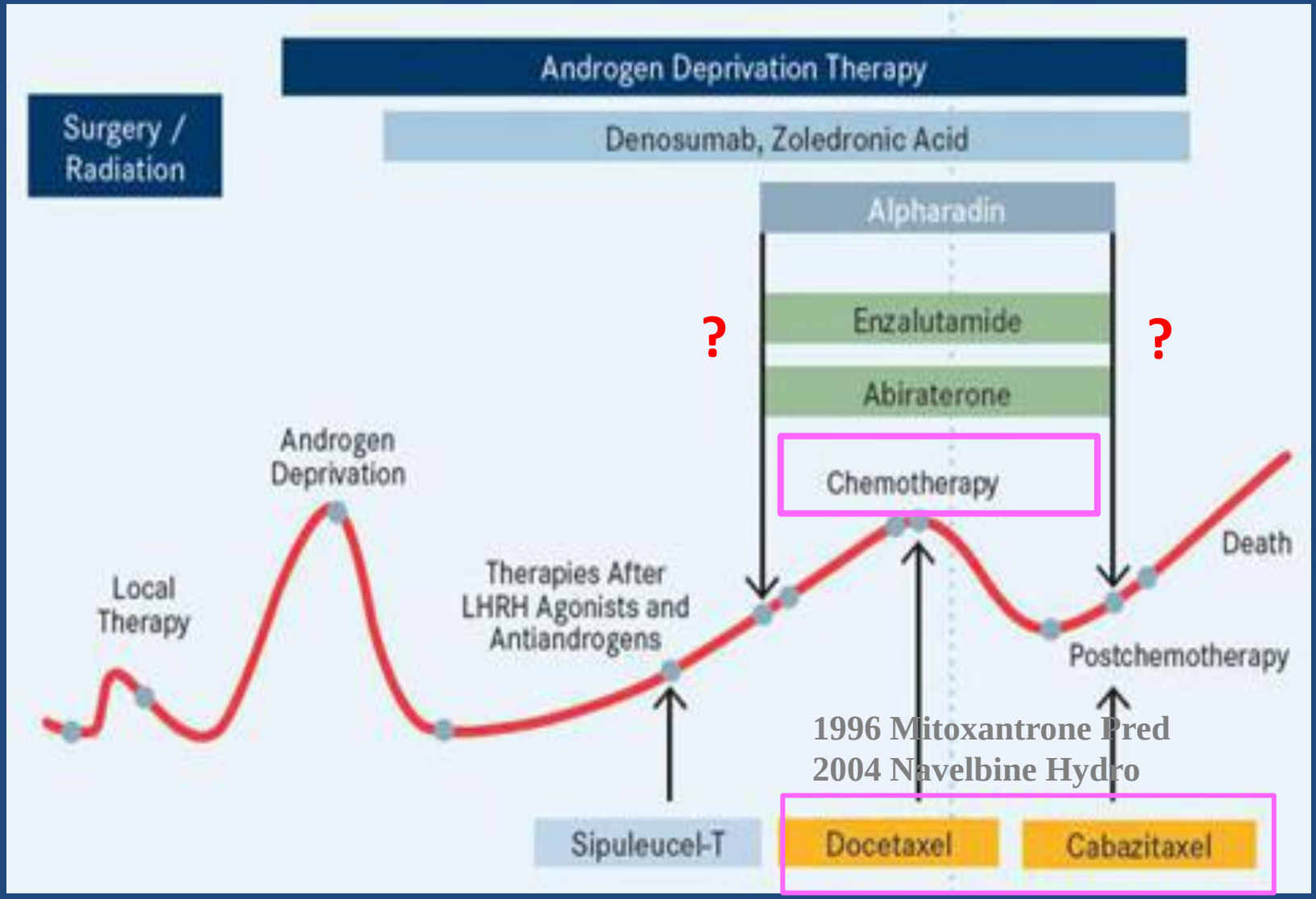


Ra-223 (Xofigo) vs Placebo



NEJM Volume 369, Pages 213-223

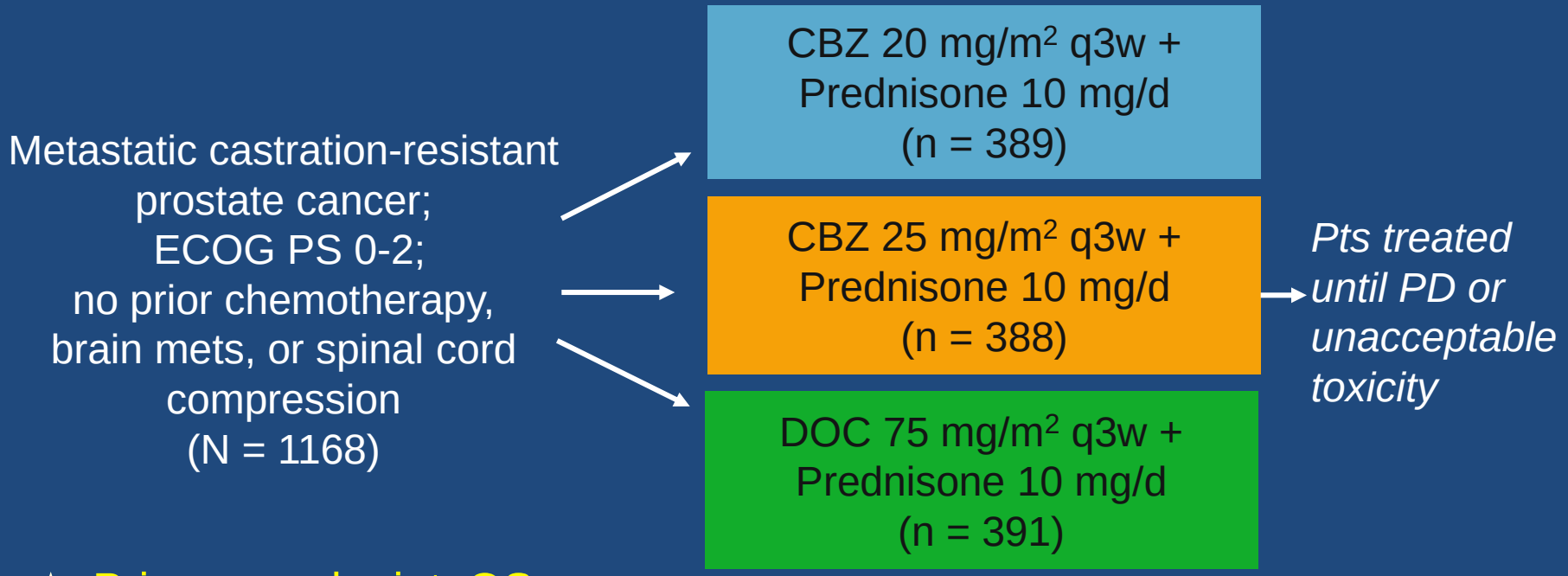
Sequence of treatments in mCRPC ?



Resistance to therapy ?

Does it always help to bring an active drug early ?

FIRSTANA: Study Design

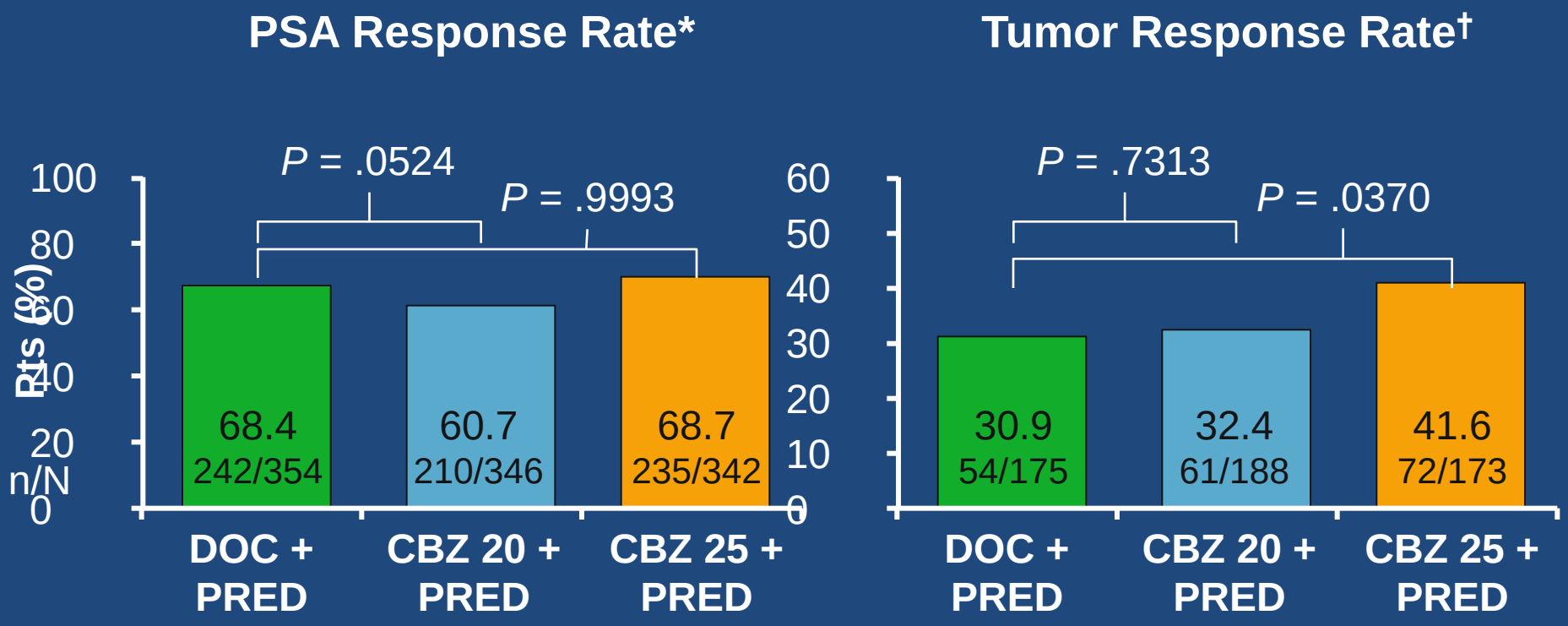


- Primary endpoint: OS
- Secondary endpoints: safety, composite PFS,* tumor response, PSA response, pain response, time to skeletal-related events, HRQoL, PK/PG
- Exploratory: circulating free DNA level

*PFS determined by progression of PSA, tumor, or pain

Sartor AO, et al. ASCO 2016. Abstract 5006.

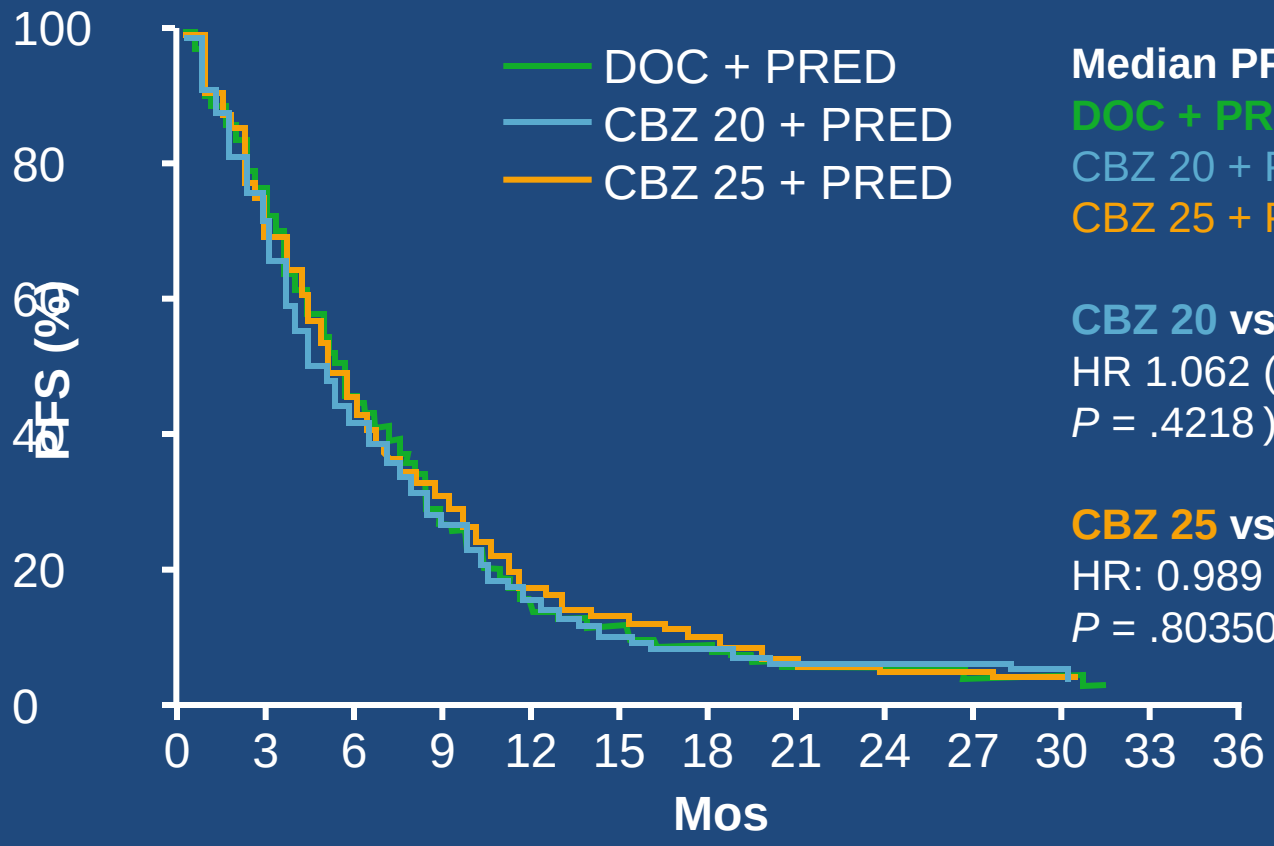
FIRSTANA: Response



*Assessed in pts with BL PSA ≥ 10 ng/mL and ≥ 1 post-BL measurement.
†Assessed in pts with BL measurable disease meeting RECIST criteria for analysis.

Sartor AO, et al. ASCO 2016. Abstract 5006. Reproduced with permission.

FIRSTANA: Progression-Free Survival



Median PFS, Mos (95% CI)

DOC + PRED	5.3 (4.86-5.78)
CBZ 20 + PRED	4.4 (3.91-5.09)
CBZ 25 + PRED	5.1 (4.60-5.72)

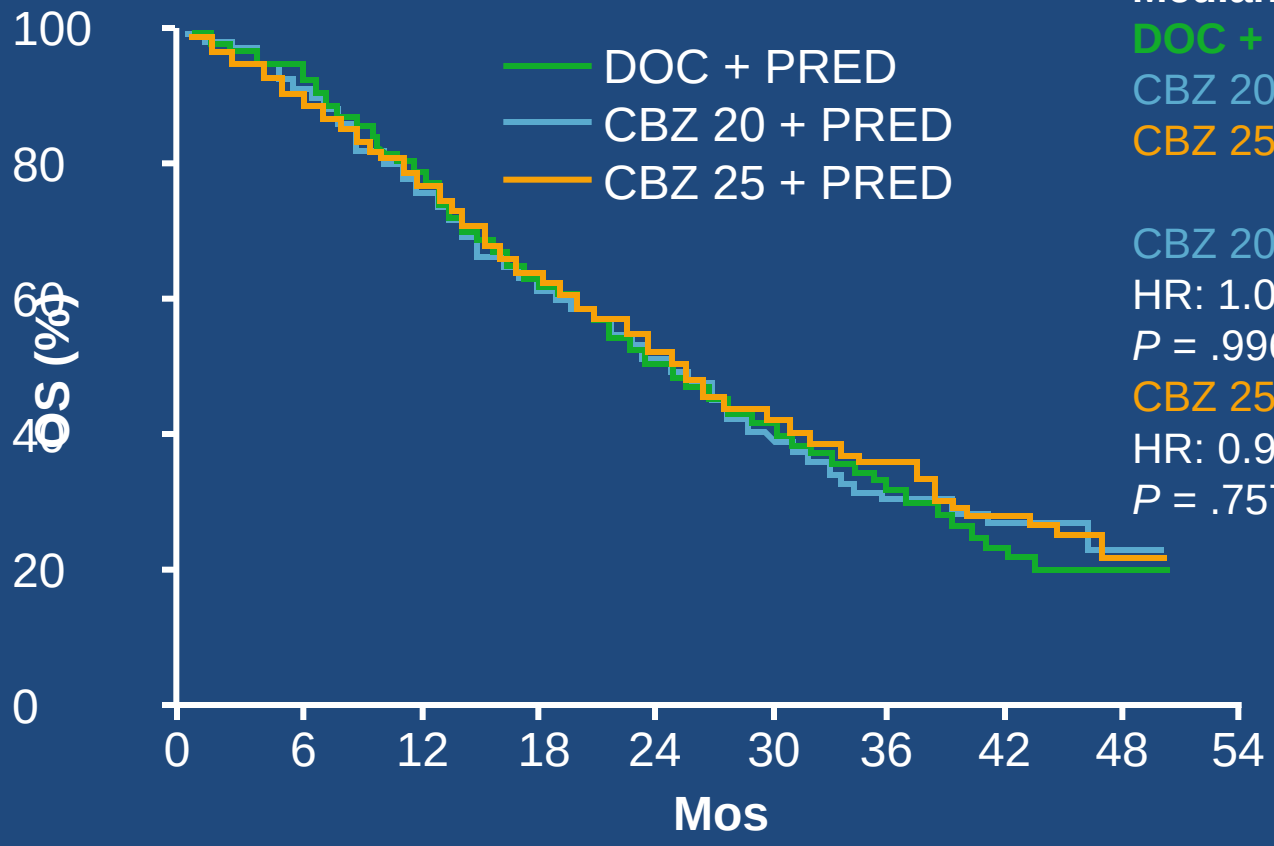
CBZ 20 vs DOC
HR 1.062 (95% CI: 0.913-1.236; *P* = .4218)

CBZ 25 vs DOC
HR: 0.989 (95% CI: 0.849-1.152; *P* = .80350)

- Small observed difference in pain progression component of PFS for CBZ 25 vs DOC (*P* = .0354) but likely not clinically significant

Sartor AO, et al. ASCO 2016. Abstract 5006.

FIRSTANA: Overall Survival



Median OS, Mos (95% CI)

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 vs DOC

HR: 1.009 (95% CI: 0.85-1.197; *P* = .9967)

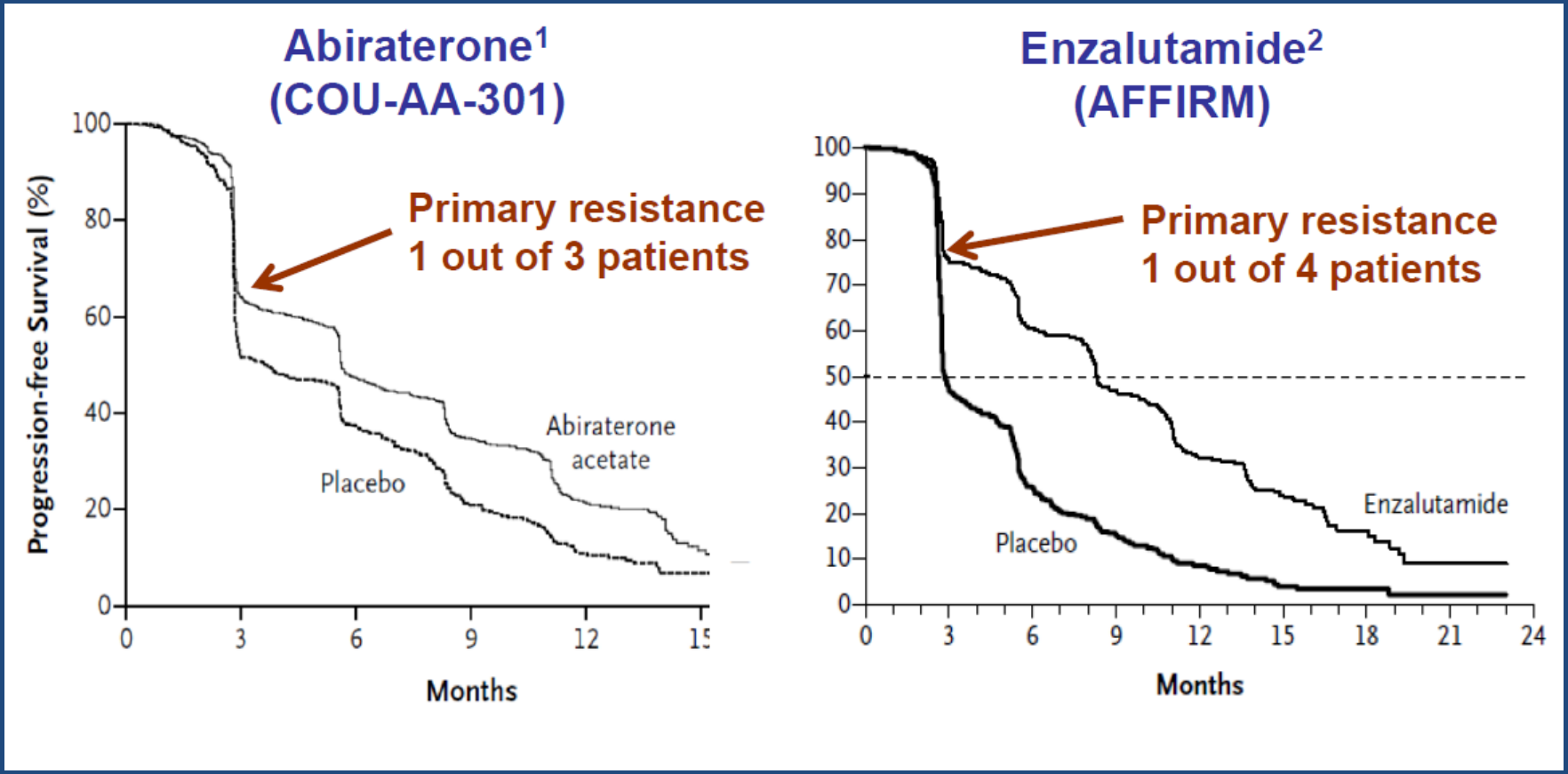
CBZ 25 vs DOC

HR: 0.97 (95% CI: 0.819-1.160; *P* = .7574)

- OS and PFS statistically comparable for each CBZ arm vs DOC

Sartor AO, et al. ASCO 2016. Abstract 5006.

Πρωτογενής αντίσταση στην ενδοκρινική θεραπεία



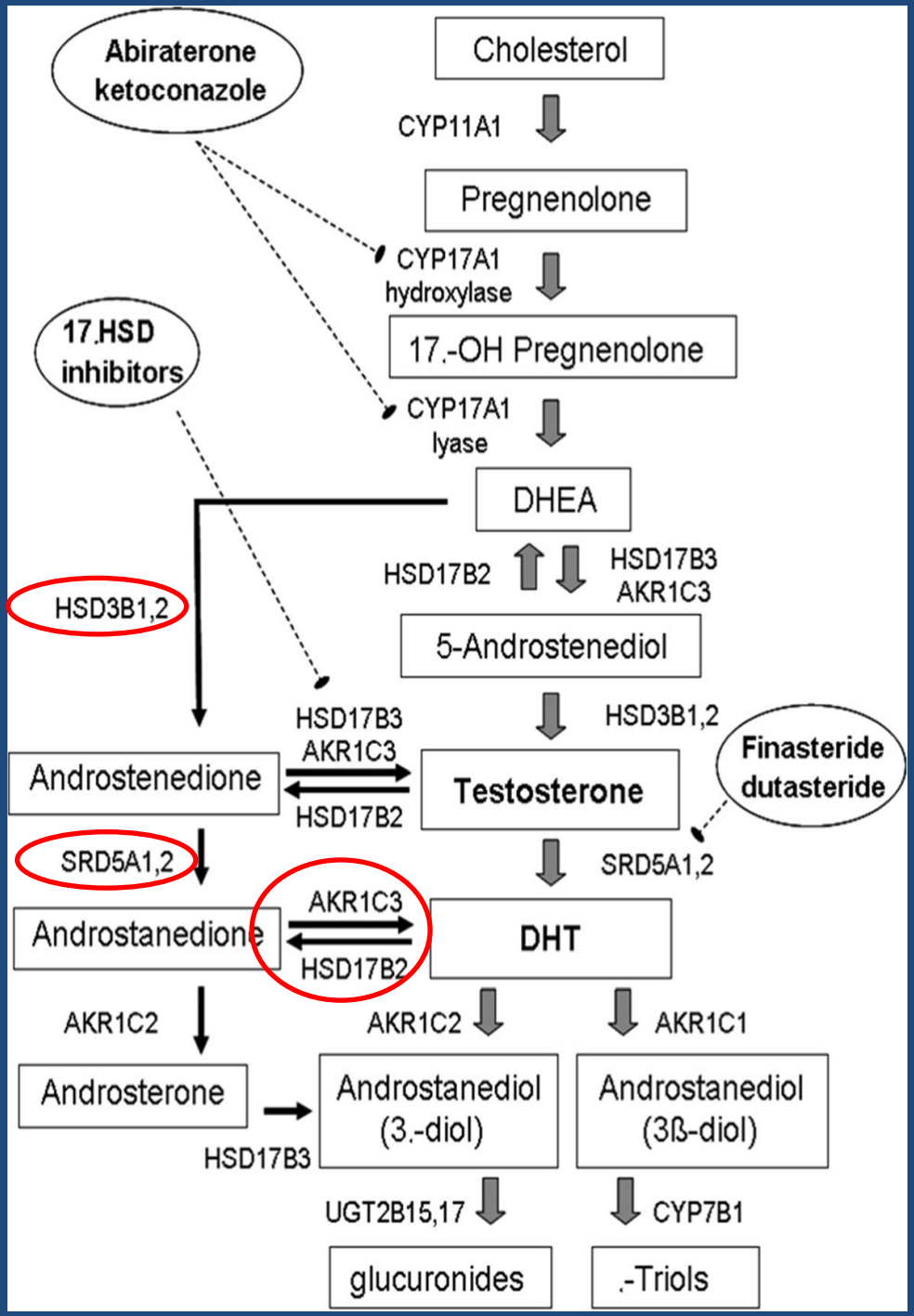
[1]De Bono et al, N Engl J Med 2011; 364: 1995–2005
[2]Scher H et al, N Engl J Med 2012; 367:1187-97

Resistance to Abiraterone

30% primary resistant

Most responding pts progress by 15 mos

- Overexpression of AR
- Amplification of AR
- Upregulation / Mutations of Steroidogenesis enzymes: CYP17, AKR1C3, HSD17B3, SDR5A2
  - HSD3B1 (1245C) Mutation
  - IL-6 → upregulation HSD3B2, AKR1C3
  - IL-6 inhibition by shRNA → downregulates AKR1C3
  - Knockdown AKR1C3 (shRNA or indomethacin) → re-sensitization to ENZA
- AR splice variants



Cai C, Cancer Res. 2011;71:6503–13.
Mostaghel EA, Clin Cancer Res. 2011;17:5913–25.
Chun JY, Clin Cancer Res. 2009;15:4815–22.
Liu C, Cancer Res. 2015;75:1413–22.

Resistance to Enzalutamide

25- 30% primary resistant

Most responding pts progress by 24 months

- Overexpression of CYP17, AKR1C3
  - Knockdown AKR1C3 (shRNA or indomethacin) → re-sensitization to ENZA
- Activating mutations in LBD of AR (i.e. Phe876Leu) (Enza = agonist ?)
- GR-mediated transcriptional activation
  - GR DBD similar to AR DBD, GR binds to several AR-regulated genes
- Activation of PI3K/Akt signaling
- AR splice variant

Eisermann K, Transl Androl Urol. 2013;2:137–47.
Korpal M. Cancer Discov. 2013;3:1030–43.
Sharifi N. N Engl J Med. 2014;370:970–1.
Denayer S, Mol Endocrinol. 2010;24:898–913.
Claessens F. Nat Rev Urol. 2014;11:712–6.

Glucocorticoid Receptor Confers Resistance to Antiandrogens by Bypassing Androgen Receptor Blockade

Vivek K. Arora,[1,2] Emily Schenkein,[1] Rajmohan Murali,[1,3] Sumit K. Subudhi,[2] John Wongvipat,[1] Minna D. Balbas,[1,4] Neel Shah,[1,4] Ling Cai,[1] Eleni Efstathiou,[5] Chris Logothetis,[5] Deyou Zheng,[6] and Charles L. Sawyers[1,7,*]

[1]Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

[2]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

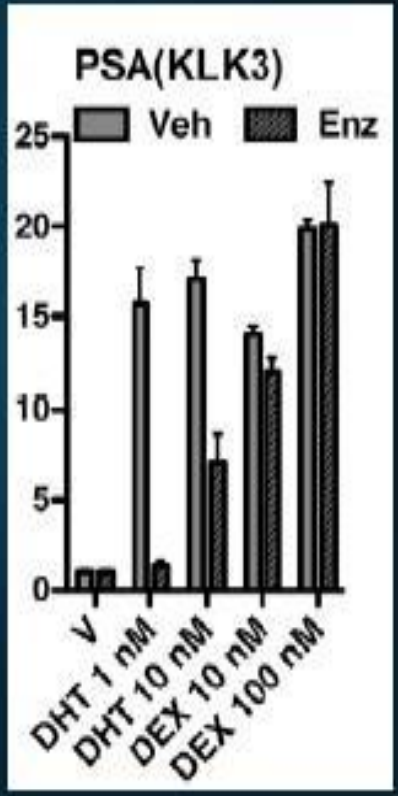
[3]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

[4]Louis V. Gerstner, Jr. Graduate School of Biomedical Sciences, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

[5]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[6]Departments of Neurology, Genetics, and Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA

[7]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

N ENGL J MED 371;11 NEJM.ORG SEPTEMBER 11, 2014

ARV7 + : higher FL-AR mRNA, PSA, AlkP, # prior horm Rxs

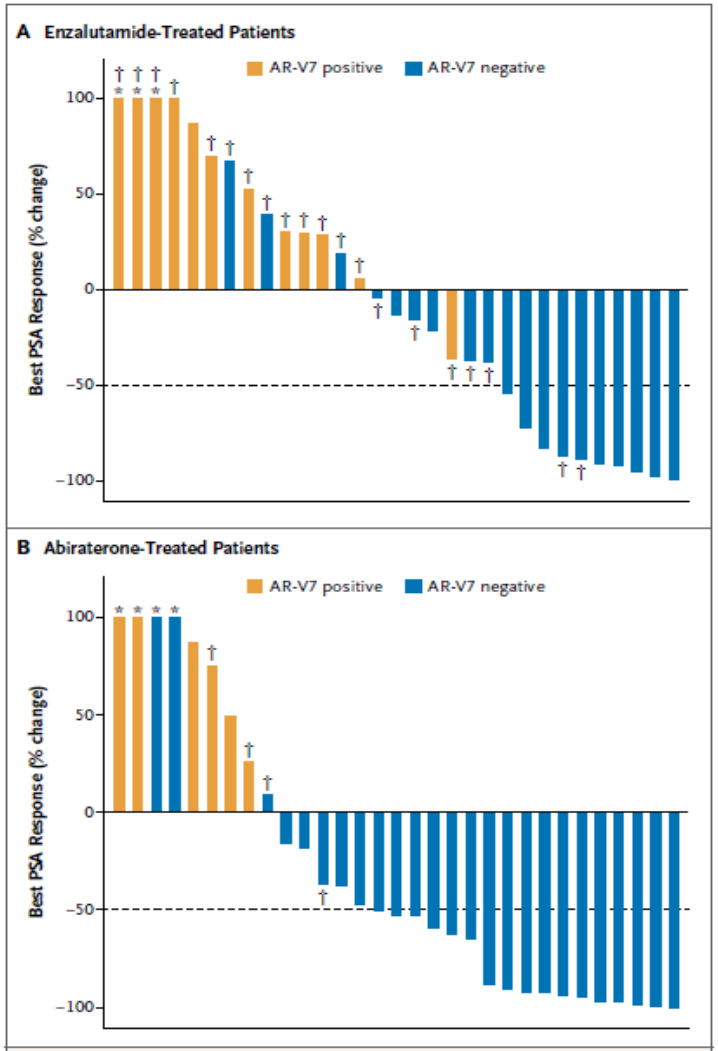


Figure 2. Waterfall Plots of Best Prostate-Specific Antigen (PSA) Responses According to AR-V7 Status.

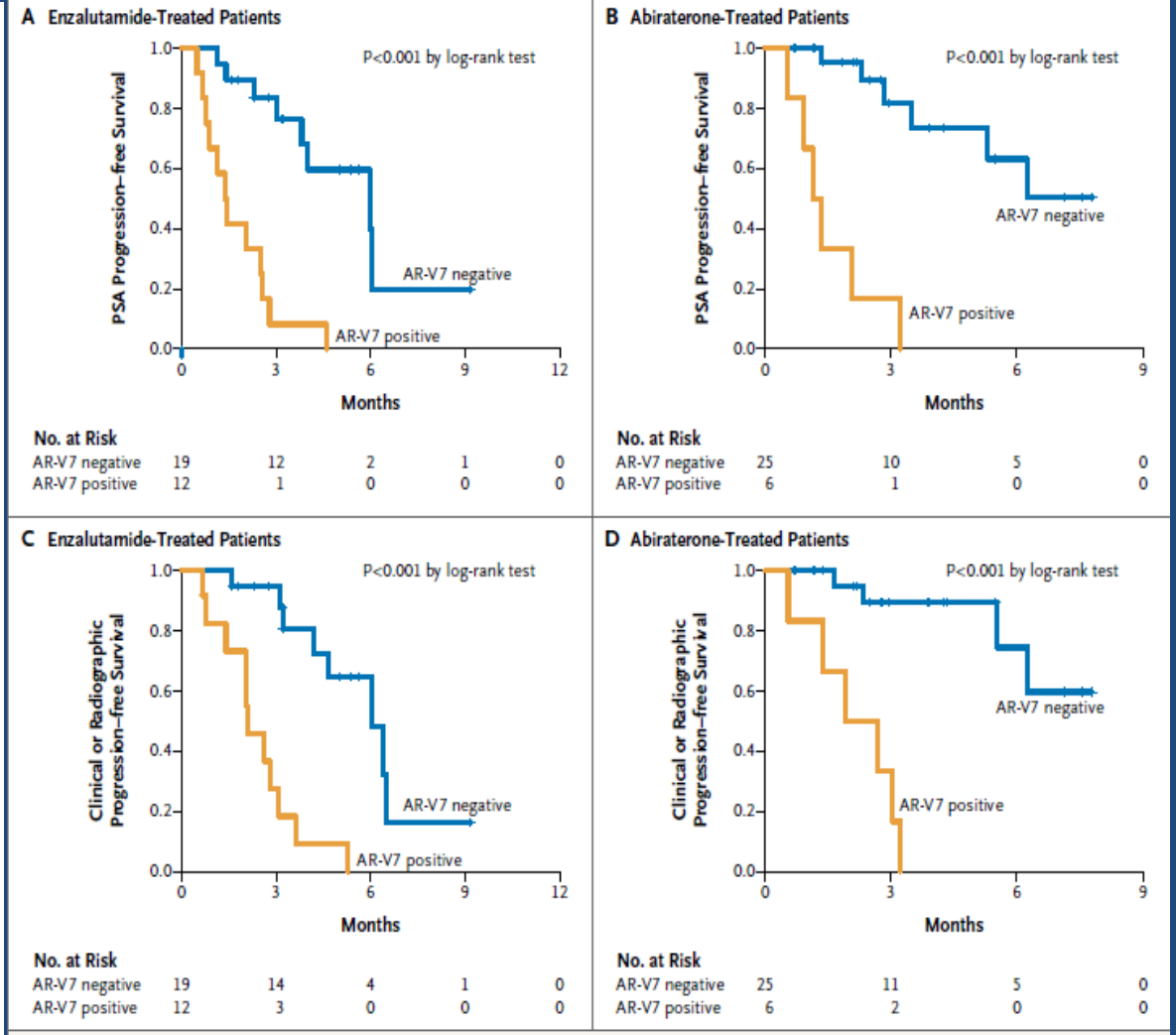


Figure 3. Kaplan–Meier Analysis of PSA Progression–free Survival and Clinical or Radiographic Progression–free Survival According to AR-V7 Status.

Outcomes: AR-V7 “conversions”

Outcome	AR-V7[–] → AR-V7[–] (n=36/42)	AR-V7[–] → AR-V7[+] (n=6/42)	AR-V7[+] → AR-V7[+] (n=16)
PSA Response	**68%** (95%CI, 52 – 81%)	**17%** (95%CI, 4 – 58%)	**0%** (95%CI, 0 – 19%)
PSA PFS	**6.1 months** (95%CI, 5.9 mo – NR)	**3.0 months** (95%CI, 2.3 mo – NR)	**1.4 months** (95%CI, 0.9 – 2.6 mo)
PFS	**6.5 months** (95%CI, 6.1 mo – NR)	**3.2 months** (95%CI, 3.1 mo – NR)	**2.1 months** (95%CI, 1.9 – 3.1 mo)

Clinical outcomes of AR-V7(–) to AR-V7(+) men were intermediate

Antonarakis ES, ASCO 2014, A 5001

Implications ?

AR-V7+ may be associated with primary and acquired resistance to ENZA & ABI

If validated AR-V7+ pts could be steered away from receiving AR-targeting drugs and could be offered alternative treatments

Onstenk W, et al. Eur Urol. 2015 Jul 15. pii: S0302-2838

Efficacy of Cabazitaxel in CRPCa is Independent of the presence of ARV-7 in CTCs

Antonarakis et al, JAMA Oncol 2015 Aug 1;1(5):582-91.

ARV7 and Efficacy of Taxane Chemotherapy in Patients With mCRPCa.

N=37 pts, starting taxane Rx, prior Abi / Enza allowed, 1o: PSA response

17/37 (46%) AR-V7 + CTCs (25% in NO prior Abi/Enza, 50% in either, 53% in both)

AR-V7+ : younger, GS≥ 8, prior Enza/Abi, > bone, PSA, ALkP, AR-FL

PSA responses [54%, 41% in AR-V7+, 65% in AR-V7 -], PSA PFS, PFS numerically better in AR-V7 Neg , But NS

AR-V7 Neg: 11% → Pos, 89% remained Neg
AR-V7 Pos: 58% → Neg, 42% remained Pos

Low conversion rate with Taxanes?
CTC disappearance ?

If so, could Tax Rx restore sensitivity to 2o hormonal therapies?

BUT clinical info is NOT supporting this now.

Antonarakis et al, JAMA Oncol 2015 Aug 1;1(5):582-91.

ARV7 and Efficacy of Taxane Chemotherapy in Patients With mCRPCa.

Compared with 62 pts from previous trial (!!!) →

In AR-V7+ men, taxanes *appear* to be more efficacious than ENZA or ABI (PSA response, PSA PFS, cPFS)

In AR-V7- men, taxanes & Enza or Abi ***may*** have comparable efficacy.

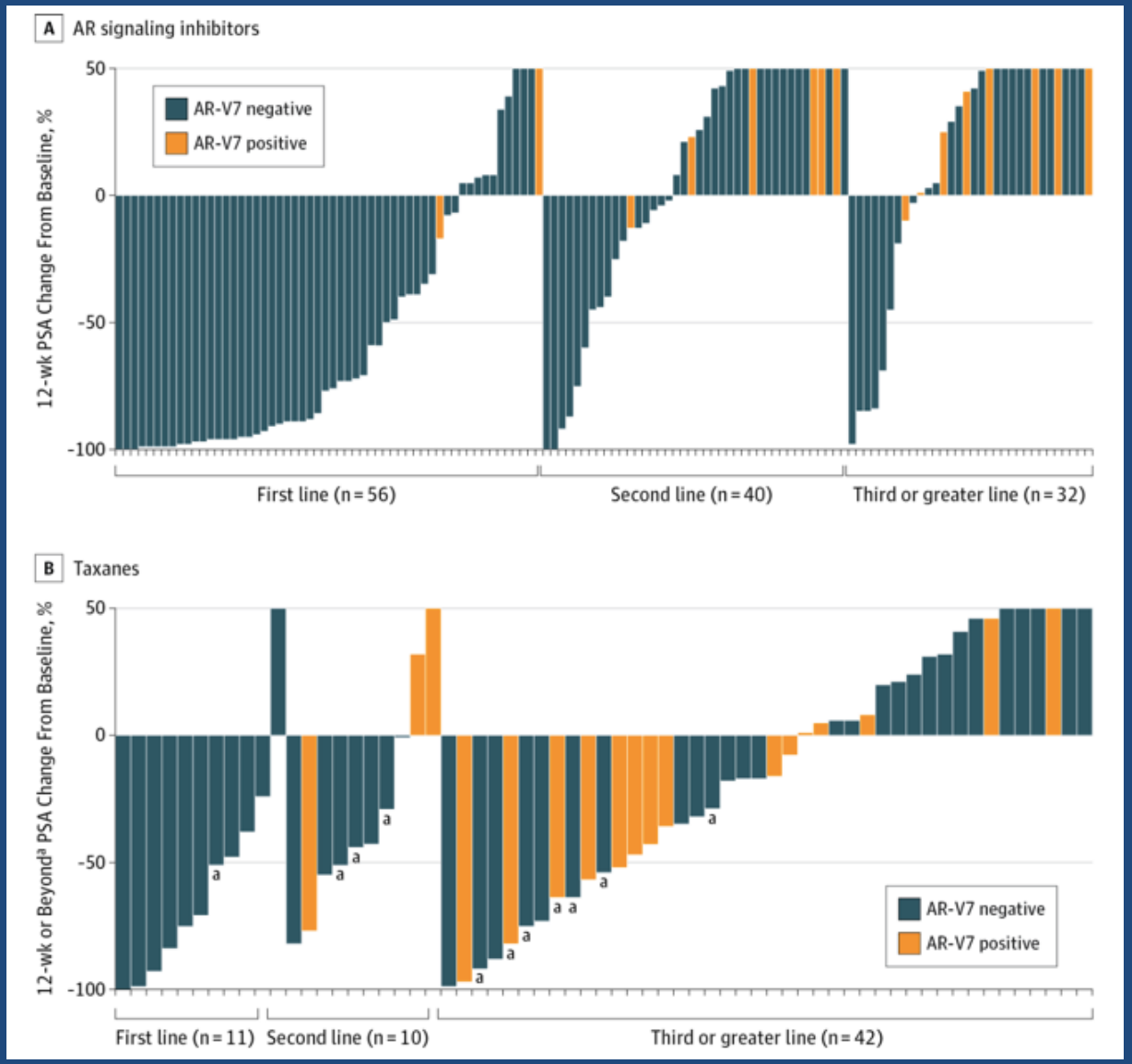
???

Size

Stage

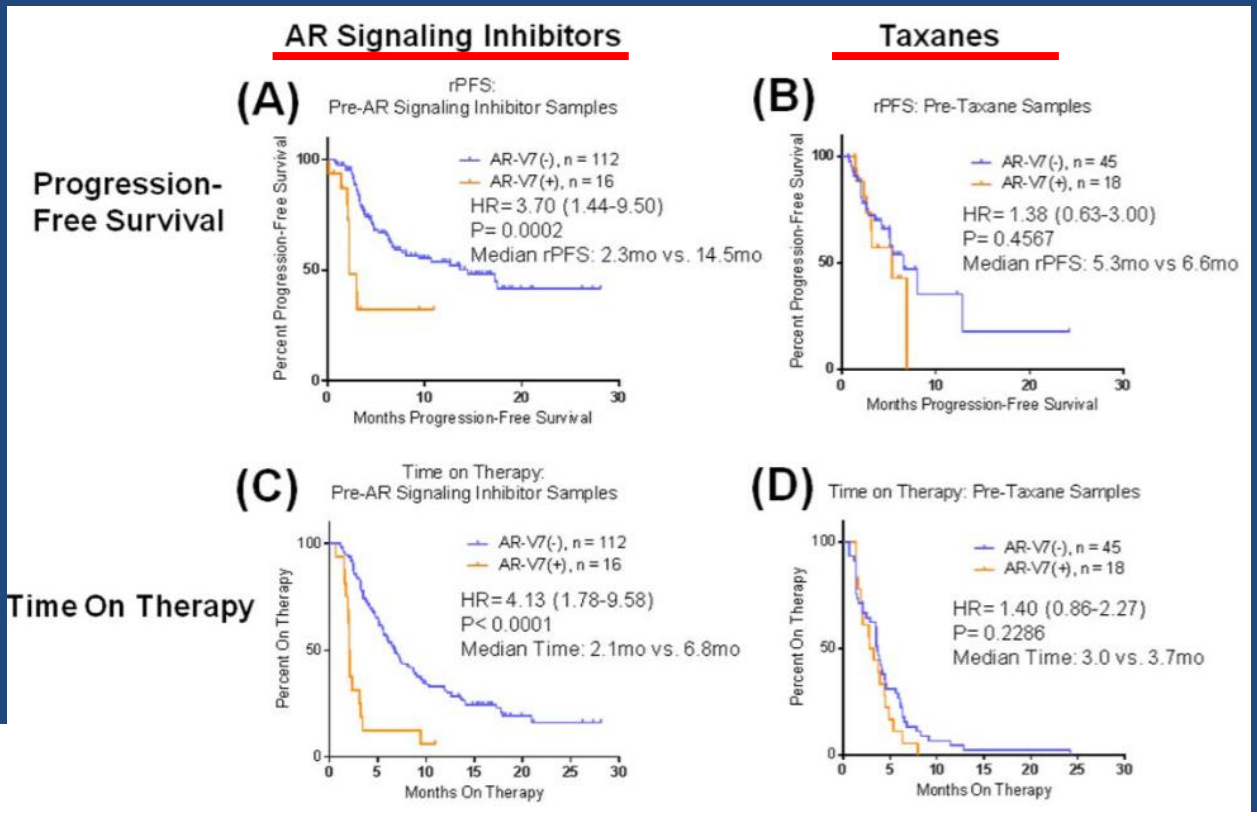
Treatment selection not random

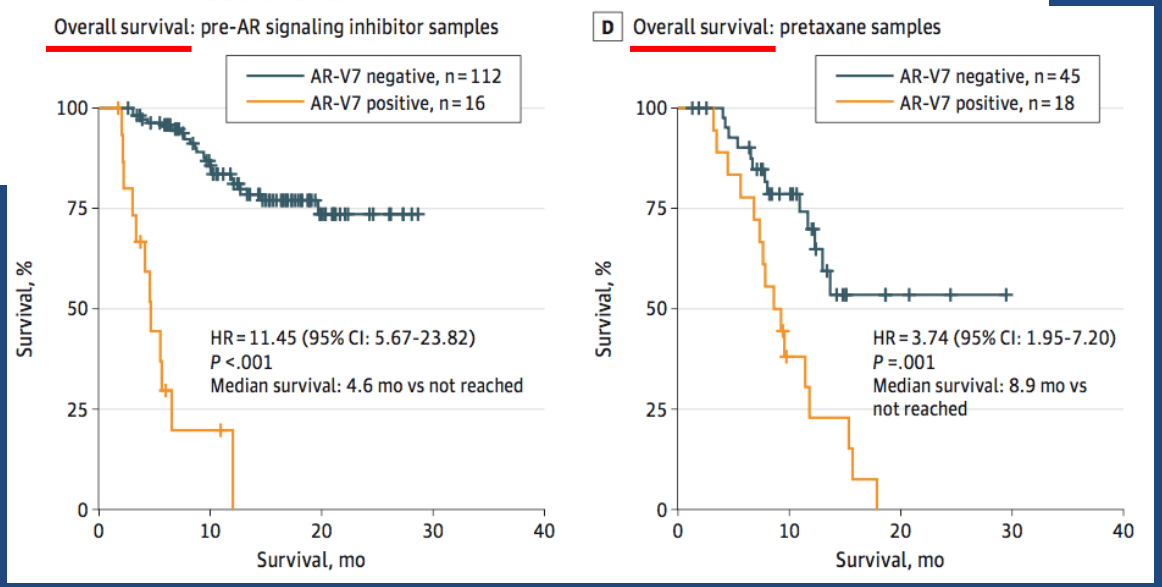
Pt selection (Tax: more hormones, less chemo, less bone, better PS)



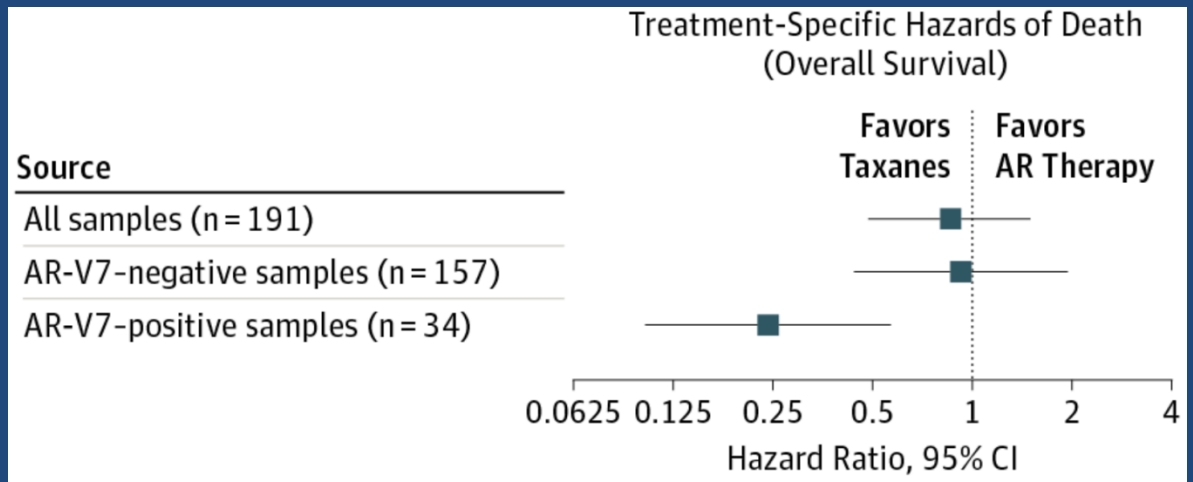
- Προοπτική συλλογή CTC's κατά την αλλαγή θεραπείας
- 161 ασθενείς συνολικά

Scher et.al. *JAMA Oncol*. Published online June 04, 2016





Scher et.al. *JAMA Oncol*. Published online June 04, 2016



AR-V7 Therapy Interaction: Multivariable Cox PH Model		
	Comparison	**Hazard Ratio (95% CI)**
AR-V7 Status and Therapy	AR-V7 positive: Taxane vs AR	0.24 (0.10 to 0.57)
	AR-V7 negative: Taxane vs AR	0.92 (0.44 to 1.95)

Multivariable Cox Proportional Hazard Analysis of Predictors of Overall Survival		
Effect	***P* Value**	**HR (95% CI)**
Line of therapy (3rd or later vs 1st or 2nd)	.16	1.62 (0.83-3.15)
Liver and/or lung metastases pretherapy	.003	2.29 (1.11-4.74)
LDH pretherapy (>250 vs ≤250 U/L)	.006	2.24 (1.26-4.00)
Patient age (>65 vs ≤65 years)	.007	0.48 (0.28-0.83)
Hemoglobin (>12 vs ≤12 g/dL)	.007	0.40 (0.19-0.82)
Therapy (taxane vs AR)	.84	0.86 (0.49-1.50)
AR-V7 status (positive vs negative)	**<.001**	**4.15 (1.76-9.77)**
AR-V7 (positive) taxane interaction	**.035**	**0.24 (0.10-0.57)**

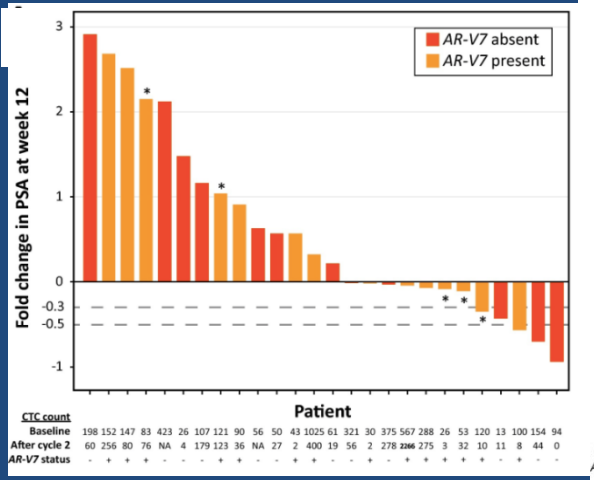
Scher et.al. *JAMA Oncol*. Published online June 04, 2016

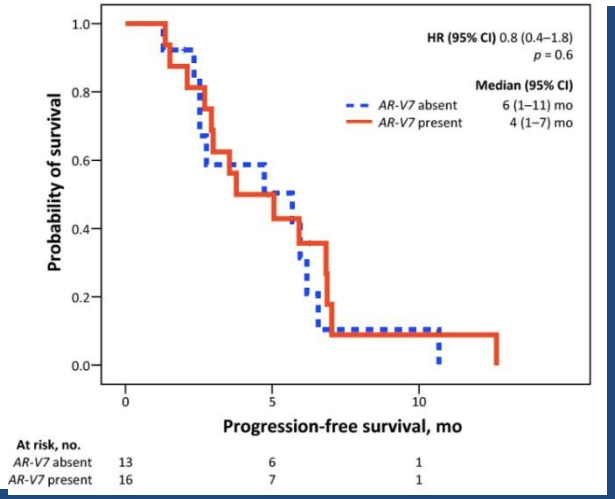
CABAZITAXEL RETAINS ACTIVITY IN AR-V7(+)

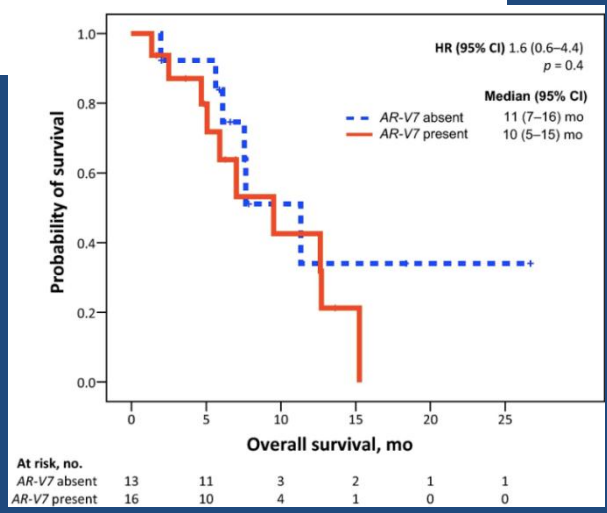
1ης e.P. Η ΣΥΣΧΕΤΙΣΗ ΜΕΤΑΞΥ AR-V7(+) ΚΑΙ ΑΠΑΝΤΗΣΗ ΣΤΟΝ ΑΡΙΘΜΟ ΤΩΝ CTC's

AR-V7	CTC response		PSA response at week 12			Best PSA response		
	No	Yes	No	≥30%*	≥50%	No	≥30%*	≥50%
No	8	2	9	3	2	7	4	2
Yes	12	3	12	2	1	12	3	1
p value	Fisher exact test, $p = 1$		χ^2 test, $p = 0.7$			χ^2 test, $p = 0.6$		

CTC = circulating tumor cells







Onstenk et.al EUROPEAN UROLOGY 68 (2015) 939–945

Sequencing ???

- Retrospective, Small patient numbers
- Lots of missing data
  - **Sites of disease**
  - **Response to prior therapy**
  - **PFS**
  - **OS**
- Limited statistical analyses
- Prospective studies of biomarkers (i.e. mutant AR / AR copy numbers / other putative predictive markers) are needed to confirm help determine appropriate sequencing

TXT POST AR inh

Baseline characteristics and outcome measures	TXT post-Abi[1] (n=86)	TXT post-Abi[2] (n=38)	TXT post-Abi[3] (n=23)	TXT post-Abi[4] (n=23)	TXT post-Abi[5] (n=365)
Median age, years (range)	71(52-85)	71 (46-87)	67		69
ECOG performance status 0-1 ≥2	 91% 9%	 68% 29%	 - -	 - -	
Gleason score ≥8	43%	37%	74%		
PSA (median, ng/mL)	-	-	260		
Metastatic sites, % Bone Lymph node Visceral	 94 23 11	 - - -	 94 23 9	 94 23 9	
Efficacy endpoints ≥50% PSA, % ≥30% PSA, % Median OS, months Median PFS, months Response, %	 26 37 11.6 4.0 9	 8 18 7.2 2.7 8	 48 65 12.4 4.0 -	 40 53 12.4 4.4 -	 40

[1]Mezynski Ann.Oncol.2012;23:2943-7
[2]Azad THE PROSTATE 74:1544-50(2014)
[3] Aggarwal Clin Genitourin Cancer. 2014 Oct;12(5):e167-72
[4] Suzman Prostate. 2014 Sep;74(13):1278-85
[5] FLAIG et al. ASCO 2015 Abstr. 168

CBZ POST TXT + AR inh

Baseline characteristics and outcome measures	Caba post-TXT-abi-enza[1] (n=37)	Caba post-TXT-Abi[2] (n=24)	Caba post-TXT-abi[3] (n=79)	Caba postTXT-Abi (n=65)[4]
Median age, years (range)	62	65	69	
ECOG performance status 0-1 ≥2	 83 11	 - -	 59 38	
PSA (median, ng/mL)	717	128	307	
Metastatic sites % Bone Lymph node Visceral	 86 54 35	 91 66.6 29	 71 - 14	
Efficacy endpoints ≥50% PSA, % ≥30% PSA, % Median OS, months Median PFS, months Response	 41 - 15,8 4,6 15%	 31.5 - 8,4 15.3%	 35 62 10.9 1,1 NR	47 7 24

14,4% ΣΤΗ TROPIC

[1]Pezzaro et.al. EUROPEAN UROLOGY 66 (2014) 459–465
[2] Sella et. al. Clinical Genitourinary Cancer Available online 10 June 2014
[3] Al Nakouzi European Urology 2014 Accepted Aprl21, 2014
[4]. Caffo et.al. J Clin Oncol. 32 (2014) Abstract 5089

SEQUENTIAL TREATMENT OF ABIRATERONE AFTER ENZALUTAMIDE IN MCRPC PATIENTS POST-CHEMOTHERAPY

Baseline characteristics and outcome measures	Abi post-enza[1] (n=30)	Abi post-enza[2] (n=38)	Abi post TXT[3] (n=103)
Median age, years (range)	70 (56-84)	71 (52-84)	67(45-85)
ECOG performance status 0-1 ≥2	 70% 23%	 68% 29%	 **66%** **34%**
Gleason score ≥8	43%	37%	
PSA (median, ng/mL)	-	232	61.7 ng/dl (3-3,000)
Metastatic sites, % Bone Lymph node Visceral	 87 60 30	 97 39 26	 50,5 5,8 43,7
Efficacy endpoints ≥50% PSA, % ≥30% PSA, % Median OS, months Median PFS, months Response, n	 3 11 11.5 3.5 0	 8 18 7.2 2.7 8	 **16,2** **7,06**

≥50% PSA response: 3-8%

Abi=abiraterone; ECOG=Eastern Cooperative Oncology Group; enza=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen. 1.Noonan KL, *et al. Ann Oncol* 2013;24:1802-7; 2. Loriot Y, *et al. Ann Oncol* 2013;24:1807-12. 3.Demicri et.al.J Clin Oncol 32, 2014 (suppl; abstr e16094)

SEQUENTIAL TREATMENT OF ENZALUTAMIDE AFTER ABIRATERONE IN MCRPC PATIENTS POST-CHEMOTHERAPY

Baseline characteristics and outcome measures	Enza post-abi[1] (n=79*)	Enza post-abi[2] (n=26)	Enza post-abi[3] (n=35)	Enza post-abi[4] (n=150†)	Enza post-abi[5] (n=24)	Enza post-abi[6] (n=61)	Enza post-abi[7] (n=23)
Median age, years (range)	74 (55-87)	72 (56-88)	72 (60-83)	70 (44-90)	72 (57-82)	69 (64-74)	70 (57-94)
ECOG performance status							
0-1	-	85%	77%	-	67%	57%	-
≥2	-	-	23%	-	33%	43%	-
PSA (median, ng/mL)	-	-	-	102	578	267	144
Metastatic sites %							
Bone	-	96	100	88	-	79	100
Lymph node	-	73	71	-	-	54	61
Visceral	-	3	17	19	-	21	48
Efficacy endpoints							
≥50% PSA, %	-	27	10	-	-	21	17
≥30% PSA, %	-	54	13	39	46	46	-
Median OS, months	-	-	7.5	-	4.8	7.3	-
Median PFS, months	3.6	4.9	3.1	-	-	2.8	1.4
Response, n	-	-	-	-	-	-	0

*75 post-abiraterone, 62 of whom received abiraterone as last treatment before enzalutamide, †122 patients had prior post-chemotherapy abiraterone and 28 received pre-chemotherapy abiraterone. Abi=abiraterone; ECOG=Eastern Cooperative Oncology Group; Enza=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen.

1. Stevenson R, *et al. J Clin Oncol* 2014;32(Suppl 4): Abstract 125.
2. Vera-Badillo FE, *et al. J Clin Oncol* 2014;32(Suppl 4): Abstract 159.
3. Schmid SC, *et al. Adv Ther* 2014;31:234-41.
6. Badrising S, *et al. Cancer* 2014;120:968-75.
7. Singh Sandhu G, *et al. J Clin Oncol* 2014;32(Suppl 4): Abstract 240.

SEQUENTIAL TREATMENT OF ENZALUTAMIDE AFTER ABIRATERONE IN MCRPC PATIENTS POST-CHEMOTHERAPY

Baseline characteristics and outcome measures	Enza post-abi[1] (n=35)	Enza post-CYP17i[2] (n=20)	Enza post-abi[3] (n=39)	Enza post-abi[4] (n=23)	Enza post-abi[5] (n=24)	Enza post-abi[6] (n=66)
Median age, years (range)	70 (57-81)	76 (64-84)	70 (54-85)	76 (65-82)	72 (57-82)	74.8 (56-94)
ECOG performance status						
0-1	-	-	64.2%	65.2%	66.7%	-
≥2	-	-	35.8%	34.8%	33.3%	-
PSA (median, ng/mL)	-	120	500	-	578	22
Metastatic sites %						
Bone	-	65	84.6	95.6	-	89.4
Lymph node	-	40	53.8	-	-	-
Visceral	-	20	15.3	17.4	-	-
Efficacy endpoints						
≥50% PSA, %	28.6	40	12.8	39	54.2	-
≥30% PSA, %	37.1	-	41.1	-	45.8	29
Median OS, months	7.1	-	Not reached	-	4.8	-
Median PFS, months	4.0	-	2.8	-	-	-
Response, n	1	-	-	-	-	-

≥50% PSA response: 12-54%

Abi=abiraterone; ECOG=Eastern Cooperative Oncology Group; Enza=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen.

1. Schrader AJ, *et al. Eur Urol* 2014;65:30-6.
2. Bournakis E, *et al.* ECC 2013. Poster presentation P413.
3. Bianchini D, *et al. Eur J Cancer* 2014;50:78-84.
4. Thomson D, *et al. J Clin Oncol* 2014;32(Suppl 4): Abstract 188.
5. Thomsen FB, *et al. Scand J Urol* 2013. [Epub ahead of print].
6. Scholz MC, *et al. J Clin Oncol* 2014;32(Suppl 4): Abstract 247.

Μέθοδοι αποφυγής αντίστασης

- Μέθοδοι που δεν στοχεύπουν στο μονοπάτι του AR (CDK4/6 inh) ?
- Πιο ισχυροι αναστολεις του AR ?
- Αναστολεις του AR με διαφορετικο μηχανισμο δρασης ?

Αναπλαστικός Καρκίνος Προστάτου

Φάσμα νόσου με ετερογένεια:

- Ιστολογική (Μικροκυτταρικό, αδενοCa με νευροενδοκρινική διαφοροποίηση, Σαρκωματοειδής, signet ring, πορογενής (Ductal)
- Βιοχημική (Χαμηλό PSA, Υψηλό CEA, ChrA, Bombesin, Calcitonin, ACTH)
- Κλινική (Υπερασβεστιαιμία, **Λυτικές** οστικές , Σπλαχνικές, μεταστάσεις
  Χαμηλό PSA, υψηλό CEA, ChrA, Bombesin, etc
  Χημειοευαίασθητο, απαντά σε Ετοποσίδη/Πλατίνα

αλλά

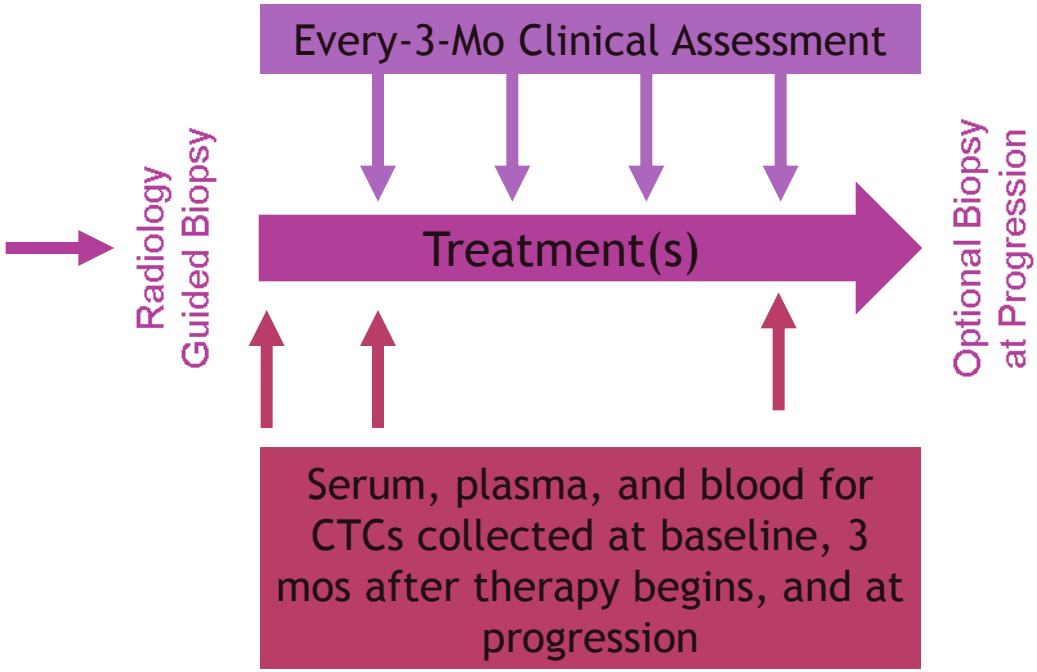
- Μέση επιβίωση < 1 χρόνο

Papandreou CN, et al: JCO 2002 Jul 15;20(14):3072-80, Results of a phase II study with doxorubicin, etoposide, and cisplatin in patients with fully characterized small-cell carcinoma of the prostate

WEST COAST PROSTATE CANCER DREAM TEAM PROJECT AND TRIAL DESIGN

- Ομαδα 6 ακαδημαϊκων ιατρικων κεντρων,
- Σκοπος η ταυτοποιηση προσαρμοστικων μονοπατιων σε ασθενεις με μεταστατικο abiraterone- & enzalutamide-ανθεκτικο καρκινο προστατη

Metastatic CRPC
Amenable to biopsy
Progressive Disease:
- After novel AR targeted rx
- "Aggressive phenotype"
- On a WCDT trial

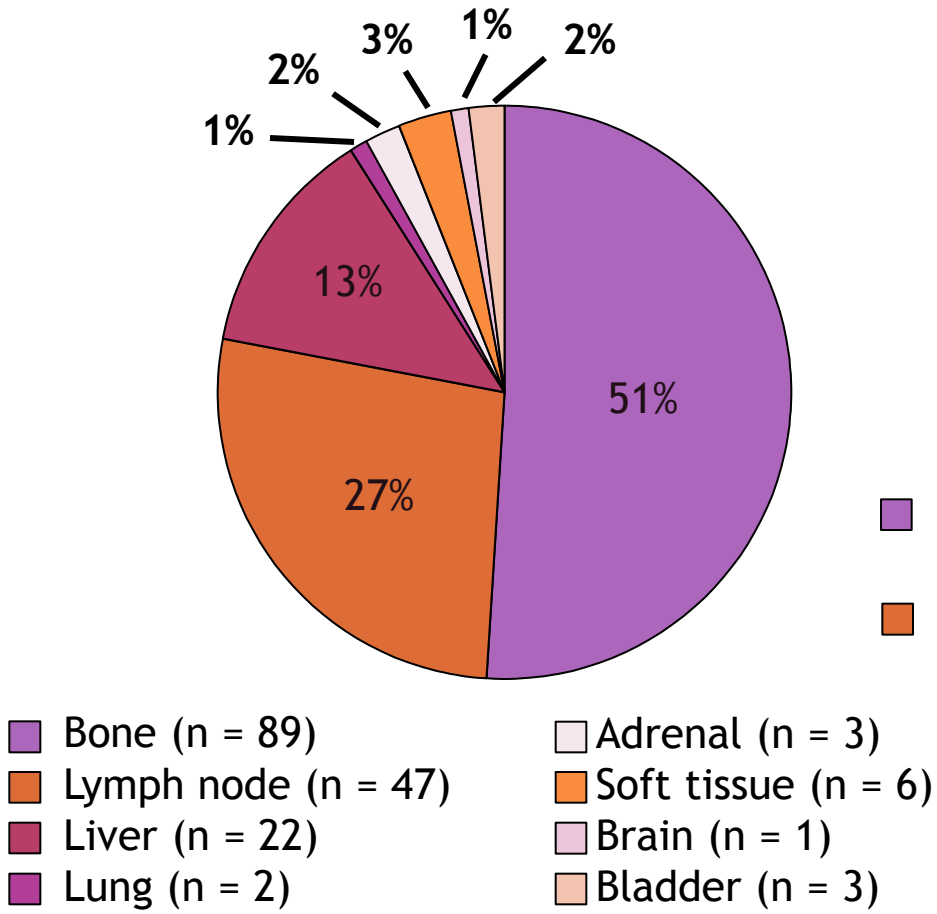


Small EJ, et al. ASCO 2015. Abstract 5003.

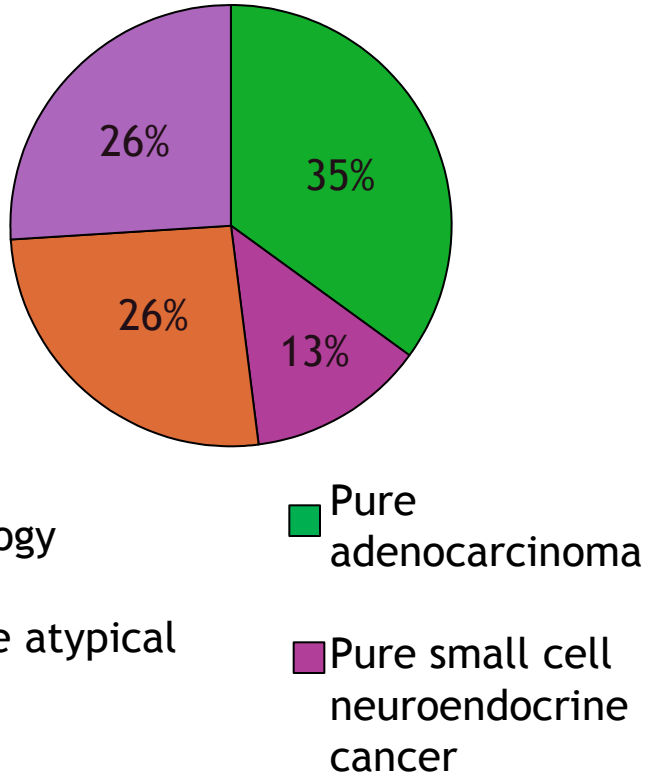
Characteristics	Patients (N = 125)/n (%)
Gleason score at diagnosis	
< 8	53 (42)
≥ 8	72 (58)
Previous treatment for mCRPC	
Abiraterone	54 (40)
Enzalutamide	13 (10)
Both	23 (17)
Neither	45 (33)
Metastatic sites	
Liver	24 (20)
Other visceral	18 (15)
Bone or lymph node only	77 (64)
No. of prior therapies for advanced disease	20 (100)
≤ 1	1 (5)
≥ 2	2 (10)
Unknown	
Median PSA, ng/mL (range)	52 (0.4-2250)
Median ALP, IU/mL (range)	92 (20-1079)
Median LDH, IU/mL (range)	204 (116-856)

Small EJ, et al. ASCO 2015. Abstract 5003.

BIOPSY: HISTOLOGY RESULTS



Histology of 124 Evaluable Biopsies

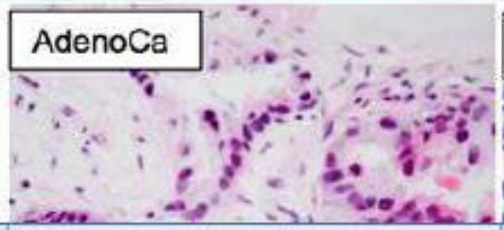
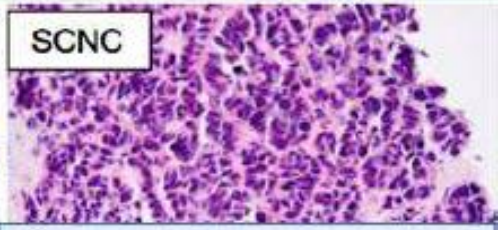


*Novel subtype of pure cell population distinct from adenocarcinoma and small cell neuroendocrine cancer.

Small EJ, et al. ASCO 2015. Abstract 5003.

Intermediate Atypical Carcinoma is a new, highly reproducible pathologic subclass

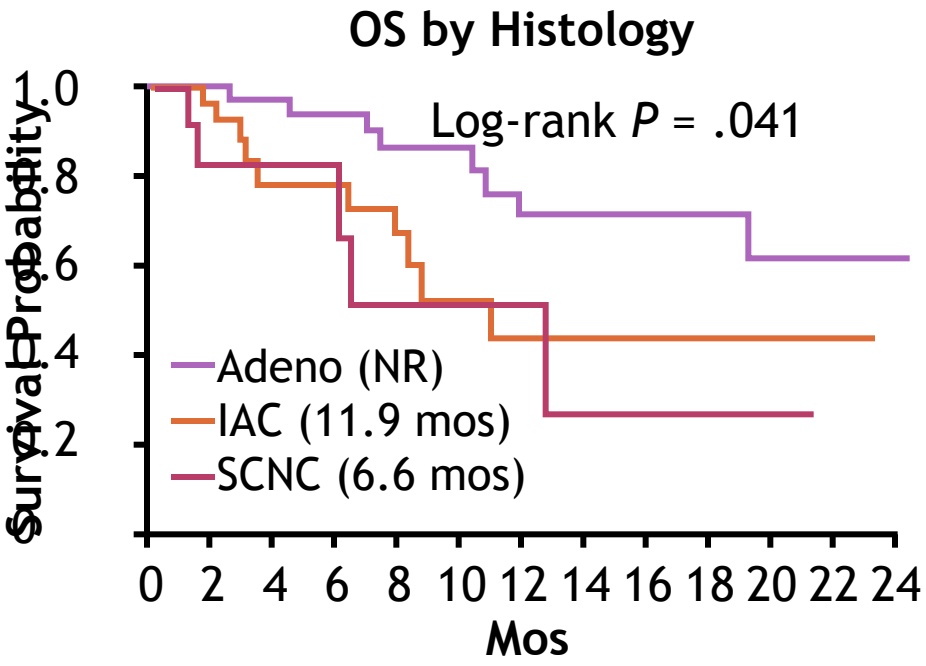
J Huang (UCLA), G Thomas (OHSU), L True (U Wash), B Robinson, M Rubin (Cornell)

Huang Criteria	AdenoCa	Intermediate Atypical Carcinoma	SCNC
	"cytologically bland"			
Cytoplasm	Abundant	Moderate to abundant	Scant
Nuclear chromatin	Clumpy, vacuolated, open chromatin pattern	Fine homogeneous chromatin pattern	Fine homogeneous chromatin pattern
Nuclear staining	Light	Dark ⟺	Dark
Nuclear shape	Some degree of irregularity	Round and regular	Irregular
Nuclear molding	No ⟺	No	Yes
Nucleoli	Prominent macronucleoli	Absent or central small nucleolus	No nucleoli
Crush artifact	No ⟺	No	Yes
Mitotic figures	Rare ⟺	Rare	Common
Glandular formation	Obvious	Vague	No

Small ASCO 2015. Abstract 5003. Reprinted with permission.

INTERMEDIATE ATYPICAL CARCINOMA: PATHOLOGY AND SURVIVAL

- ΝΕΟΣ, ΥΨΗΛΑ ΑΝΑΠΑΡΑΓΩΓΙΜΟΣ ΙΣΤΟΛΟΓΙΚΟΣ ΥΠΟΤΥΠΟΣ
  - Μεταστάσεις σε οστά, LN's και ηπατικό παρέγχυμα
  - Μέτριο έως άφθονο κυτταρόπλασμα, λεπτή ομογενής χρωματίνη, βαθυχρωματικούς πυρήνες, απουσία ή πολύ μικρά πυρήνια, σπάνιους αδενικούς σχηματισμούς, σπάνιες μιτώσεις
  - Παρόμοια επίπεδα δεικτών νευροενδοκρινικής διαφοροποίησης σε IAC & SCNC και υψηλότερα από ότι σε ασθενείς με αδενοκαρκίνωμα
  - Chromogranin A, *P* = .029
  - Neuron-specific enolase, *P* = .001



- Ασθενείς με IAC έχουν πτωχή επιβίωση, παρόμοια με αυτών με SCNC και διαφορετική από αυτούς με ADC (*P* = .041)

INTERMEDIATE ATYPICAL CARCINOMA: GENOMICS

- In genomic signature analysis, IAC appears as a transitional pattern between SCNC and adenocarcinoma
  - Associated with intermediate expression of genes used as markers to differentiate these 2 tissue types
  - In select 50-gene signatures for each histology type, expression of IAC samples fell between SCNC and adenocarcinoma ($P < .001$)

Small EJ, et al. ASCO 2015. Abstract 5003.

original article

Annals of Oncology 20: 703–708,
doi:10.1093/annonc/md
Published online 29 January

Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features

Y. Loriot, C. Massard, M. Gross-Goupil, M. Di Palma, B. Escudier, A. Bossi & K. Fizazi*

Department of Medicine, Institut Gustave Roussy, Villejuif, France

Received 27 May 2008; revised 1 October 2008; accepted 2 October 2008

Background: There is currently no standard treatment for patients with castration-resistant prostate cancer (CRPC) whose disease progresses after docetaxel-based chemotherapy. The purpose of this study was to prospectively assess the anticancer activity and tolerance of the carboplatin–etoposide combination in this setting while evaluating neuroendocrine (NE) features.

Patients and methods: Patients with CRPC and metastases who experienced failure after first-line docetaxel-based chemotherapy were treated with carboplatin (area under the curve 5, day 1) and etoposide (80 mg/m^2/day from days 1 to 3), repeated every 3 weeks. The association between serum chromogranin A (CgA), neuron-specific enolase (NSE), prostate-specific antigen-doubling time (PSADT), and treatment efficacy was studied.

Results: Forty patients with CRPC who had received docetaxel with (n = 20) or without (n = 20) estramustine received the carboplatin–etoposide combination as second-line chemotherapy. A prostate-specific antigen (PSA) response defined as a PSA decline ≥50% was achieved in nine patients (23%). Median progression-free survival (PFS) was 2.1 months (range 0.6–9.6) and median overall survival was 19 months (range 2.1–27.7). Pain response was achieved in 15 (53%) of 28 assessable patients. Toxicity, including mainly grades 3–4 anaemia (25%) and febrile neutropenia in only 2% of patients, was manageable. Baseline CgA, NSE, or PSADT were not significant predictors for response or PFS. The PSA response rates were 18% and 31% in patients with normal and elevated serum CgA, respectively. It was 25% and 20%, respectively, in patients with normal and elevated serum NSE.

Conclusions: Combining carboplatin and etoposide as second-line chemotherapy in patients with CRPC is active and well tolerated in spite of a limited PFS. Activity was observed in CRPC with and without NE features.

Key words: chemotherapy, chromogranin A, neuron-specific enolase, prostate cancer

Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: results of the French Genito-Urinary Tumor Group (GETUG) P01 trial

A. Fléchon[1]*, D. Pouessel[2], C. Ferlay[3], D. Perol[3], P. Beuzeboc[4], G. Gravis[5], F. Joly[6], S. Oudard[7], G. Deplanque[8], S. Zanetta[9], P. Fargeot[9†], F. Priou[10], J. P. Droz[1] & S. Culine[11]

[1]*Department of Medical Oncology, Centre Léon Bérard, Lyon;* [2]*Department of Medical Oncology, Centre Val d'Aurelle, Montpellier;* [3]*Department of Biostatistic, Centr Léon Bérard, Lyon;* [4]*Department of Medical Oncology, Institut Curie, Paris;* [5]*Department of Medical Oncology, Institut Paoli-Calmettes, Marseille;* [6]*Department of Medical Oncology, Centre François Baclesse, Caen;* [7]*Department of Medical Oncology, Hôpital Européen Georges Pompidou, Paris;* [8]*Department of Medical Oncology, Fondation Hôpital Saint Joseph, Paris;* [9]*Department of Medical Oncology, Centre G.F. Leclerc, Dijon;* [10]*Department of Medical Oncology, CHD Les Oudairies, La Roche Sur Yon;* [11]*Department of Medical Oncology, Hôpital Henri Mondor, Créteil, France*

Received 8 November 2010; revised 20 December 2010; accepted 30 December 2010

Background: In the evolution of metastatic castration-resistant prostate cancer (mCRPC), patients present visceral metastases with or without neuroendocrine differentiation in 20% of cases.

Patients and methods: We assessed the efficacy and toxicity of a platinum-based chemotherapy regimen in mCRPC patients with either neuroendocrine differentiation defined by high serum levels of chromogranin A (CgA) and neuron-specific enolase (NSE) or visceral metastases. Patients received the combination of carboplatin and etoposide every 3 weeks. Efficacy end points included prostate-specific antigen (PSA) and neuroendocrine marker response, objective response and toxicity.

Results: Of the 60 patients included from April 2005 to January 2008, 78.6% had bone metastases, 46.4% had lymph node involvement and 57.1% had liver and/or lung localizations. The objective response rate was 8.9% in the 46 patients with measurable disease. A neuroendocrine response was observed in 31% of cases for NSE and 7% for CgA. The PSA response rate was 8%. The most common grade 3–4 treatment-related toxic effects were neutropenia (65.5%), thrombocytopenia (32.7%) and anemia (27.3%). There was 7.2% febrile neutropenia, with one toxicity-related death. The median follow-up was 9.3 months [95% confidence interval (CI) 0.2–27.1] and the median overall survival 9.6 months (95% CI 8.7–12.7).

Conclusion: The benefit–risk ratio of this regimen seems unfavorable due to poor response and high toxicity.

Key words: chemotherapy, chromogranin A, metastatic castration-resistant prostate cancer, neuron-specific enolase, visceral metastases

Take home messages 2016 - 1

WORK IN GROUPS: UROLOGISTS, PATHOLOGISTS, RADIOTHERAPISTS, MED. ONCOLOGISTS

HSPCa

Men with high risk metastatic prostate cancer, especially those presenting with metastases or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT

Men with localized M0 prostate cancer who are to receive local treatment with radiotherapy should NOT be offered Docetaxel in addition to ADT

CRPCa

Chemo in symptomatic mCRPCa or in pts with visceral metastases

Cross-resistance between AR targeting drugs

Cabazitaxel retains activity after AR targeting agents

Take home messages 2016 - 2

CRPCa

Ideal treatment sequence not known.

Resistance mechanisms and biomarkers, if elucidated better, could provide insight into treatment selection

Upon clinical suspicion of anaplastic/ NePCa

Short response (<1 year) to 1st-line ADT, Lack of undetectable PSA with 1st ADT
High Gleason score (8-10), Short PSA doubling time (< 4-6 mo)
Visceral metastases, Predominantly **lytic** bone mets
Disproportionally low PSA to tumor burden, Presence of B symptoms
discuss it with a medical oncologist and discuss it early …

SCPCa and "anaplastic" "IAC" share neuroendocrine pathways and their reliance on AR is little if any – treatments aiming at AR are not efficacious

Ευχαριστώ πολύ