Systemisk behandling av prostatakreft

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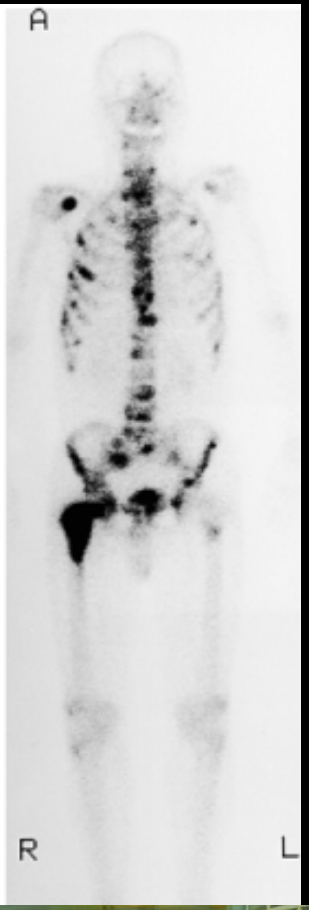
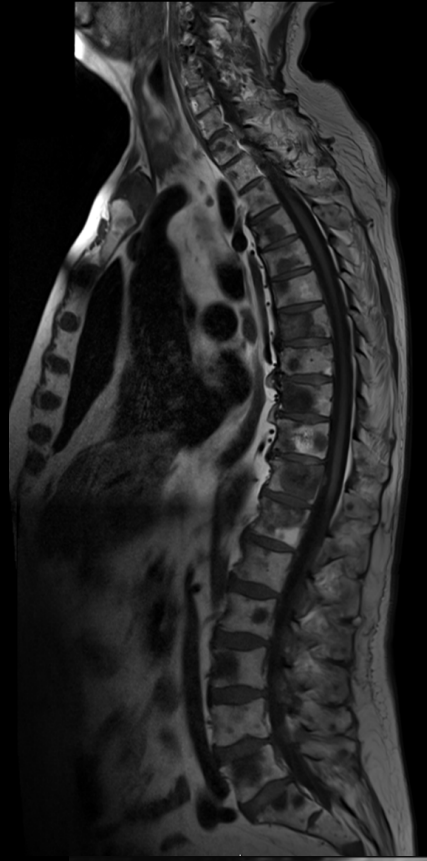
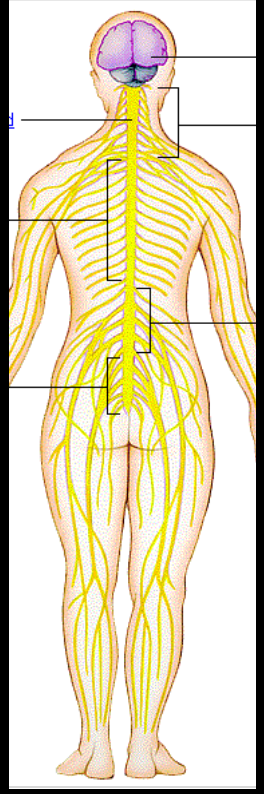
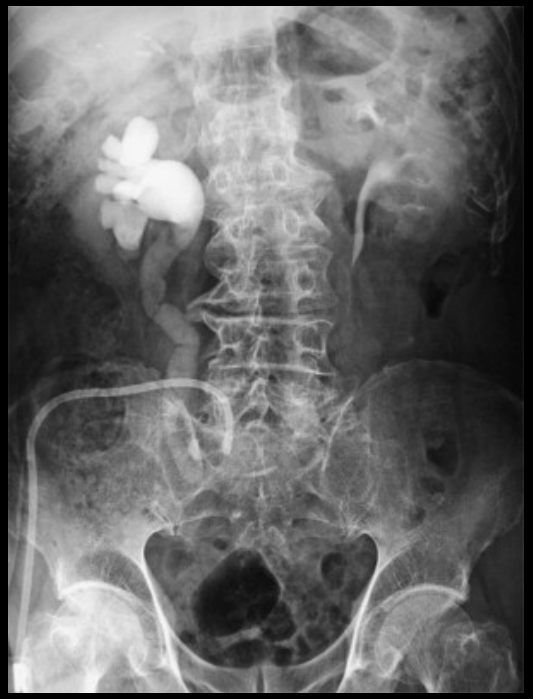
Bindinger

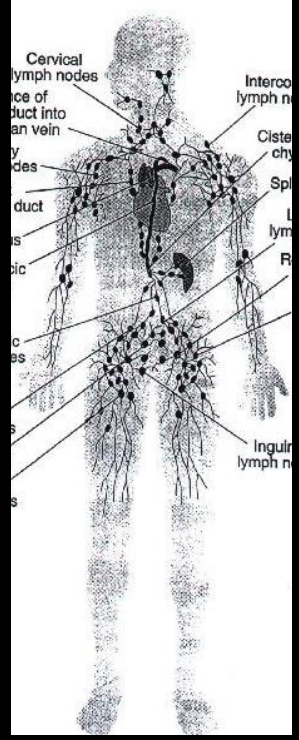
- ”Advisory boards”
  - Bayer, Astellas
- Foredragshonorar
  - Amgen, Astellas, Dagens Medisin, Bayer
- Oppdragsforskning
  - Astellas, Abbvie
- Forfatterhonorar
  - Novartis

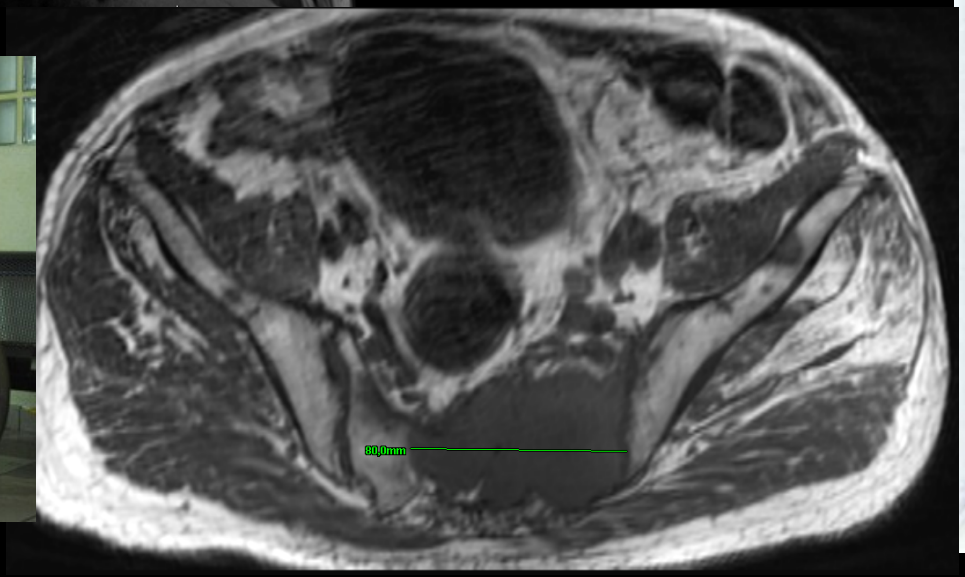


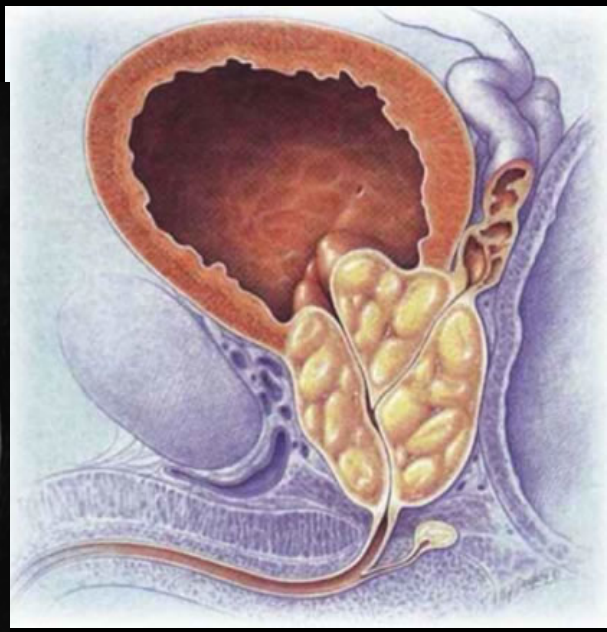




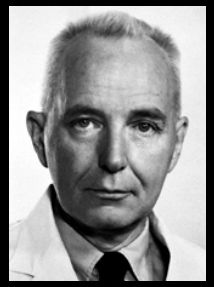








Arne Berg 2016



Charles Huggins
1901-77

Forløp ved metastatisk prostatakreft

Diagnose

8% primærmetastatiske 2010-14

Sykdomskontroll med kastrasjonsbehandling

≈90% respons
Responsvarighet 0 - >20 år
Omlin. Eur Urol 2013

”Gamle”antiandrogener
Lavdose steroider

Kastrasjonsresistens

Asymptomatisk PSA-stigning/ Radiologisk progresjon

Symptomer

Zometa
Xgeva

Død

Taxotere induksjon

Gravis Lancet 2013 , ASCO GU 2015
Sweeney NEJM 2015
James ASCO 2015

Taxotere Tannock NEJM 2004. Petrylak NEJM 2004. Fosså Eur Urol 2007. Kellokumpu-Lehtinen Lancet 2013

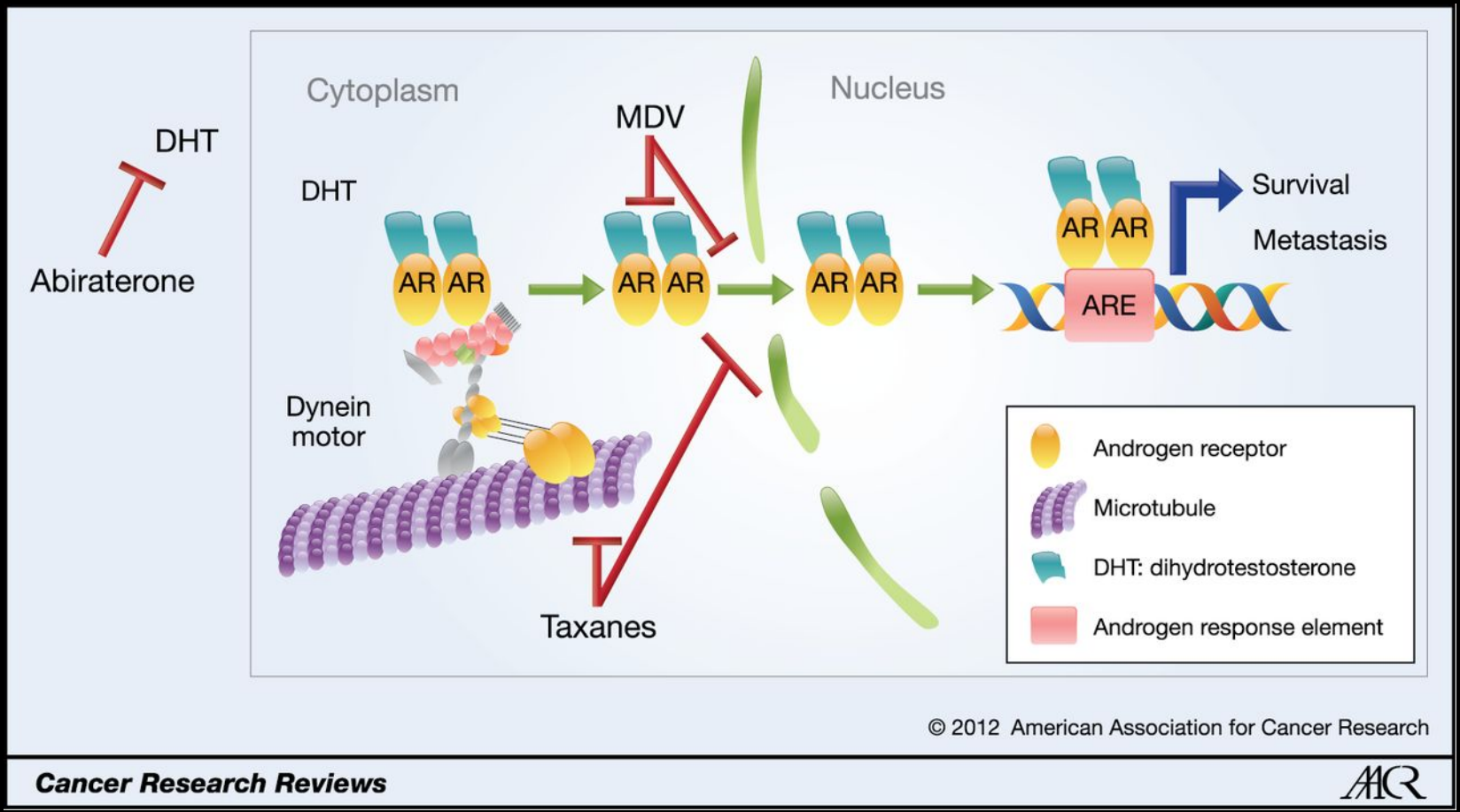
Jevtana De Bono Lancet 2010

Zytiga De Bono NEJM 2011. Fizazi Lancet Oncol 2012. Ryan NEJM 2012. Ryan Lancet 2015

Xtandi Scher NEJM 2012. Beer NEJM 2014

Xofigo Parker NEJM 2013

Provenge Kantoff NEJM 2010

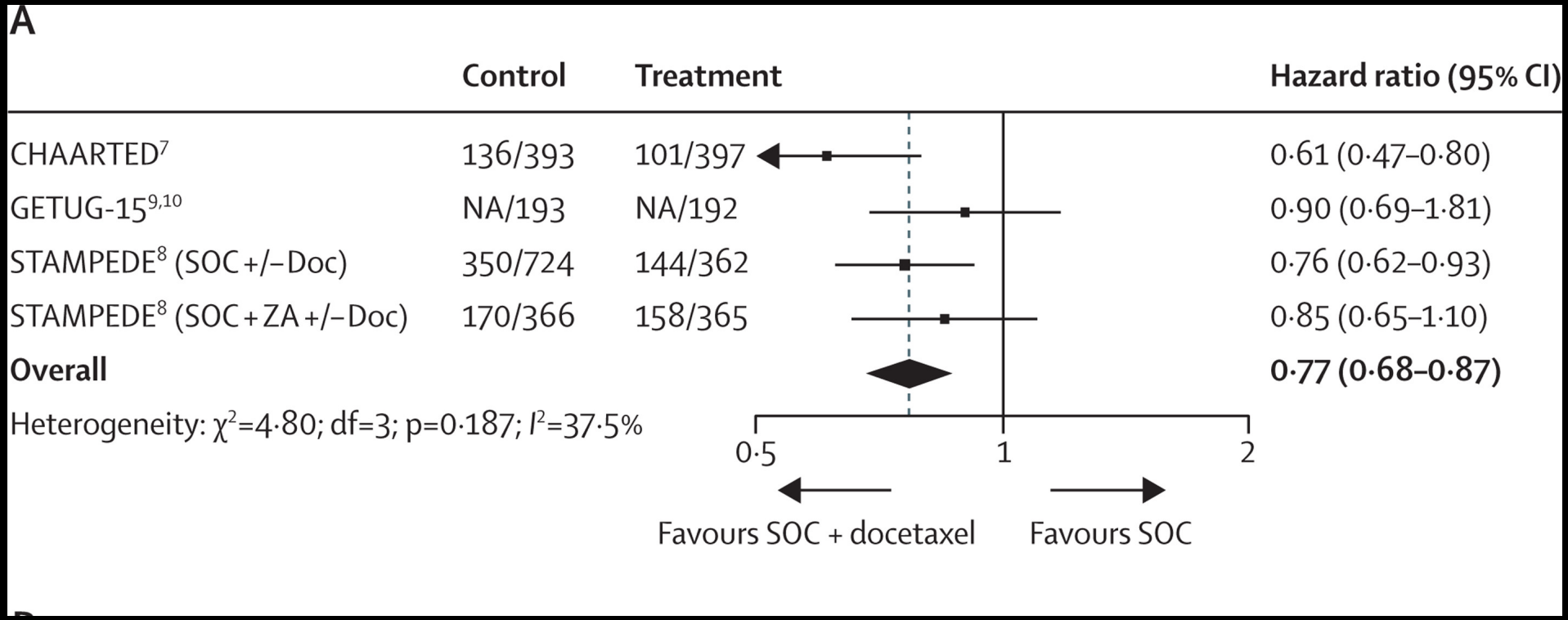


”Nye” behandlingsmuligheter som gir livsforlengelse og symptomkontroll

- Induksjonskjemoterapi ved metastatisk hormonsensivit prostatakreft
- Sekvensiell behandling ved metastatisk kastrasjonsresistent prostatakreft
  - Aktiv behandling ved asymptomatisk progresjon av mCRPC
  - Livsforlengende behandling for pasienter som ikke tåler kjemoterapi
    - Xtandi, Zytiga, Xofigo

Induksjonskjemoterapi ved metastatisk prostatakreft

Metaanalyse Overall Survival

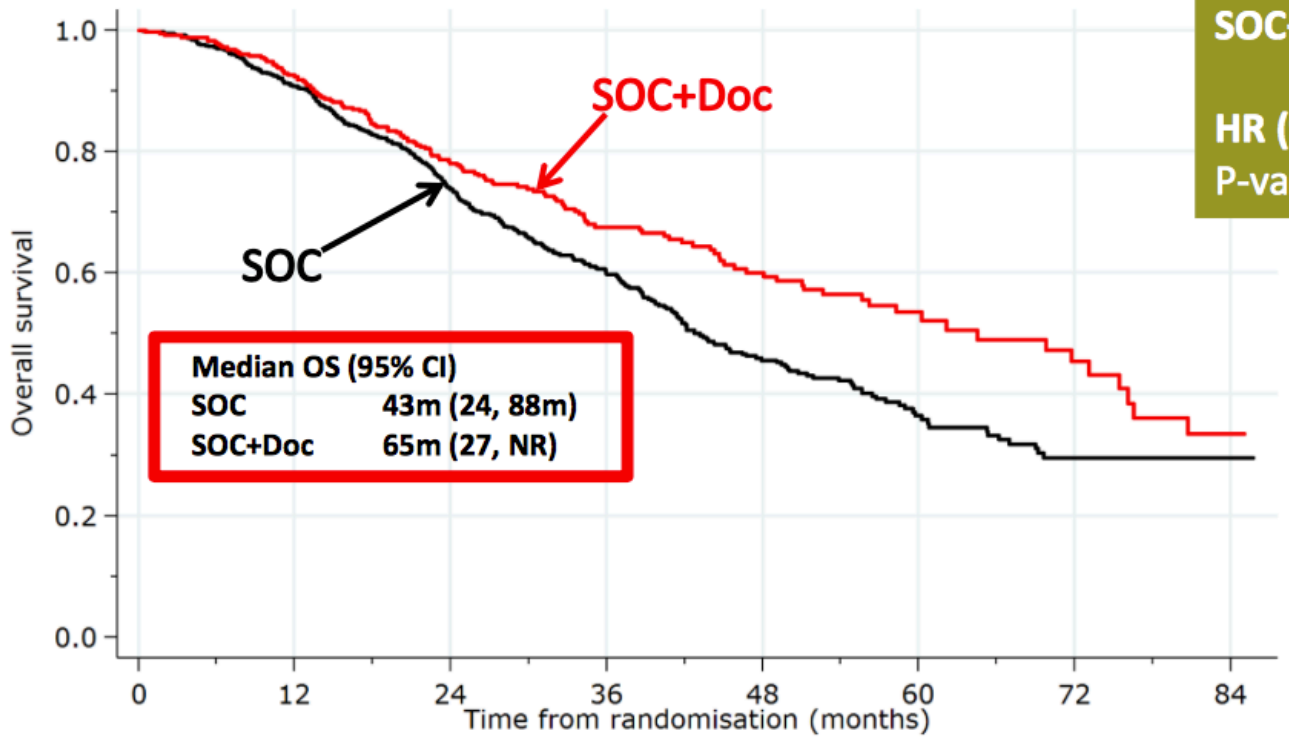


Vale. Lancet oncol 2015

STAMPEDE:

6 kurer docetaxel med prednisolon

Docetaxel: Survival – M1 Patients



Group														
At risk (events)														
SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC+Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

SOC	**343 deaths**
SOC+Doc	**134 deaths**
HR (95%CI)	**0.73** (0.59, 0.89)
P-value	**0.002**

Non-PH p-value 0.23

Restricted mean OS time

SOC	49.3m
SOC+Doc	56.1m
Diff (95%CI)	6.8m (2.8, 11.0m)

James. ASCO 2015. Abstract 5001

How similar are the men participating in these studies?

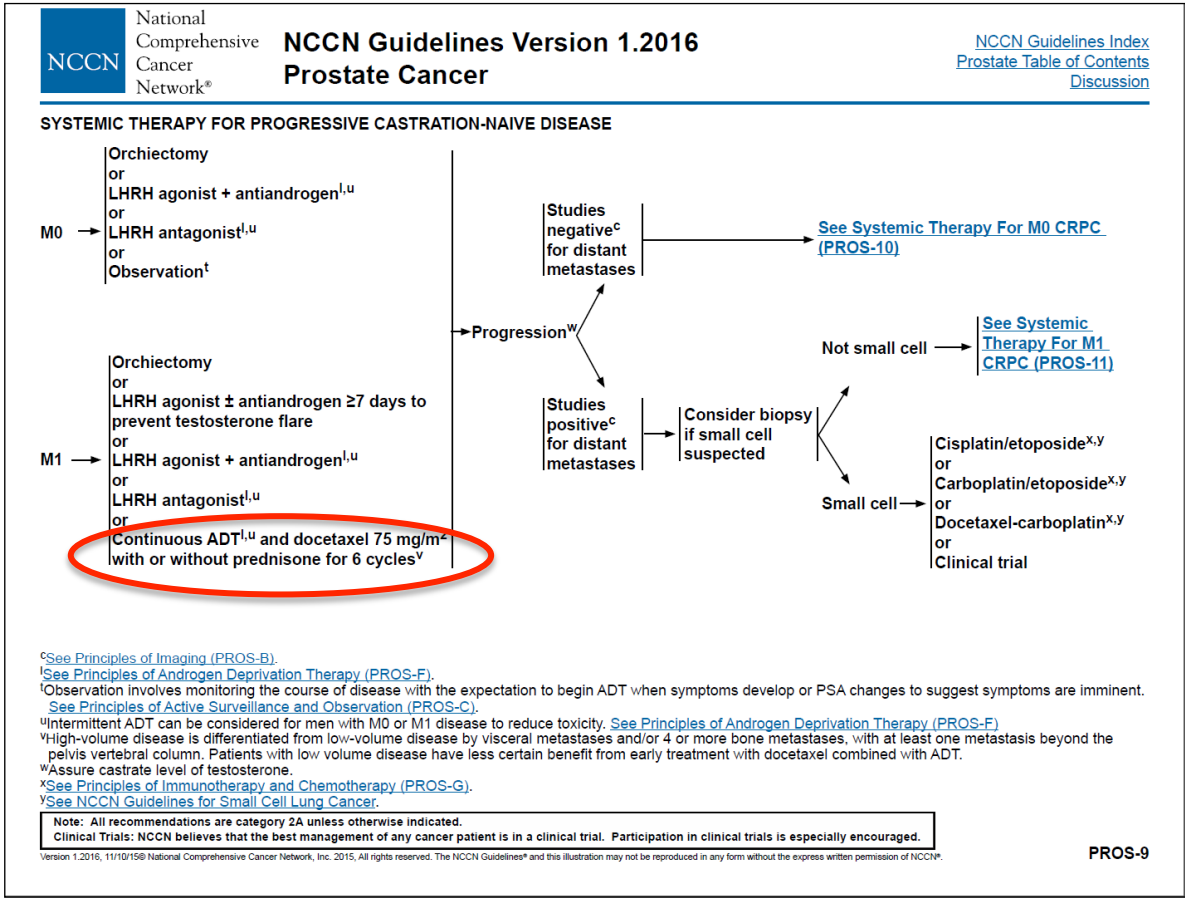
	Median age	% with mets at presentation	% high risk*
GETUG-15	64	71%	52%
CHAARTED	63	75%	65%
STAMPEDE	65	Most of them	Unknown

*high-volume" disease was defined as visceral metastases and/or ≥4 bone metastases with at least one metastasis beyond the pelvis or vertebral column.

These trials do NOT represent men with slowly progressive disease who develop metastases several years after diagnosis (+/- local treatment)

Tannock. ASCO 2015

GUIDELINES



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Prostate Cancer

NCCN Guidelines Index
Prostate Table of Contents
Discussion

SYSTEMIC THERAPY FOR PROGRESSIVE CASTRATION-NAIVE DISEASE

M0 → Orchiectomy or LHRH agonist + antiandrogen[l,u] or LHRH antagonist[l,u] or Observation[t]

M1 → Orchiectomy or LHRH agonist ± antiandrogen ≥7 days to prevent testosterone flare or LHRH agonist + antiandrogen[l,u] or LHRH antagonist[l,u] or Continuous ADT[l,u] and docetaxel 75 mg/m²[v] with or without prednisone for 6 cycles[v]

→ Progression[w]

Studies negative[c] for distant metastases → See Systemic Therapy For M0 CRPC (PROS-10)

Studies positive[c] for distant metastases → Consider biopsy if small cell suspected

Not small cell → See Systemic Therapy For M1 CRPC (PROS-11)

Small cell → Cisplatin/etoposide[x,y] or Carboplatin/etoposide[x,y] or Docetaxel-carboplatin[x,y] or Clinical trial

[c] See Principles of Imaging (PROS-B).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[t] Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[u] Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F)
[v] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
[w] Assure castrate level of testosterone.
[x] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[y] See NCCN Guidelines for Small Cell Lung Cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PROS-9

ESMO:

-"ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naive disease in men fit enough for chemotherapy." Annals of Oncology 2015.

EAU: ikke oppdatert pr. 030216

Norsk handlingsprogram: ikke oppdatert pr. 030216

Metastatisk kastrasjonsresistent prostatakreft

Mulighet for lokal kontroll?

69 åring henvist med PSA-stigning etter 4 år AD

- Diagnose 2010
  - T3BN1(CT; lymfeknutekonglomerat a. iliaca externa) M0
  - GS 4+4. PSA 39
  - LHRH-analog
- Nå PET-CT: Kun opptak i prostata og kjent lymfeknute
- RT 64Gy mot prostata og lymfeknute; 50Gy mot bekkenfelt. *Uendret endokrinbehandling*
- PSA-kontroll et år etter RT

Overlevelse ved metastatisk kastrasjonsresistent prostatakreft

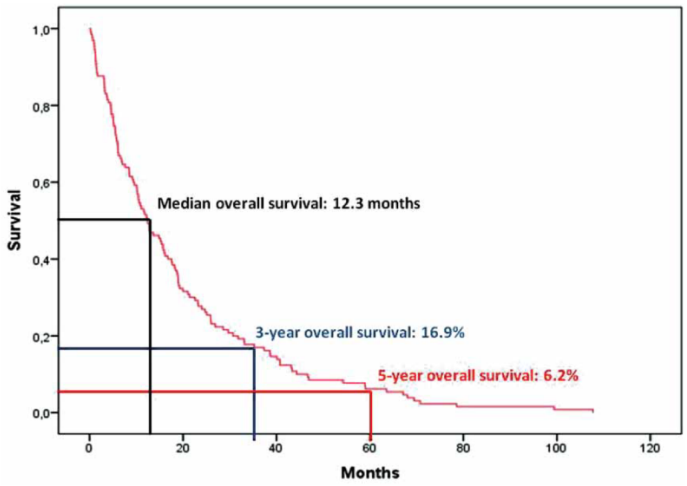


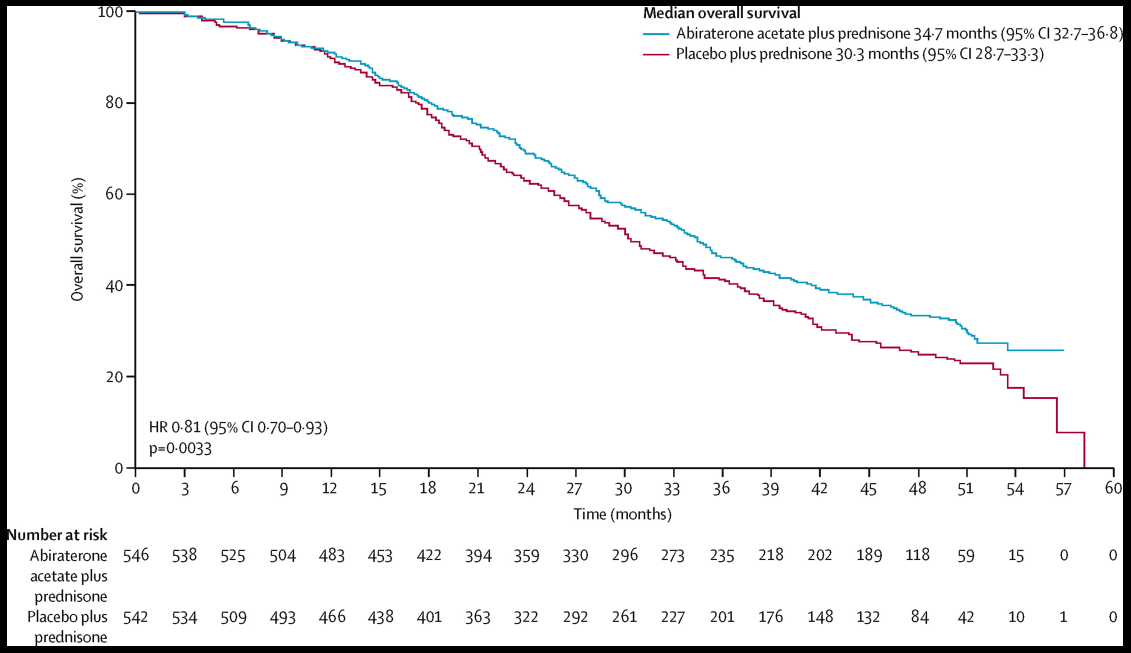
Figure 1. Kaplan–Meier curve showing median, 3 and 5 year overall survival of patients with metastatic castrate-resistant prostate cancer.

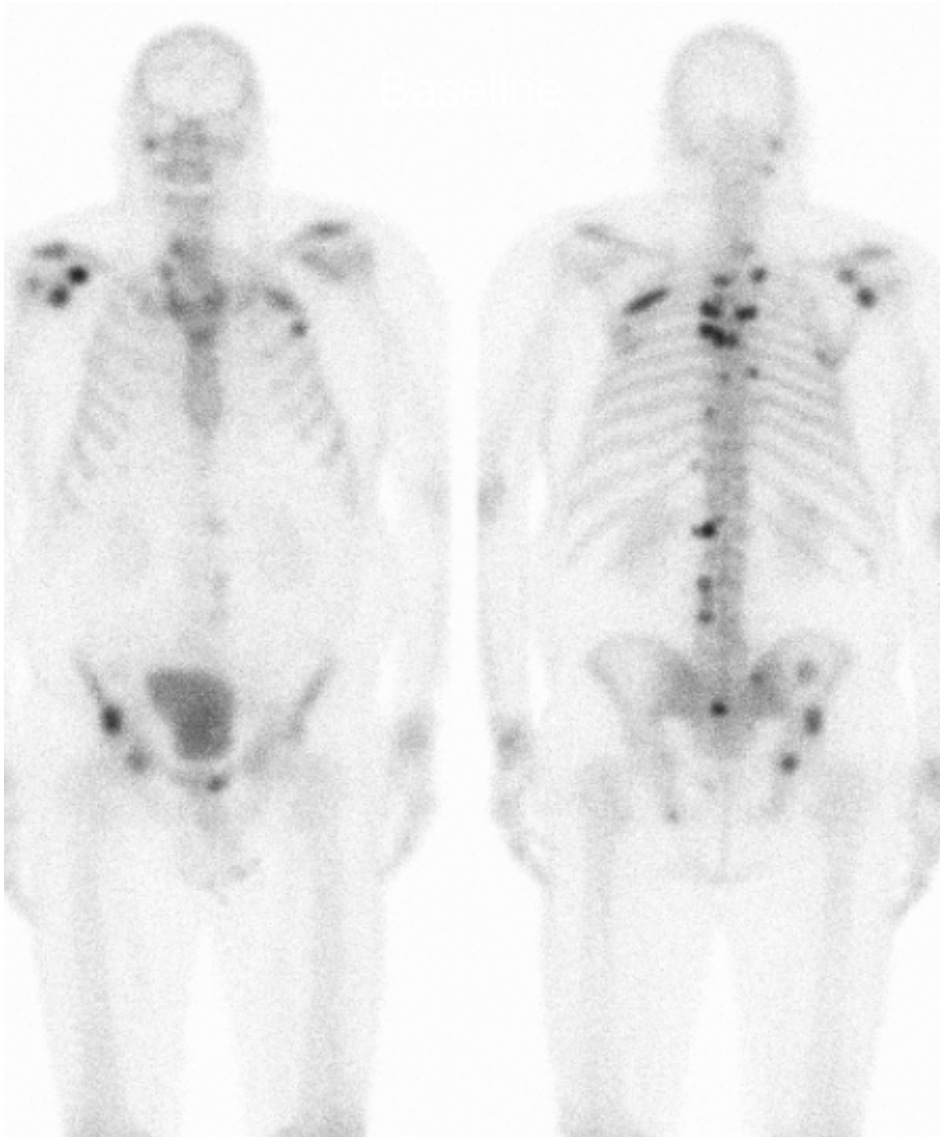
Uselektert matierale uten livsforlengende behandling:
-Median OS 12.3 mnd

Löffeler. Scand J Urol 2015

Selektert matierale med tidlig sekundær endokrinterapi og mulighet for sekvensiell livsforlengende behandling:
-Median OS 30.3-34.7 mnd

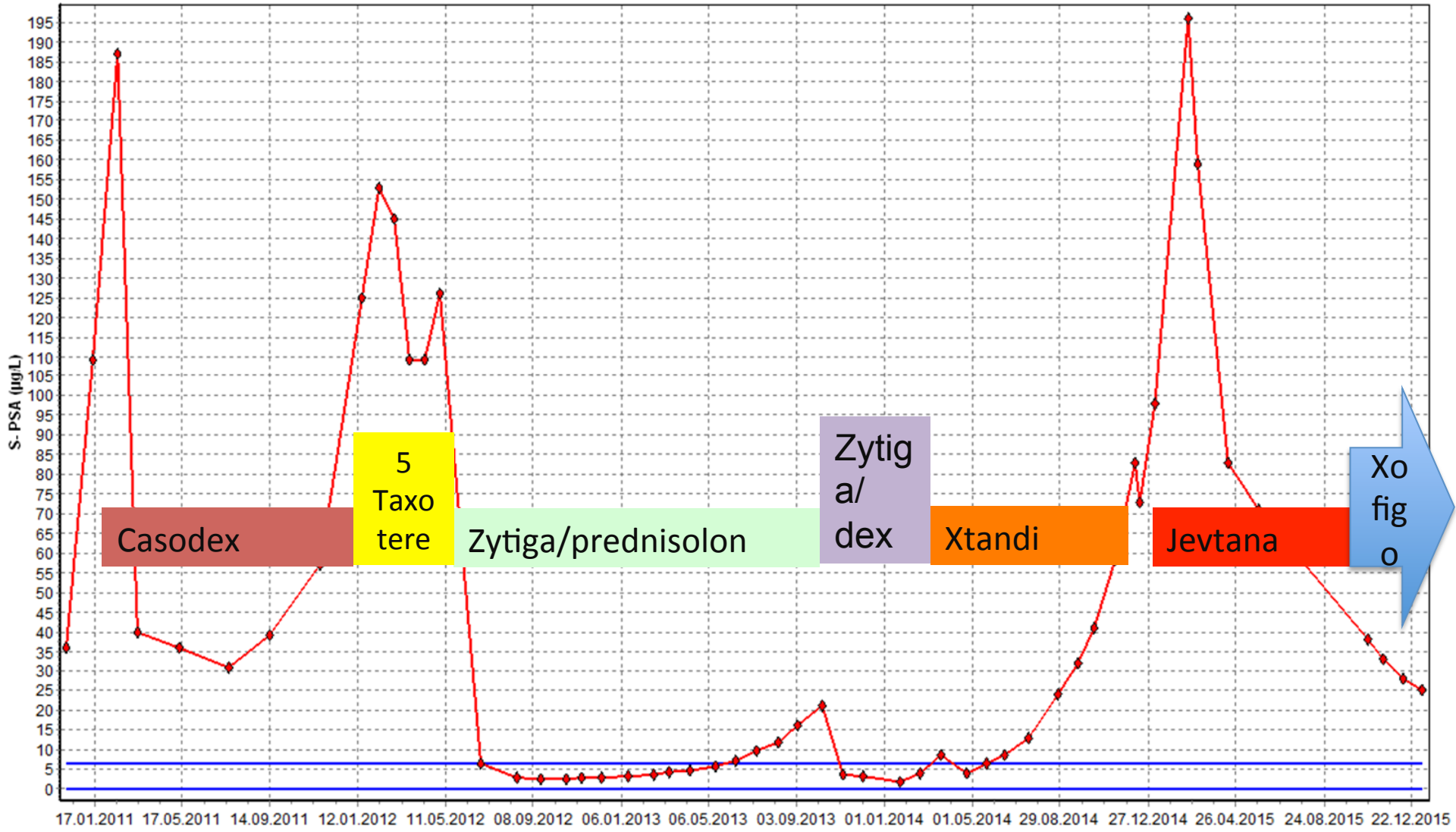
Ryan. Lancet 2015





Mann født 37
CaP 2008
Skjelettmetastaser
ved diagnose

Slide fra Wenche Gustafson



Enanton fra 2008

Smerter ved mCRPC i 2011, deretter smertefri med godt funksjonsnivå

Slide fra Wenche Gustafson

Før:

Vanlig å avvente utvidet systembehandling til symptomgivende progresjon eller forventning om snarlig symptomutvikling

Nå

- 2 studier (COU-302 og Prevail) gir meget godt grunnlag for å anbefale optimalisert endokrin behandling ved asymptomatisk progresjon av kastrasjonsresistent metastatisk cancer prostata
  - Øket overlevelse
  - Forlenget tid til funksjonstap
  - Forlenget tid til opiatkrevende smerter
  - Forlenget tid til behandling med kjemoterapi
- Provenge (ikke tilgjengelig i Norge)

Det vi ikke vet…..

….om tidlig kjemoterapi ved asymptomatisk progresjon gir tilsvarende eller bedre effekt på overlevelse og utsettelse av symptomgivende progresjon….

Final data COU-AA-302. Median follow-up 49.2mnd

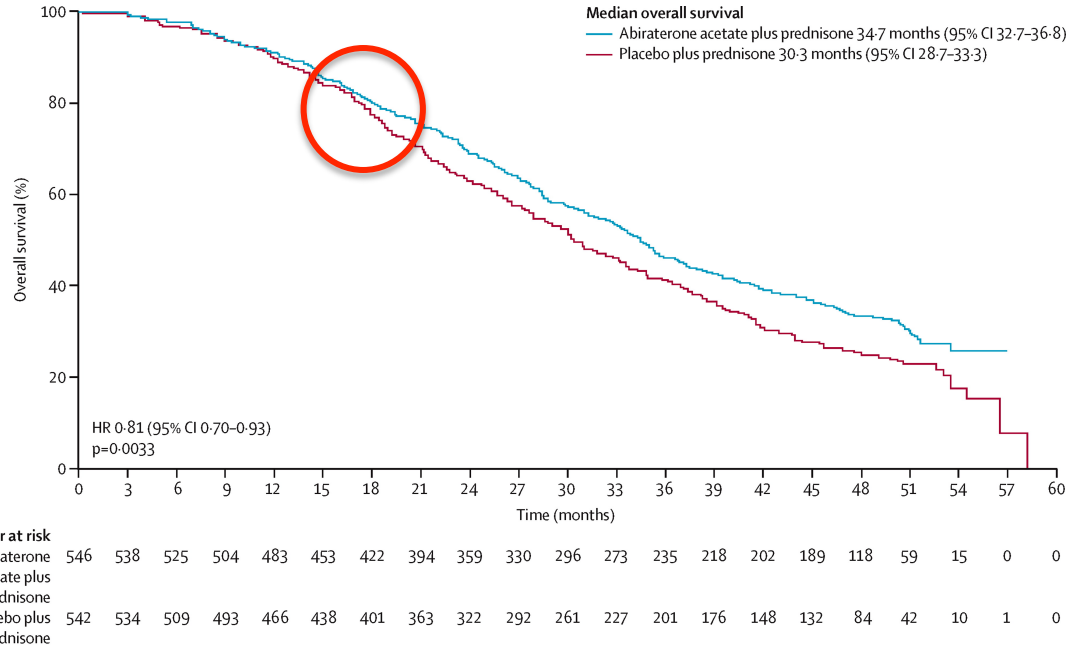


Table 1
Subsequent therapy for prostate cancer

	Abiraterone acetate group (n=546)	Placebo group (n=542)
Patients with subsequent therapy	365 (67%)	435 (80%)
Abiraterone acetate	69 (13%)	238 (44%)
Cabazitaxel	100 (18%)	105 (19%)
Docetaxel	311 (57%)	331 (61%)
Enzalutamide	87 (16%)	54 (10%)
Ketoconazole	42 (8%)	68 (13%)
Radium-223	20 (4%)	7 (1%)
Sipuleucel-T	45 (8%)	32 (6%)

Data are n (%).

Median behandlingsvarighet:
Abi/pred: 13.8mnd (IQR 8.3-27.4)
Plac/pred: 8.3mnd (IQR 3.8-16.6)

Ryan. Lancet 2015

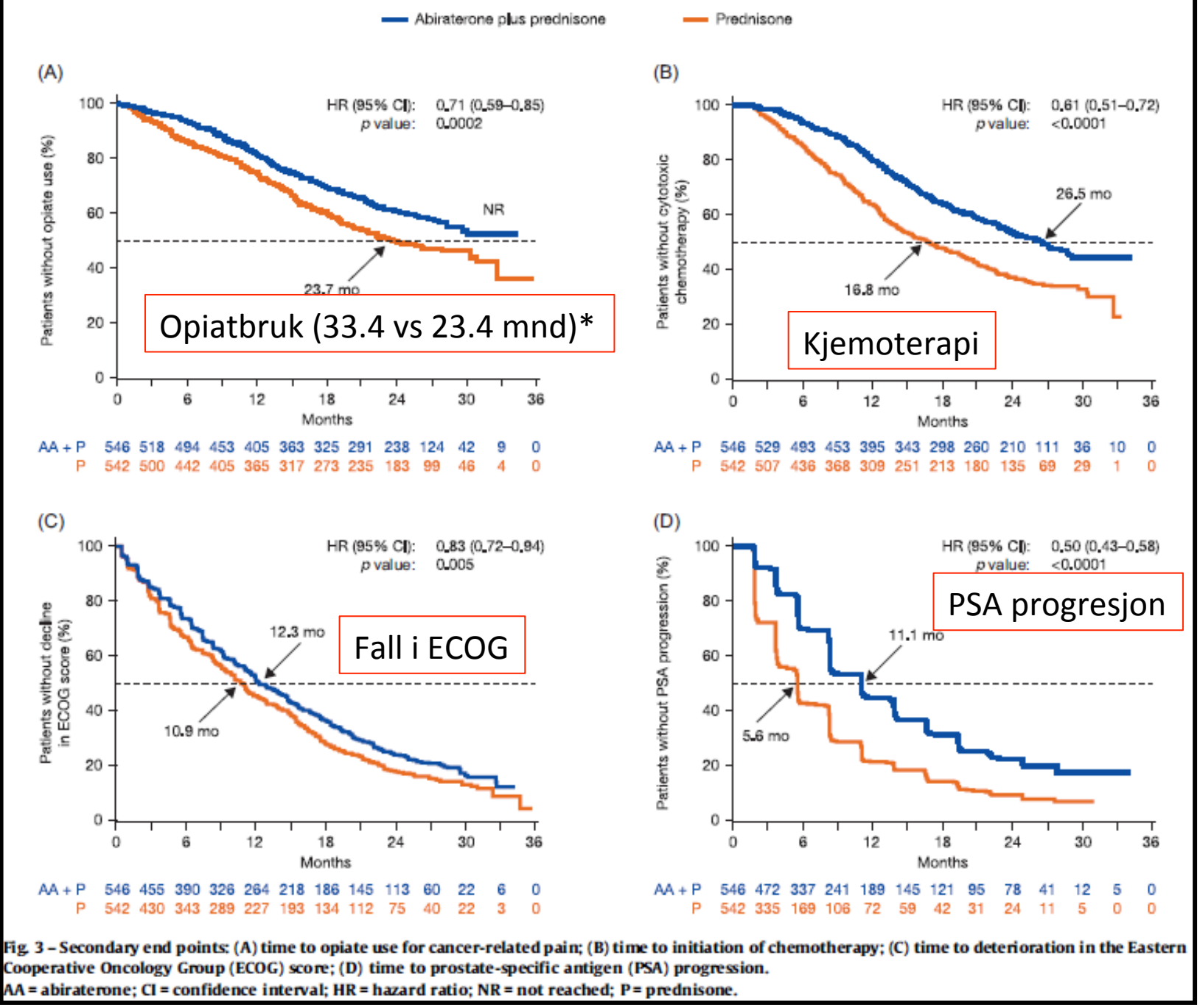


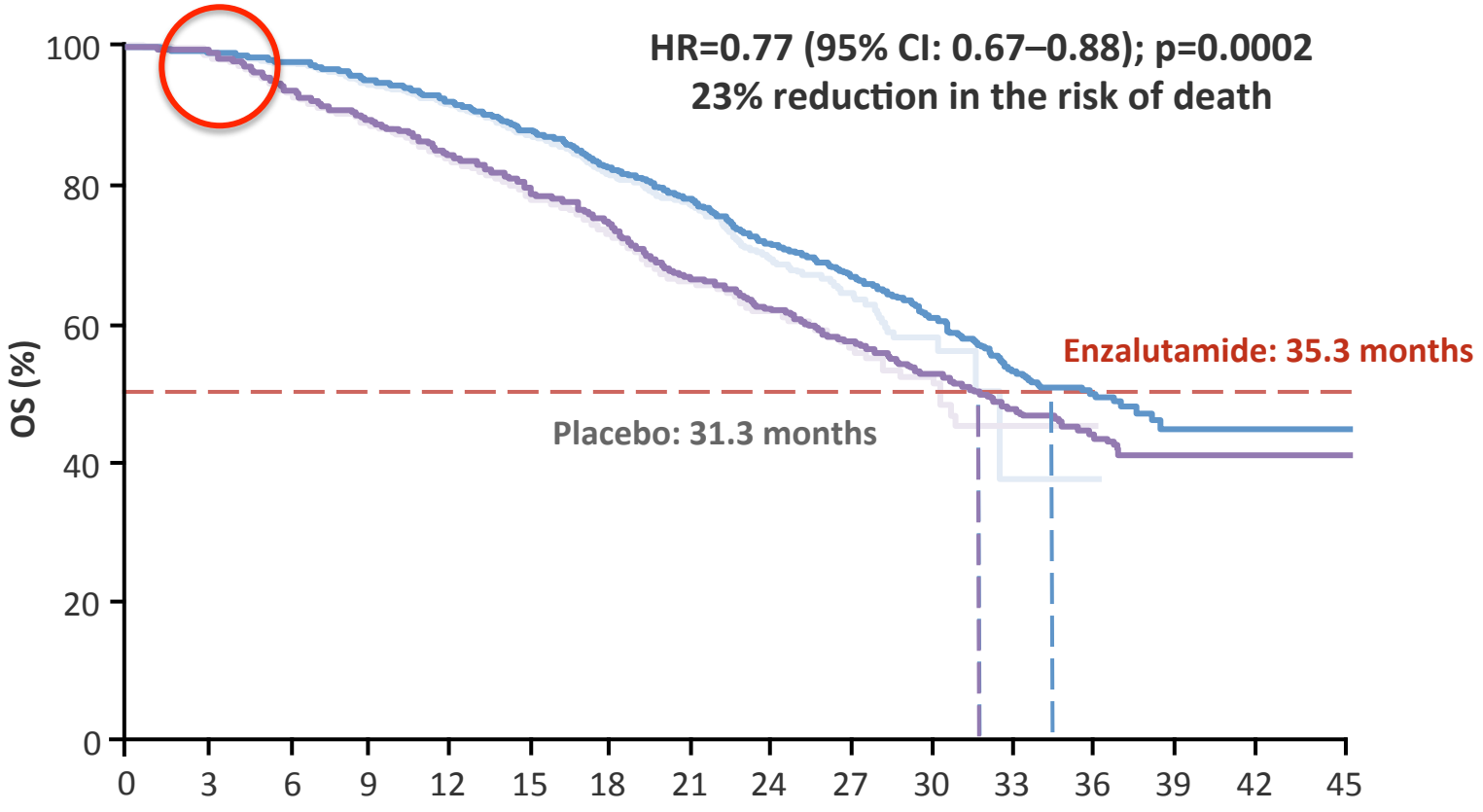
Fig. 3 – Secondary end points: (A) time to opiate use for cancer-related pain; (B) time to initiation of chemotherapy; (C) time to deterioration in the Eastern Cooperative Oncology Group (ECOG) score; (D) time to prostate-specific antigen (PSA) progression.
AA = abiraterone; CI = confidence interval; HR = hazard ratio; NR = not reached; P = prednisone.

*Ryan Lancet 2015

Rathkopf. Eur Urol 2014

Final OS Prevail

(31 mnd median oppfølging, 20% crossover i placebogruppen)



Interim analysis																
Enzalutamide. n	872	863	850	824	797	745	566	395	244	128	33	2				
Placebo, n	845	835	781	744	701	644	484	328	213	102	27	2				
Final analysis																
Enzalutamide, n	872	863	850	824	798	758	710	665	597	441	289	174	86	21	2	0
Placebo, n	845	835	782	745	702	657	612	551	504	365	254	153	72	16	2	0

*Data cut-off date: 1 June 2014

CI=confidence interval; HR=hazard ratio; OS=overall survival.

Tombal B *et al*. EAU 2015; Oral presentation. LBA2.

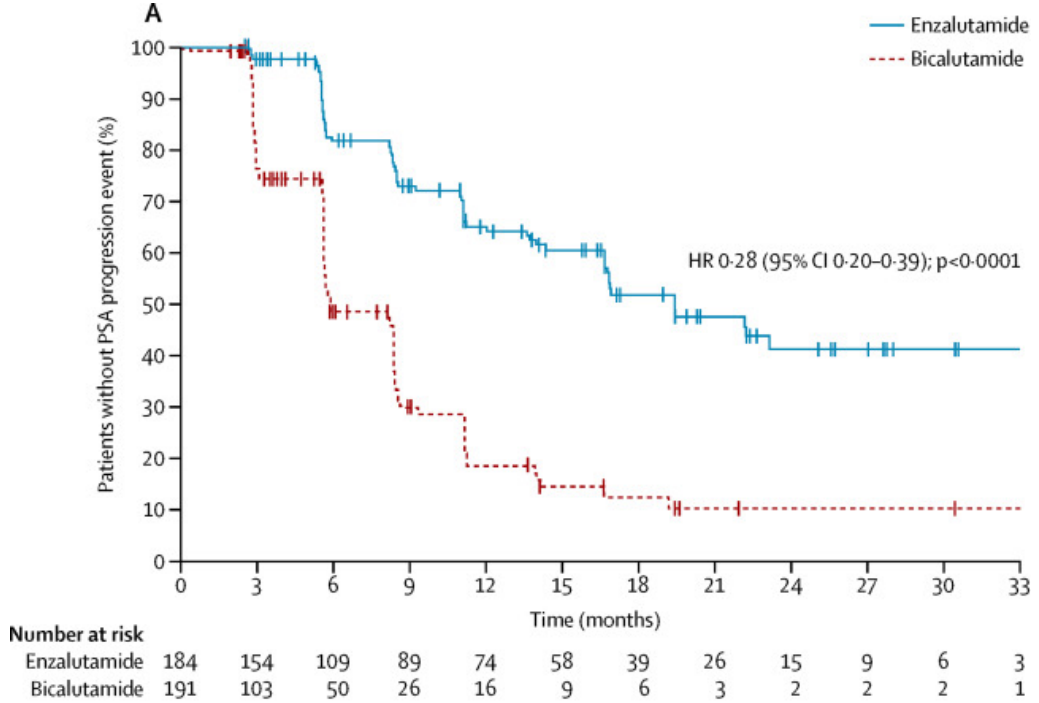
Table 1. Secondary and Prespecified Exploratory End Points.*

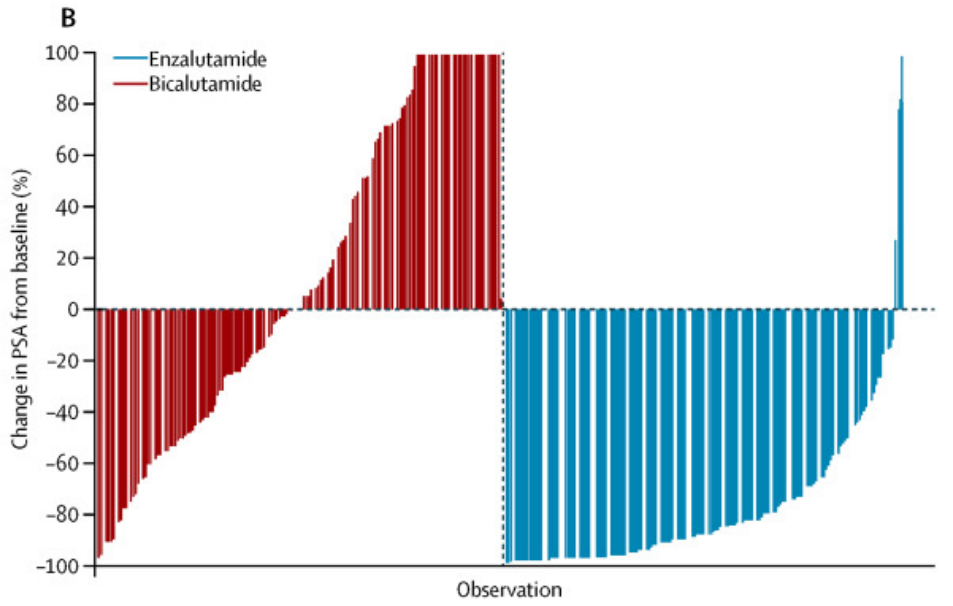
End Point	Enzalutamide (N=872)	Placebo (N=845)	Hazard Ratio (95% CI)	P Value
Median time until initiation of cytotoxic chemotherapy — mo	28.0	10.8	0.35 (0.30–0.40)	<0.001
Median time until decline in the FACT-P global score — mo†‡	11.3	5.6	0.63 (0.54–0.72)	<0.001
Median time until first skeletal-related event — mo§	31.1	31.3	0.72 (0.61–0.84)	<0.001
Median time until PSA progression — mo¶	11.2	2.8	0.17 (0.15–0.20)	<0.001
Confirmed change in PSA‖				
Patients with ≥1 post-baseline PSA assessment — no. (%)	854 (98)	777 (92)		
PSA decline of ≥50% from baseline — no./total no. (%)	666/854 (78)	27/777 (3)		<0.001
PSA decline of ≥90% from baseline — no./total no. (%)†	400/854 (47)	9/777 (1)		<0.001
Patients with measurable soft-tissue disease — no. (%)**	396 (45)	381 (45)		
Objective response	233 (59)	19 (5)		<0.001
Complete response	78 (20)	4 (1)		
Partial response	155 (39)	15 (4)		

* A complete definition of study end points is provided in Table S1 in the Supplementary Appendix. CI denotes confidence interval, and PSA prostate-specific antigen.
† This category was a prespecified exploratory end point.
‡ A decline on the Functional Assessment of Cancer Therapy–Prostate (FACT-P) scale was defined as decrease of 10 points or more on the global score, which ranges from 0 to 156, with higher scores indicating a better quality of life.
§ The hazard ratio is a more accurate measure of treatment effect than are estimates of the median time until the event for late-occurring events in this study.
¶ PSA progression was based on criteria of the Prostate Cancer Clinical Trials Working Group 2.
‖ Only patients with baseline and post-baseline assessments are included.
** Only patients with measurable soft-tissue disease at baseline, as assessed on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1, are included.

Beer. NEJM 2014

Bør man prøve gamle (og billige) antiandrogener før Zytiga/Xtandi?





Shore. Lancet Oncol 2016

Lavdose steroider som sekundær endokrin behandling

Table 1 – Clinical studies of corticosteroids in castration-resistant prostate cancer

Study	Daily dose, mg	*n*	PSA response rate, %	Median TTPSA progression, mo
Prednisolone				
Berry et al [9]	10	60	24	4.1
Tannock et al [8]	10	81	22	-
Fossa et al [13]	20	50	26	4
de Bono et al [6]	10	398	16	6.6
Fossa et al [3]	20	101	21	3.4
Sternberg et al [7]	20	50	9	2.5
Sartor et al [14]	20	29	33	2
Ryan et al [10]	10	542	24	5.6
Dexamethasone				
Nishimura et al [11]	0.5–2	37	62	9
Storlie et al [15]	1.5–2.25	38	61	8
Morioka et al [16]	1.5	27	59	5.4
Saika et al [16]	1.5	19	28	7.3
Venkitaraman et al [4]	0.5	102	50	7.4
Shamash et al [12]	2	135	50	8.1

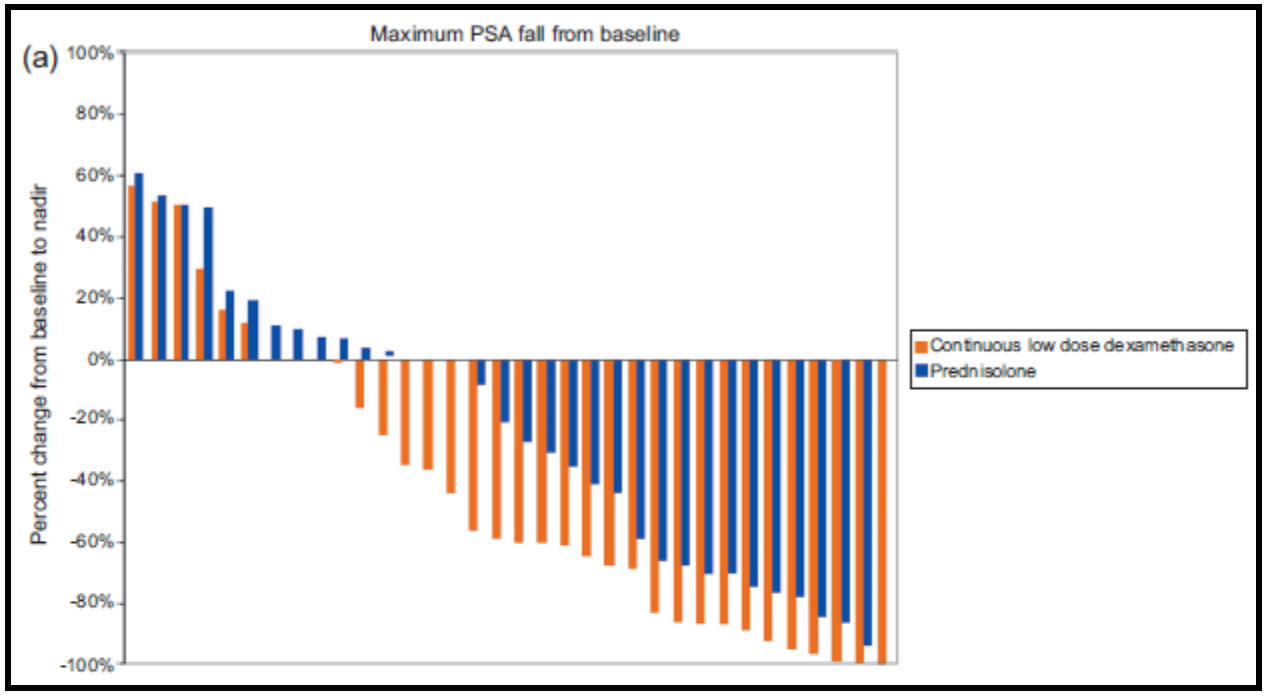
PSA = prostate-specific antigen; TTPSA = time to prostate-specific antigen progression.

Venkitaraman. Eur Urol 2015

A Randomised Phase 2 Trial of Dexamethasone Versus Prednisolone in Castration-resistant Prostate Cancer

Ramachandran Venkitaraman [a], *David Lorente* [b], *Vedang Murthy* [c], *Karen Thomas* [d], *Lydia Parker* [b], *Ruth Ahiabor* [b], *David Dearnaley* [b], *Robert Huddart* [b], *Johann De Bono* [b], *Chris Parker* [d,*]

n=75
Median time to PSA-progression 9.7 vs 5.1 mnd
PSA-respons (>50% fall) 41% vs 22%
PSA-respons ved pred-dex shift 37% (7/19)



Eur Urol 2015

Bør man prøve lavdose steroider før abi/enza?

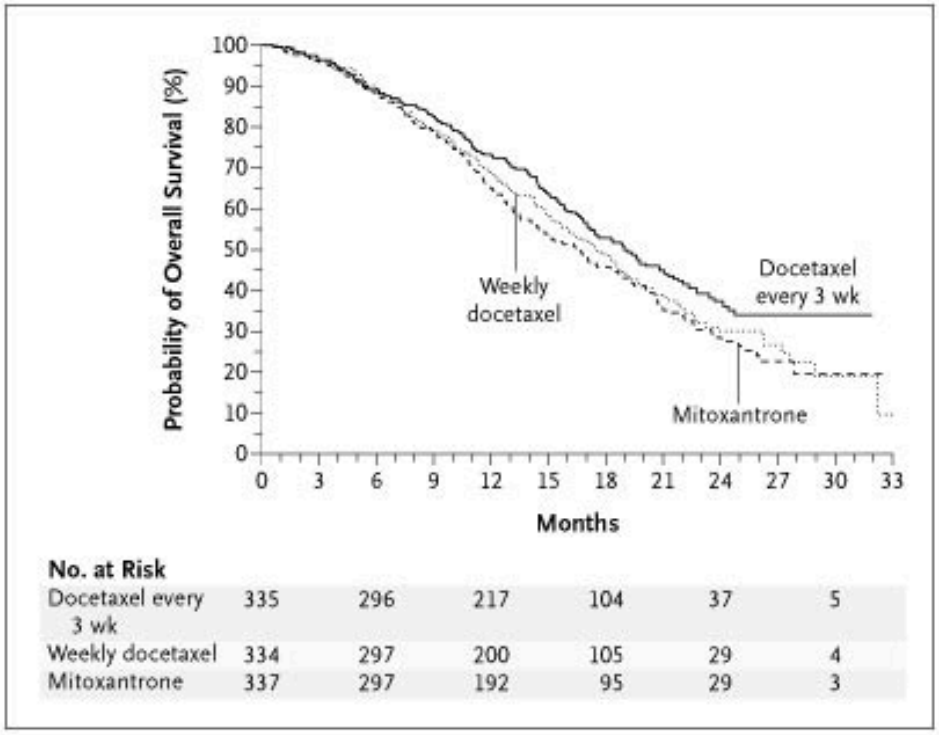
- Gode responsrater og rimelig pris taler for (gitt at man har "tid til" progresjon)
- COU-302 taler kanskje mot….
- Usikker effekt på OS
- Dexamethason 0.5 mg x 1 er førstevalg fremfor prednisolon 5 mg x 2.

Abiraterone eller Enzalutamid?

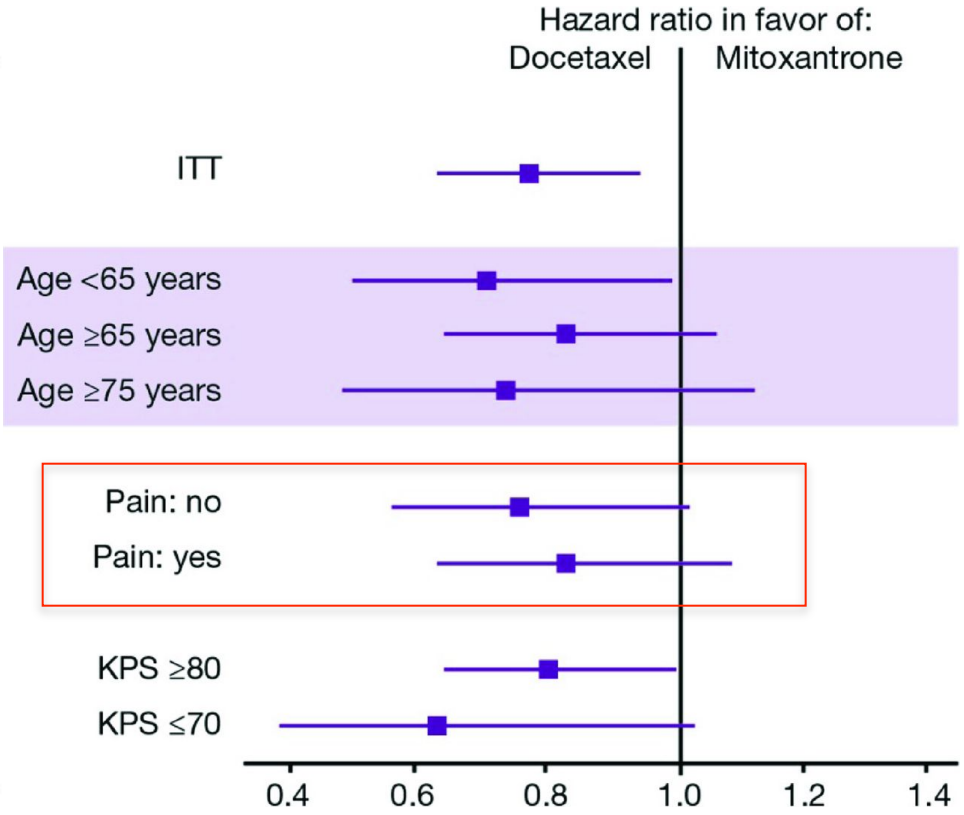
- Samme indikasjon
- Sannsynlig lik effekt
- Noe ulik bivirkningsprofil
- Noe ulik mhp interaksjoner
- Noe ulik mht administering og tilleggsmedisinering

- Konklusjon: Individuell vurdering

Kjemoterapi



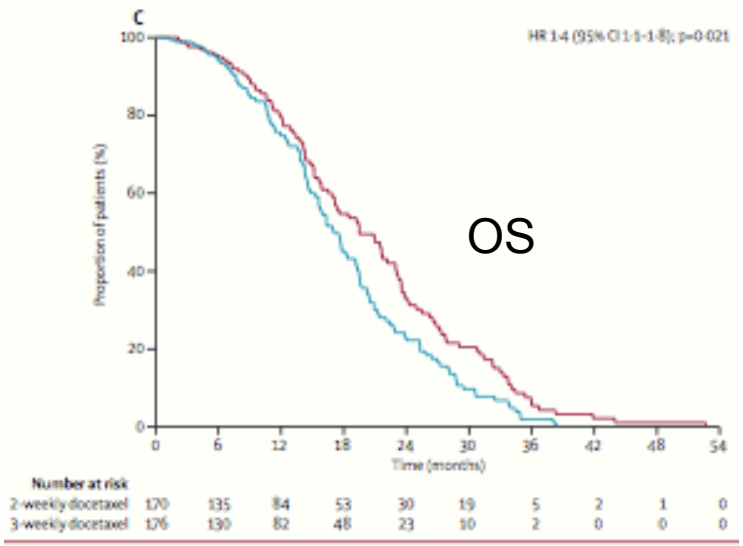
Tannock. NEJM 2004



Aapro M S The Oncologist 2012;17:16-22

2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial

Pirkko-Liisa Kellokumpu-Lehtinen, Ulrika Harmenberg, Timo Joensuu, Ray McDermott, Petteri Hervonen, Claes Ginman, Marjaana Luukkaa, Paul Nyandoto, Akseli Hemminki, Sten Nilsson, John McCaffrey, Raija Asola, Taina Turpeenniemi-Hujanen, Fredrik Laestadius, Tiina Tasmuth, Katinka Sandberg, Maccon Keane, Ilari Lehtinen, Tiina Luukkaala, Heikki Joensuu, for the PROSTY study group

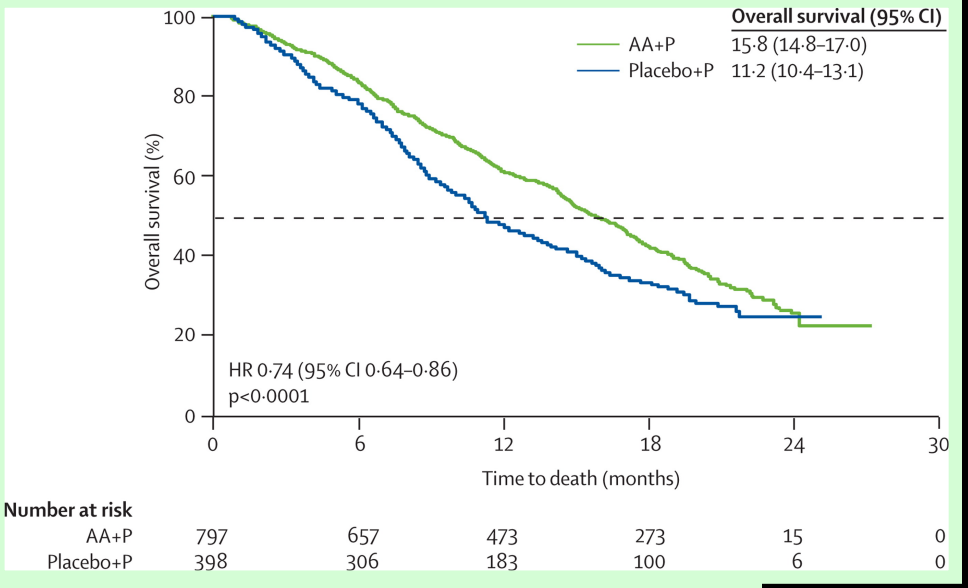


OS

	2-weekly docetaxel (n=170)		3-weekly docetaxel (n=176)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Haematological				
Neutropenia	40 (24%)	61 (36%)	6 (3%)	93 (53%)
Leucopenia	49 (29%)	22 (13%)	36 (20%)	51 (29%)
Anaemia	144 (85%)	1 (1%)	142 (81%)	1 (1%)
Thrombocytopenia	20 (12%)	1 (1%)	20 (11%)	0
Febrile neutropenia	0	6 (4%)	0	25 (14%)
Non-haematological				
Fatigue	125 (74%)	25 (15%)	137 (78%)	26 (15%)
Myalgia	59 (35%)	4 (2%)	62 (35%)	2 (1%)
Infection without neutropenia	50 (29%)	18 (11%)	53 (30%)	21 (12%)
Infection with neutropenia	0	11 (6%)	0	43 (24%)
Diarrhoea	61 (36%)	2 (1%)	77 (44%)	4 (2%)
Nausea	58 (34%)	2 (1%)	84 (48%)	2 (1%)
Vomiting	21 (12%)	1 (1%)	20 (11%)	0
Raised alkaline phosphatase concentration	70 (41%)	16 (9%)	82 (47%)	11 (6%)
Raised AST concentration	28 (16%)	1 (1%)	33 (19%)	1 (1%)
Arthralgia	50 (29%)	1 (1%)	67 (38%)	2 (1%)
Pain	109 (64%)	11 (6%)	113 (64%)	12 (7%)
Watery eyes	86 (51%)	3 (2%)	93 (53%)	3 (2%)

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)	Hazard ratio (95% CI)	p value
Median (95% CI) TTTF (months)	5·6 (5·0–6·2)	4·9 (4·5–5·4)	1·3 (1·1–1·6)	0·014
Median (95% CI) TTP or death (months)	15·8 (13·6–18·1)	14·6 (13·2–16·0)	1·3 (1·0–1·6)	0·047
Median (95% CI) overall survival (months)	19·5 (15·9–23·1)	17·0 (15·0–19·1)	1·4 (1·1–1·8)	0·021
PSA response	84 (49%)	74 (42%)	..	0·486
Best response to treatment				0·952
Complete or partial response	39 (23%)	38 (22%)	..	..
Stable disease	78 (46%)	80 (46%)	..	..
Disease progression	14 (8%)	19 (11%)	..	..
Not available	39 (23%)	39 (22%)	..	..

Kellokumpo-Lehtinen. Lancet 2013

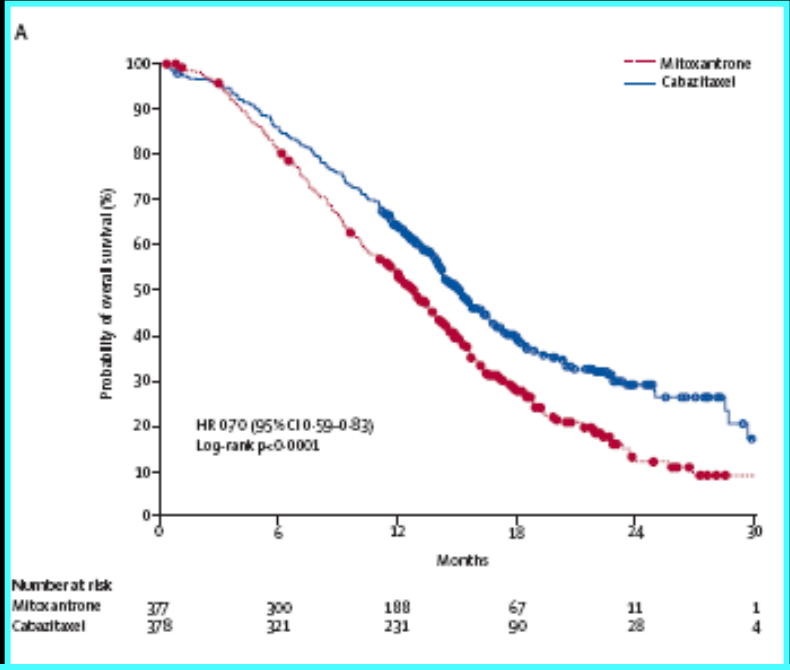


Abiraterone + pred vs placebo + pred

Median OS: 15,8 vs 11,2 mnd

HR 0,74 (0,64-0,86)

Fizazi Lancet Oncol 2012



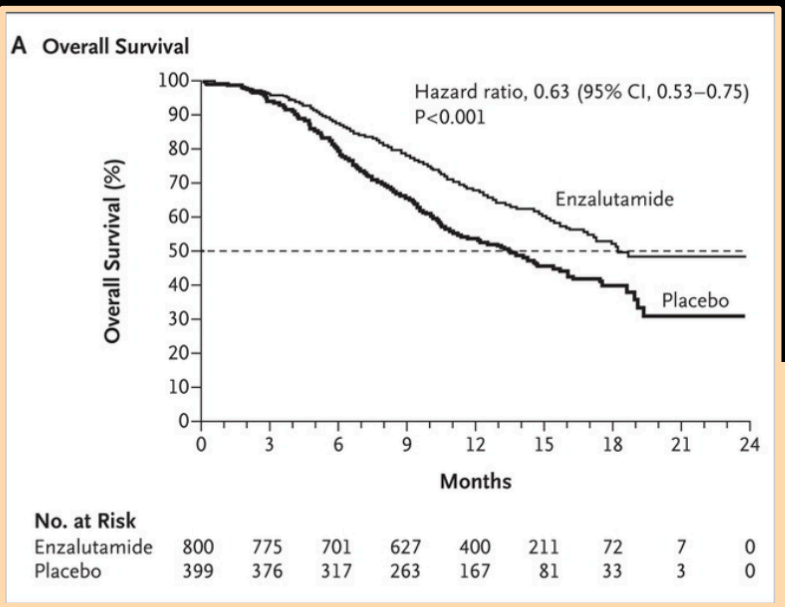
Cabazitaxel + pred vs Mitoxantrone + pred

Median OS: 15,1 vs 12.7 mnd

HR 0,7 (0,59-0,83)

De Bono Lancet 2010

Post-docetaxel

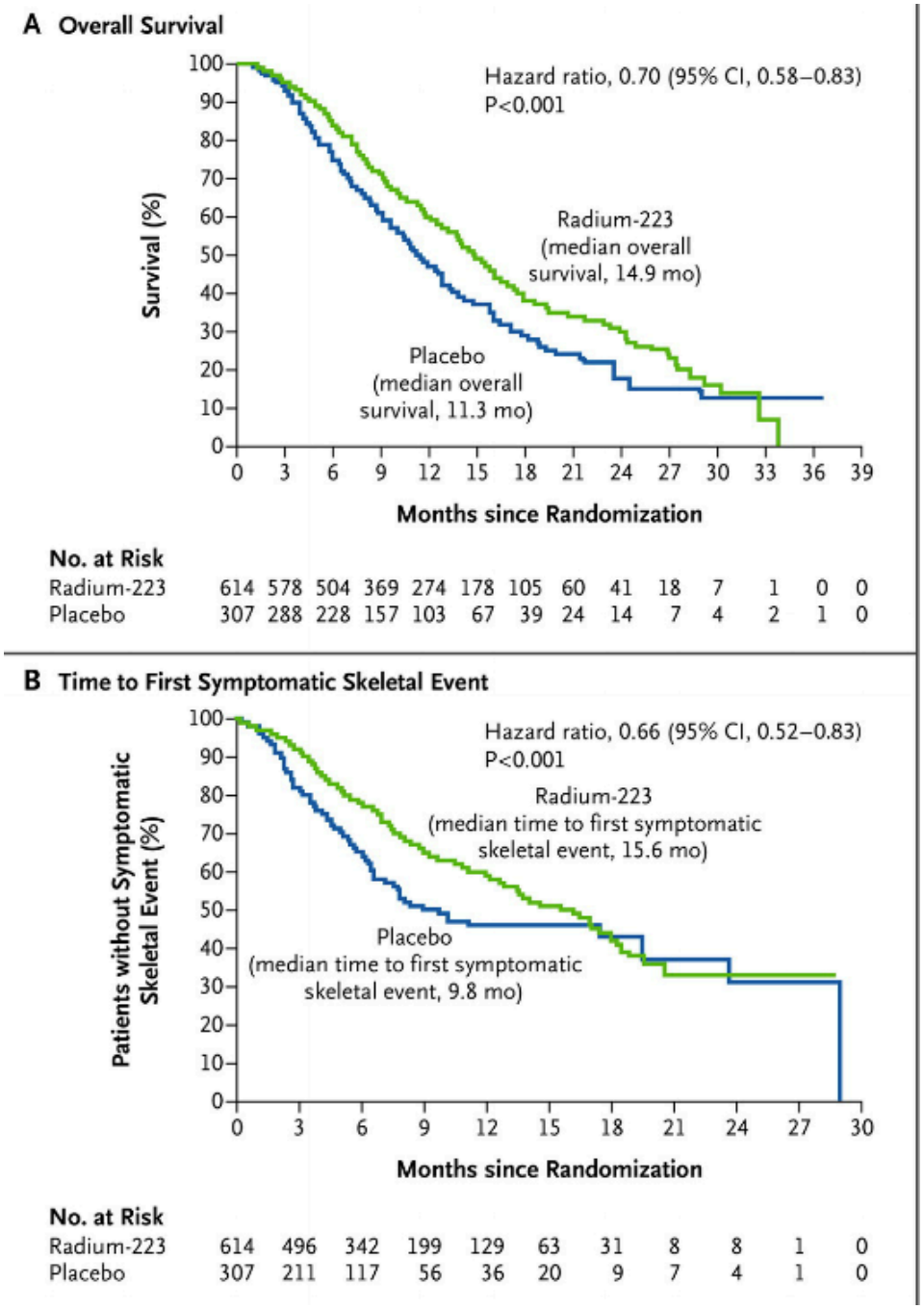


Enzalutamide vs placebo

Median OS: 18,4 vs 13,6 mnd

HR 0,63 (0,53-0,75)

Scher NEJM 2012

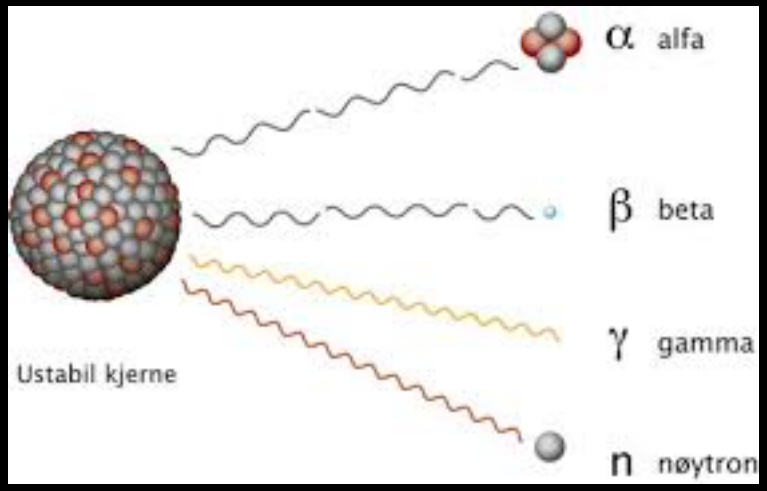


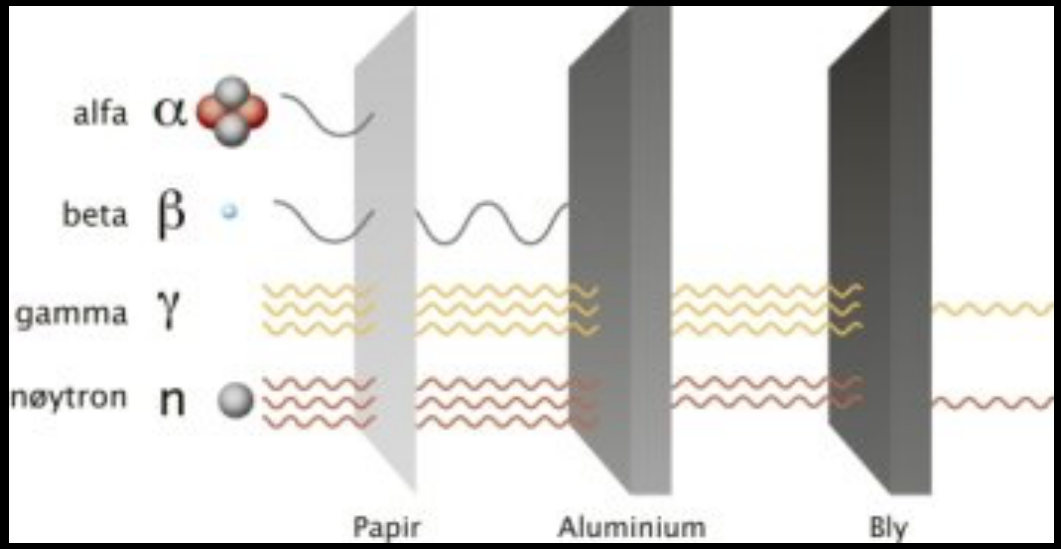
Radium-223 (Xofigo®)

- Indikasjon: mCRPC med symptomgivende skjelettmetastaser og uten kjente viscerale metastaser
- Bestilles 8 dager før administrasjon – må kastes hvis det ikke brukes
- Bivirkninger: Sjelden trombocytopeni/nøytropeni

Parker. NEJM 2013

Group → / Period ↓	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	1 H																	2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	*	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	**	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo
*			57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	
**			89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr	

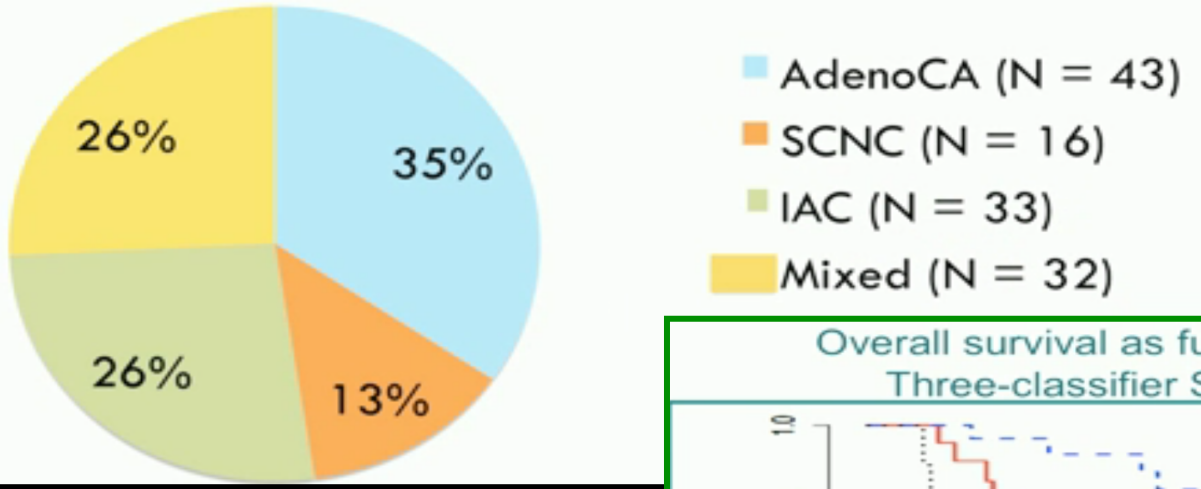




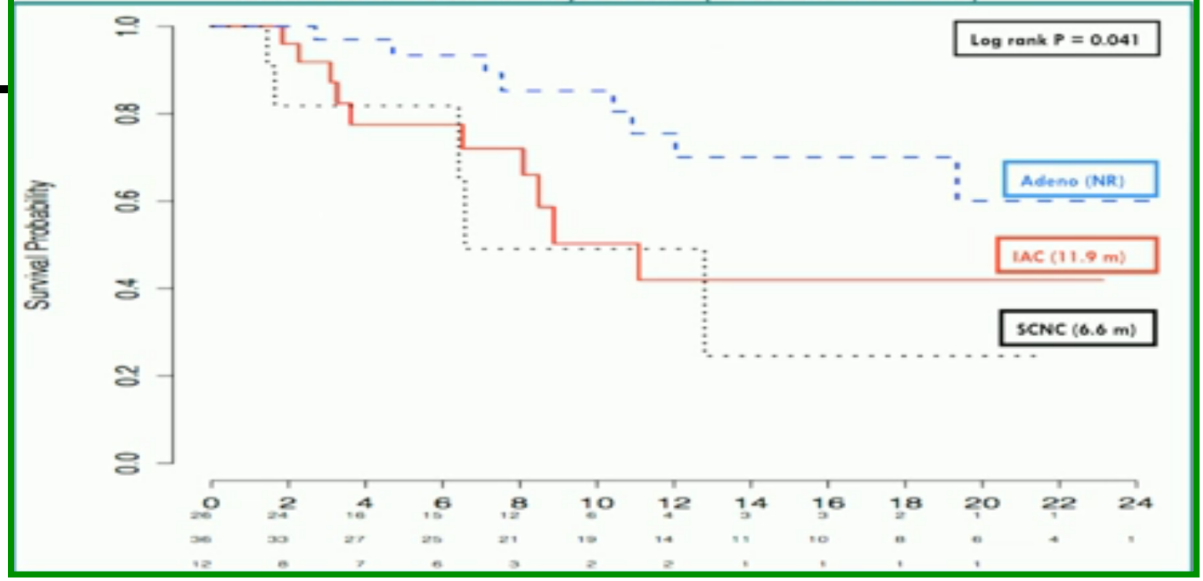
Characterization of neuro-endocrine prostate cancer in patients with mCRPC resistant to abiraterone or enzalutamide

Histology of 124 Evaluable Biopsies

74 % were "pure" with a single histologic subtype (**isolated by LCM)
Remainder (26%) were comprised of mixed populations

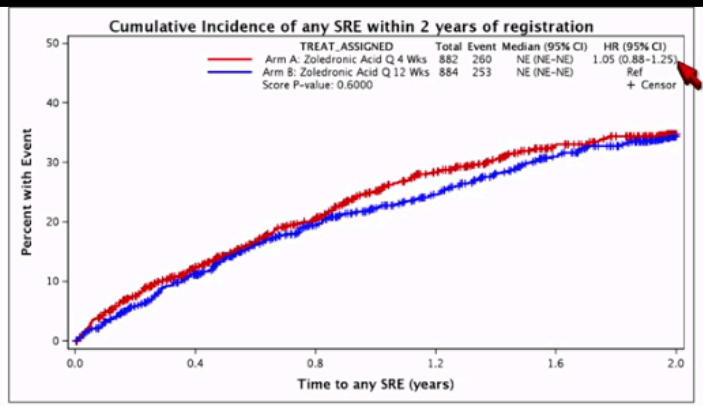


Overall survival as function of biopsy pathology
Three-classifier System (from time of bx)



Small. ASCO 2015. Abstract 5003

Zoledronsyre hver 4. uke mot hver 12. uke i 2 år



No significant difference in time to SRE between ZA q 4 weeks vs. ZA q 12 weeks (p = 0.60[1])

	Q Month N = 911	Q 3 Months N = 911	HR (P-value)
Total ZA dose (median)	56 mg	24 mg	— (< 0.01)
Dose delays	62%	37%	— (< 0.01)
Any SRE	260	253	1.05 (0.60)
Any SRE – breast pts (N = 820)	113	119	0.90 (0.43)
Any SRE – prostate pts (N = 660)	107	101	1.15 (0.31)
Any SRE – myeloma pts (N = 265)	35	30	1.30 (0.29)
Bone RT	185	163	1.16 (0.18)
Bone fractures	62	79	0.78 (0.13)
Spinal cord compression	23	30	0.75 (0.30)
Bone surgery	22	42	0.51 (0.01)
Jaw osteonecrosis	18	9	— (0.08)
Grade 2-4 creatinine increase	11	5	— (0.46)

Abstr#9501 (Himelstein) ASCO 2015

”State of the art” metastatisk prostatakreft 2016

- Livslang kastrasjon
- Vurdere 6 kurer docetaxel ved oppstart kastrasjonsbehandling.
- Aktiv behandling ved asymptomatisk progresjon.
- Sekvensiell behandling med aktive medikamenter så lenge pasienten har godt funksjonsnivå og tåler behandlingen.
- Optimal rekkefølge og kombinasjoner er ukjent.