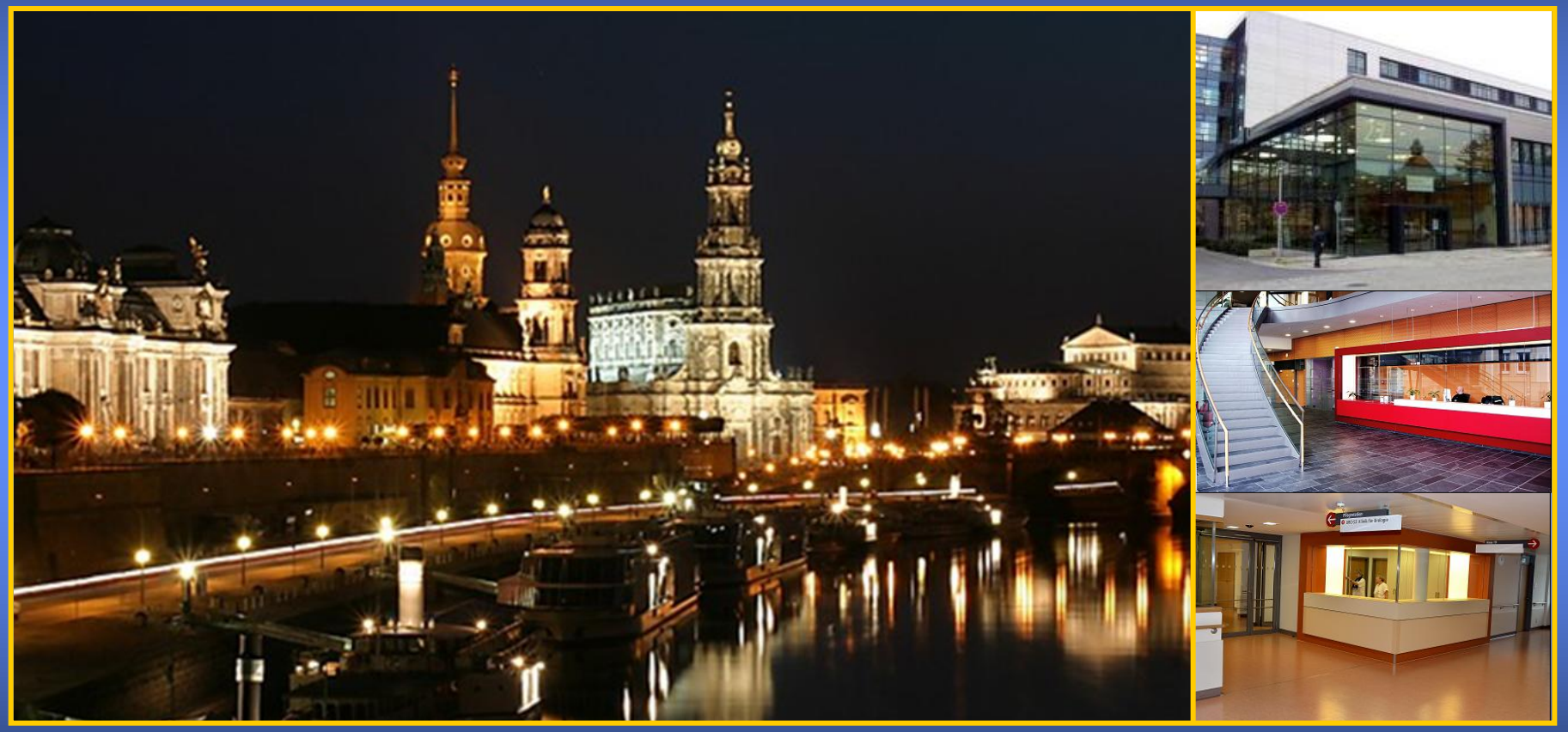
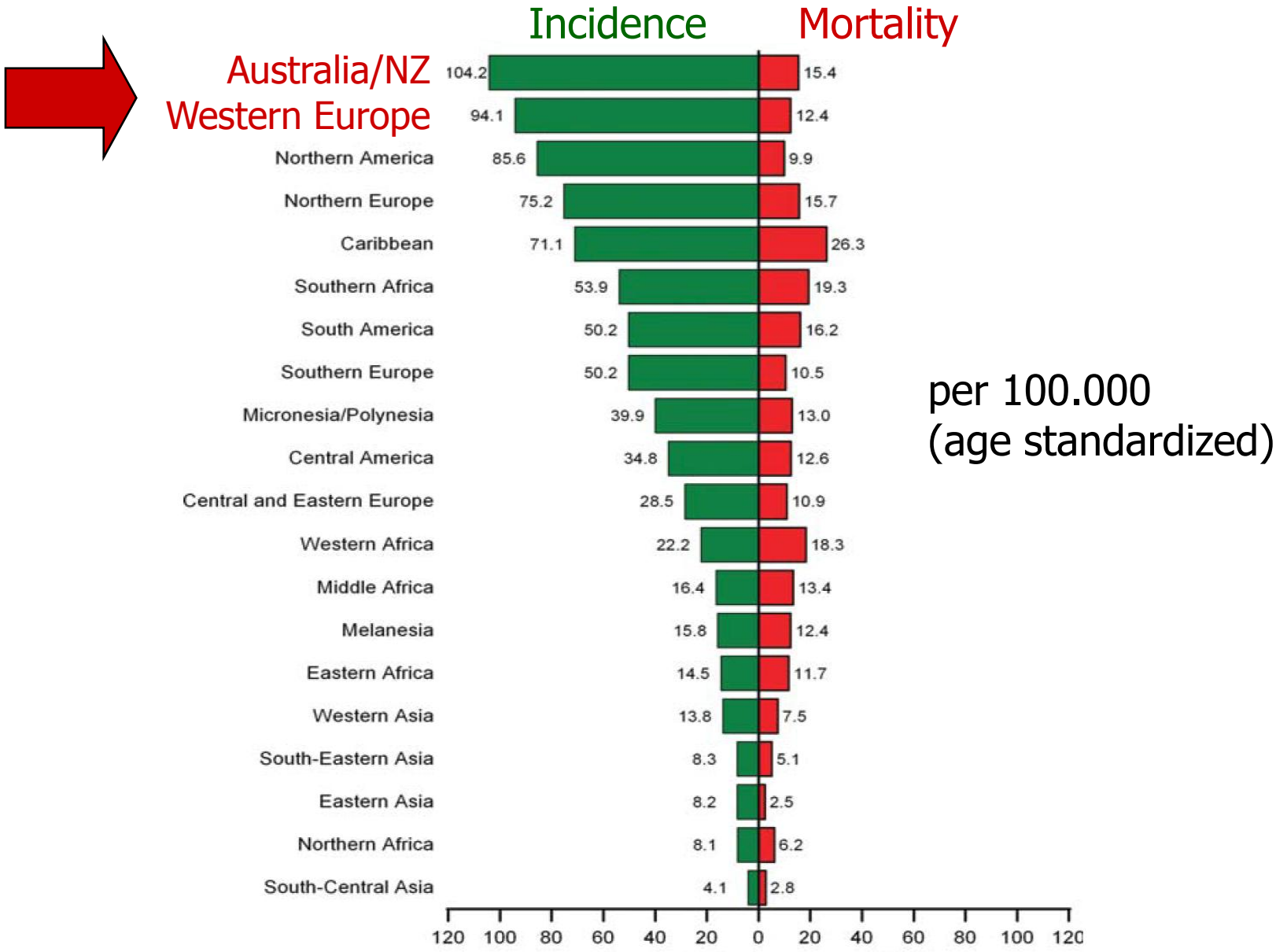
The many faces of advanced stage prostate cancer



M. Wirth
Professor and Chairman, Dept. of Urology
Dresden University of Technology

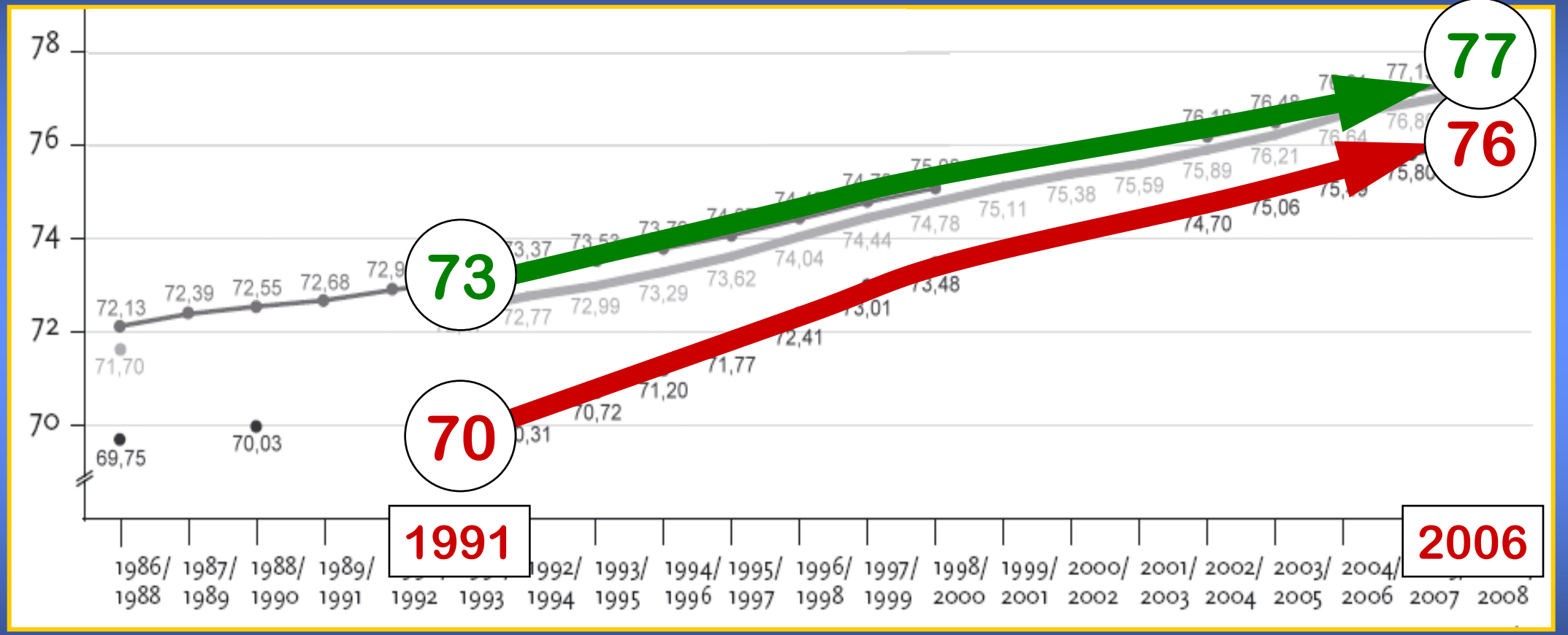
Epidemiology

Prostate cancer incidence and mortality worldwide



Jemal et al., CA Cancer J Clin 2011

Male life expectancy, example: Germany



West

East

www.gbe-bund.de

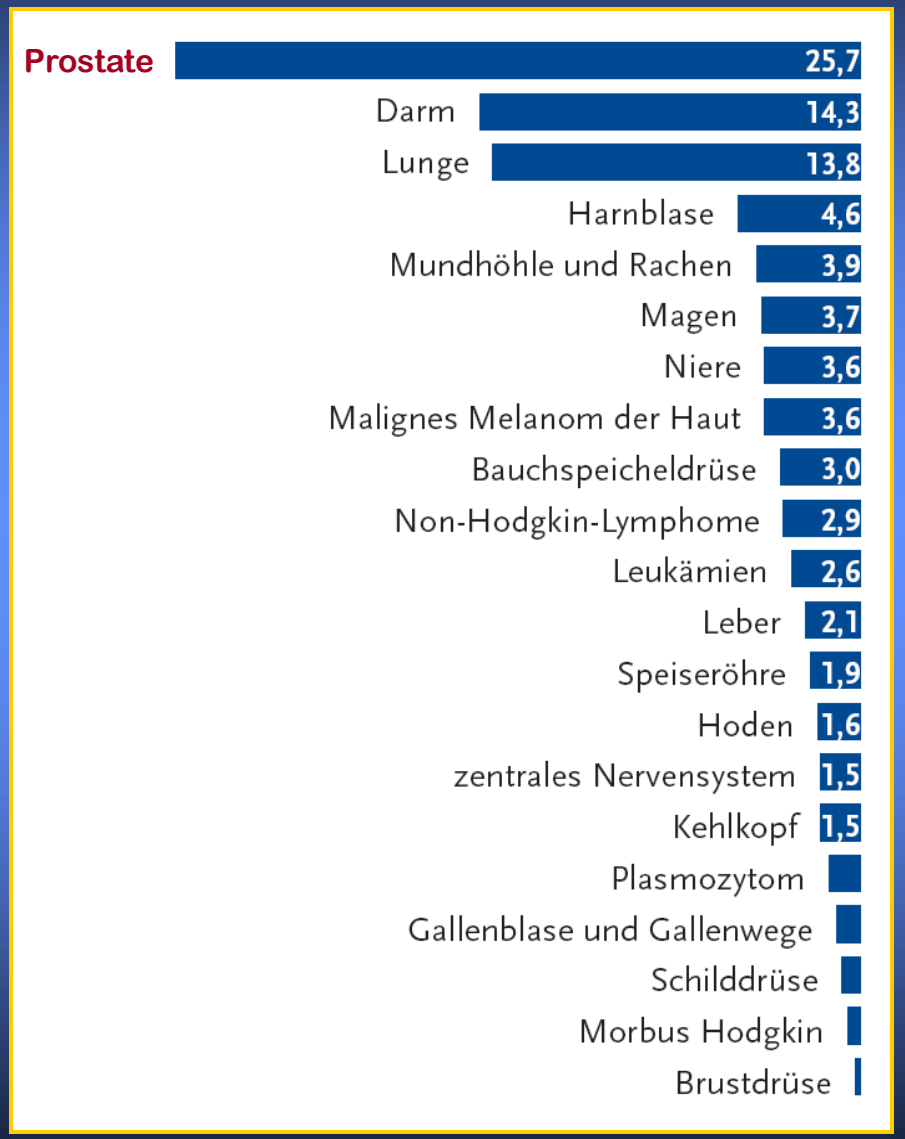
Proportion diagnosed with prostate cancer by age range in the US

Age [years]	Proportion
35–44	0.6 %
45–54	9.1 %
55–64	30.7 %
65–74	35.3 %
75–84	19.9 %
85+	4.4 %

60 %

Brawley et al., World J Urol 2012

Castration resistant prostate cancer: epidemiology



63.440 new CaP cases/year in Germany

10-20 % become castration resistant*

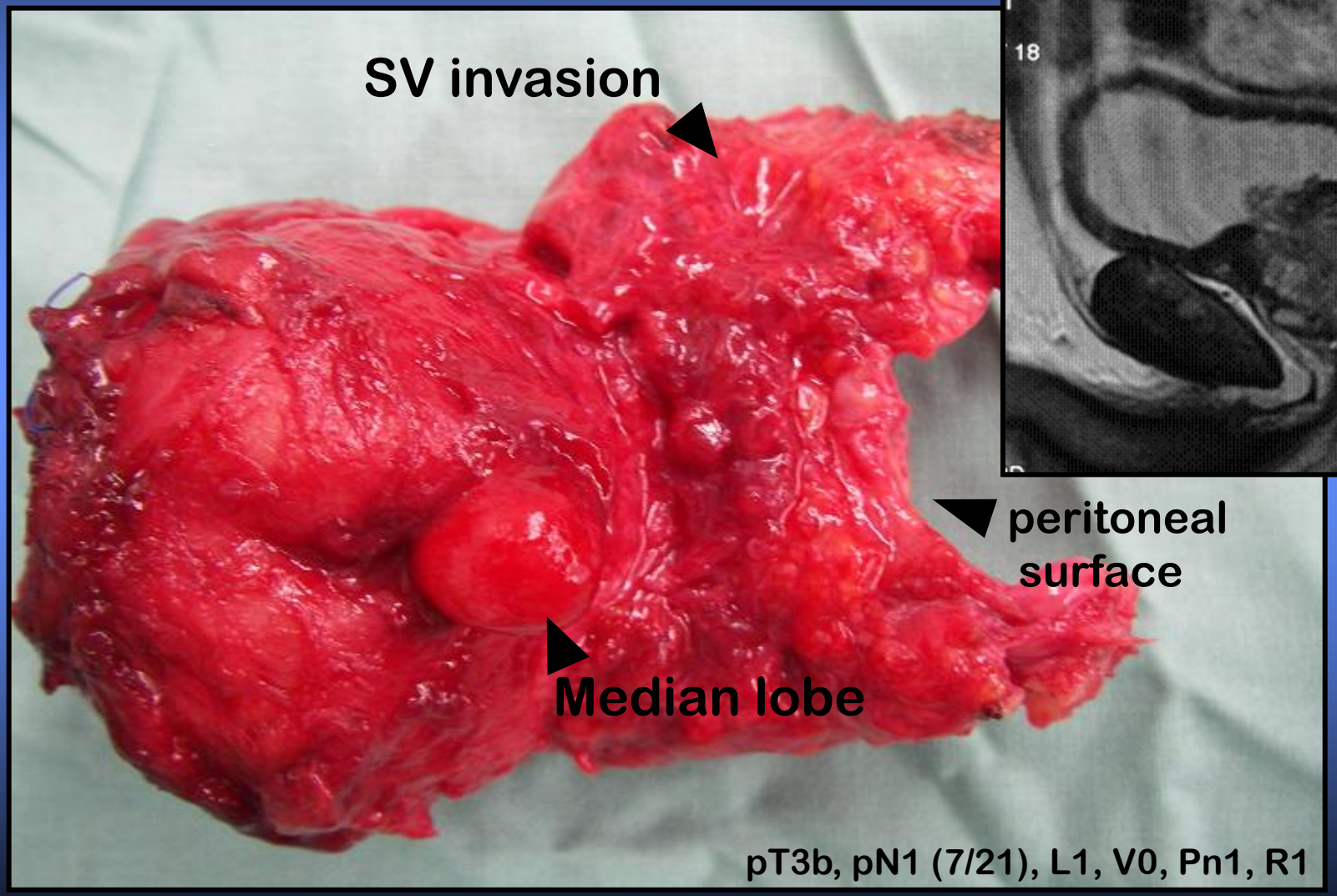
ca. 6-12.000 new CRPC cases/year in Germany (12.134 deaths)

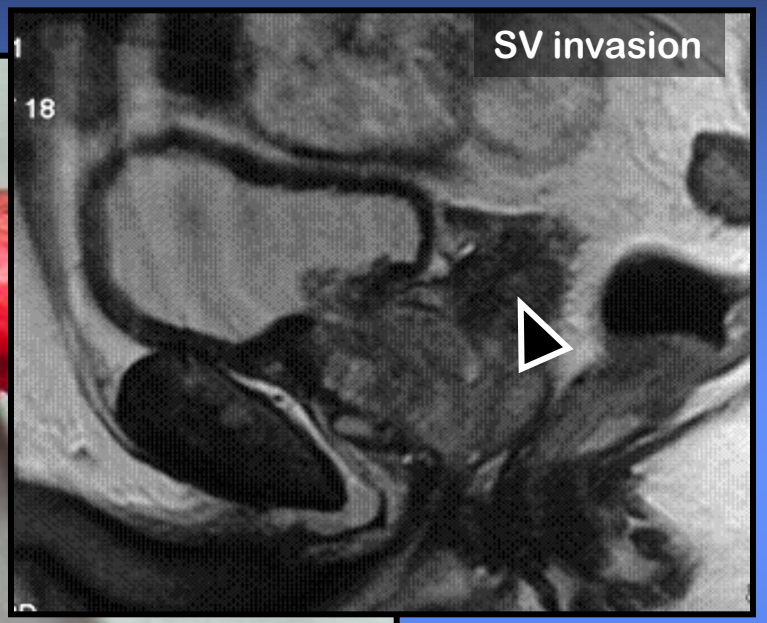
Krebs in Deutschland 2012: www.rki.de

*Kirby et al., Int J Clin Pract 2011

Local treatment for advanced disease?

66 years, 8/8 coed Gleason score 8, PSA 221 ng/ml, cT2-3, bone scan negative



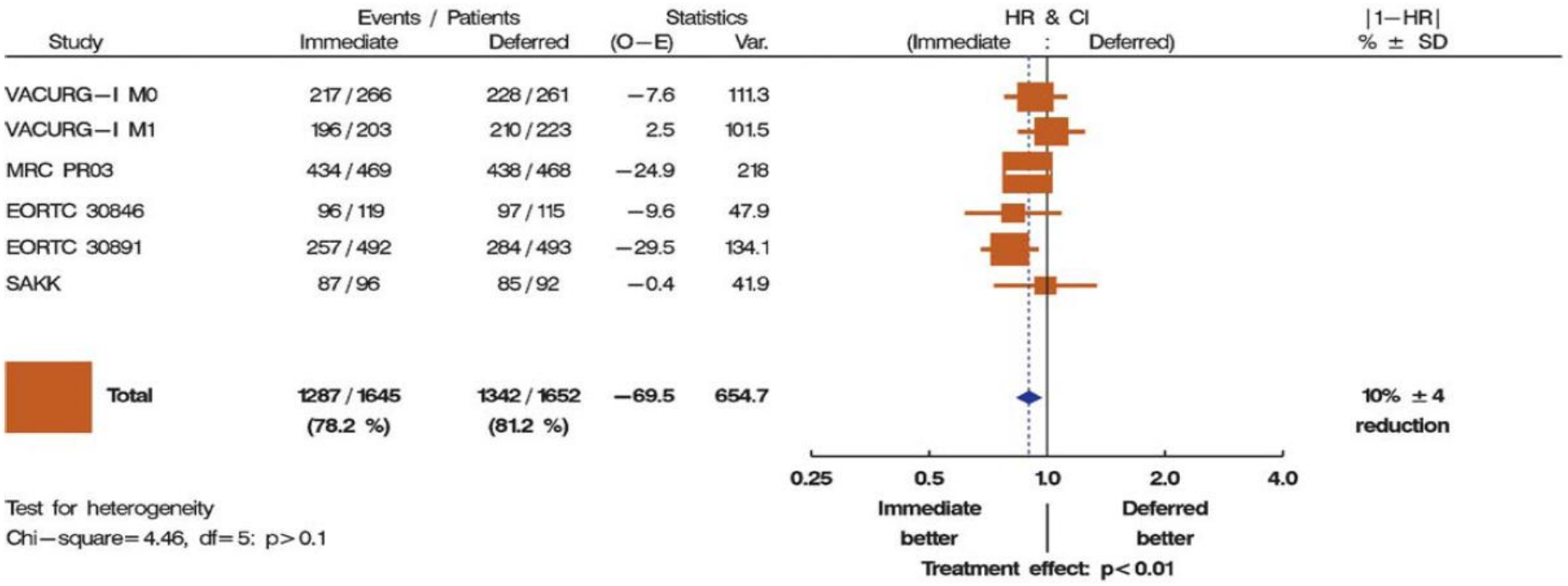


?

Local therapy for advanced prostate cancer?

Metaanalysis: early vs. deferred hormonal therapy plus RT/RPE

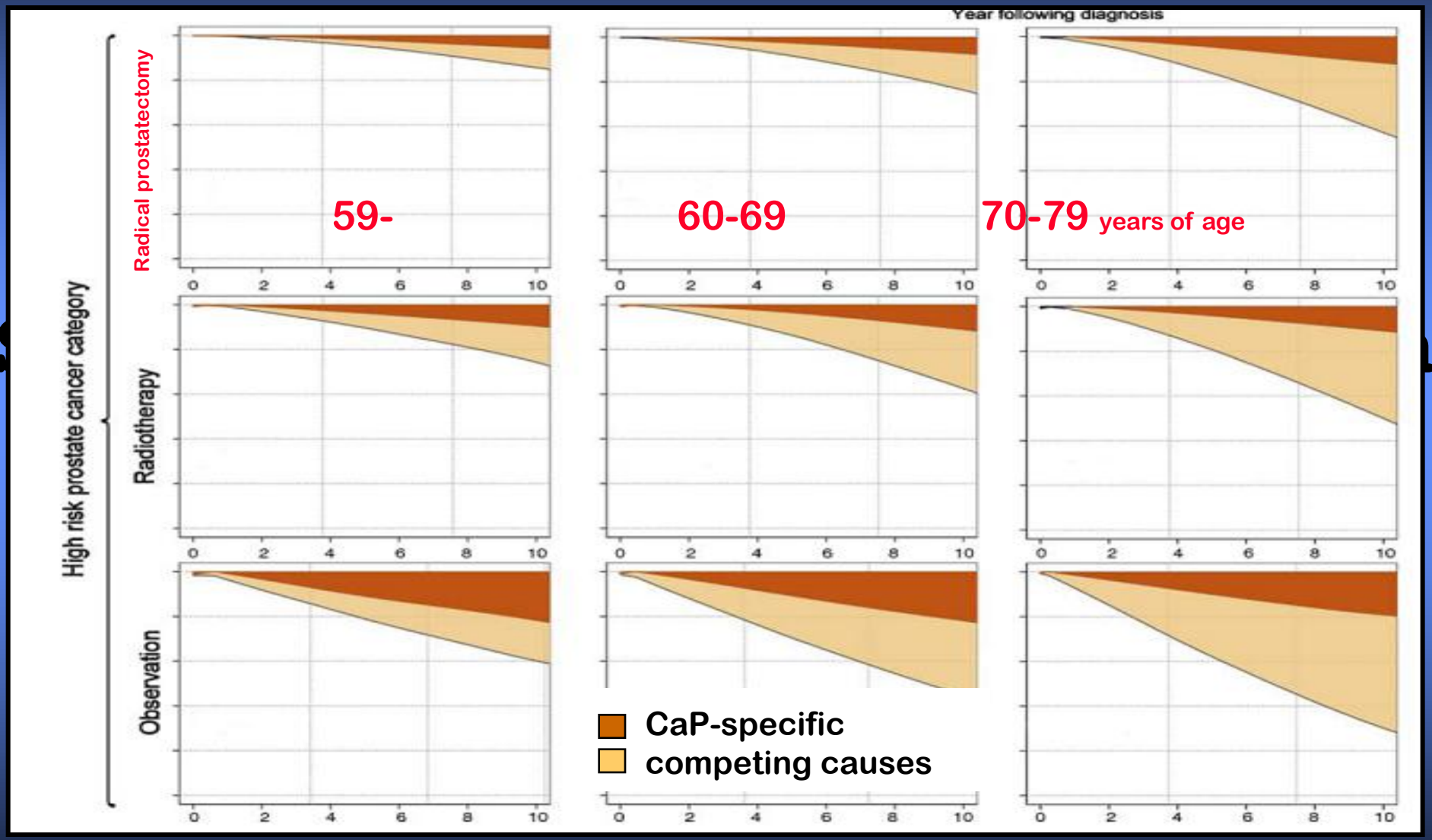
Overall survival



Verhagen et al., Eur Urol 2010

High-risk CaP: survival, competing risk analysis

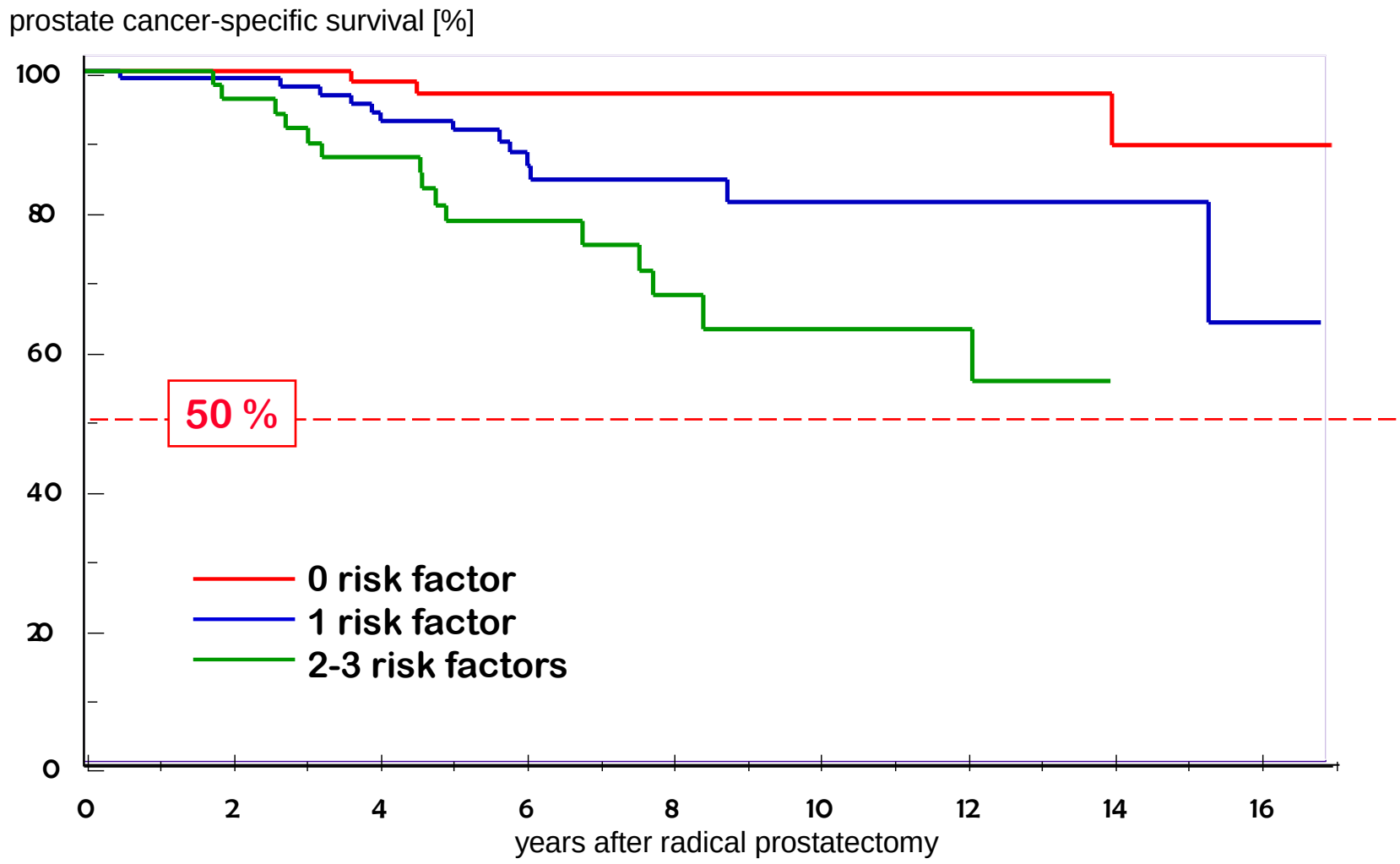
(SEER, n = 404 604, T2c or Gleason score 8–10)



Abdollah et al., Eur Urol 2010

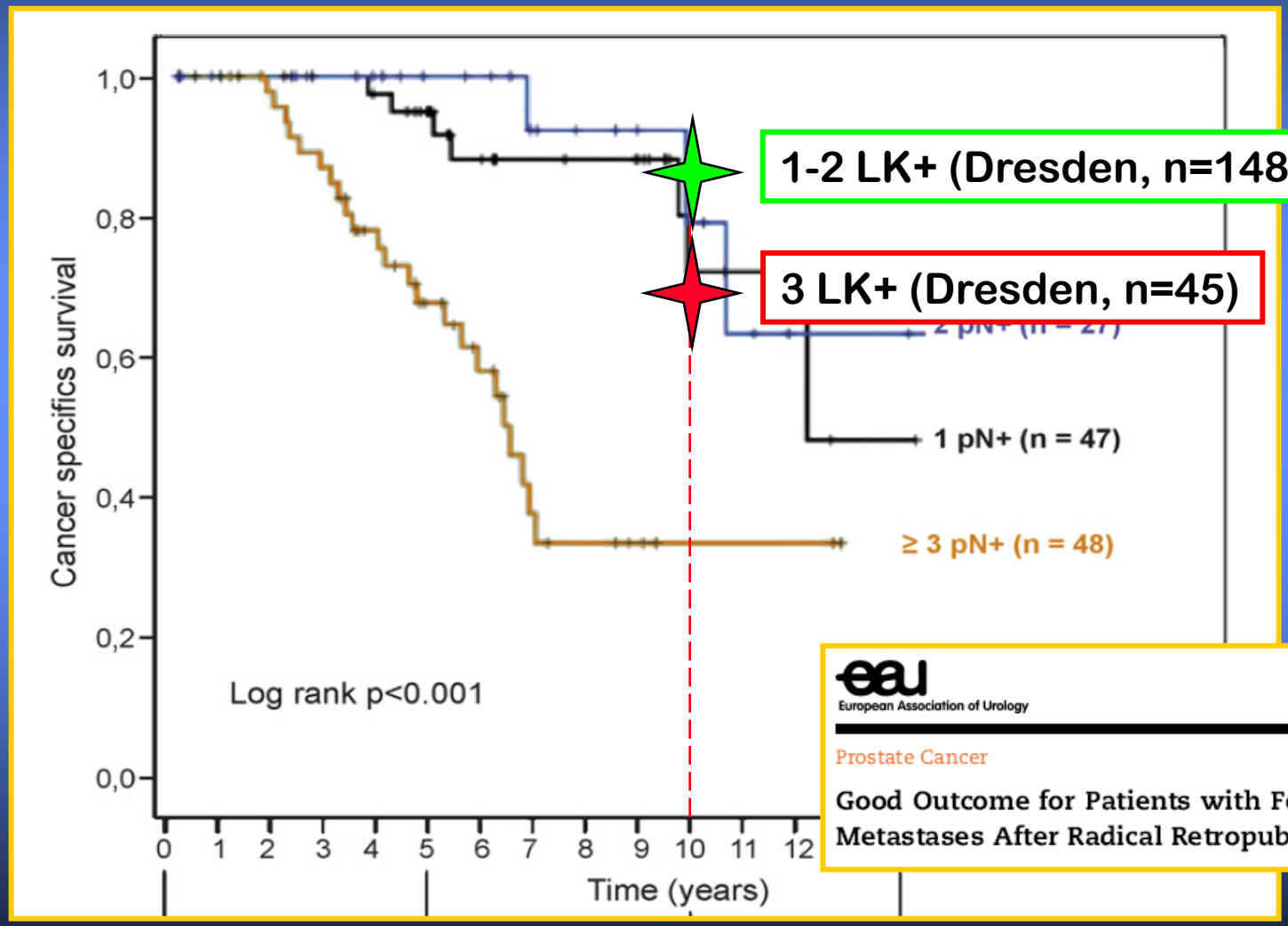
pN+: High survival rates after RPE

Risk factors Gleason score 8+, 3+ positive nodes, age 70+ (n=193)



Froehner, Wirth et al., Urol Int 2012

Positive lymph nodes: role of adjuvant hormonal therapy (n=122)



Schumacher, Studer et al., Eur Urol 2008 versus Froehner, Wirth et al., Urol Int 2012

Adjuvant radiotherapy after RPE: S3-guideline 2011

Category	Recommendation for adjuvant RTX
pT2R1	option
pT3R0 with risk factors (SV+…)	option
pT3R1	standard

➡ alternative option in all category: percutaneous RTX for PSA-rise from defined zero value*

*confirmed PSA > 0,2 ng/ml

Wirth et al.: Interdisciplinary S3 guideline on diagnostics and treatment of prostate cancer
http://www.aezq.de/edocs/pdf/info/s3-leitlinie-prostatakarzinom

Castration resistant prostate cancer

Castration resistant CaP - definition

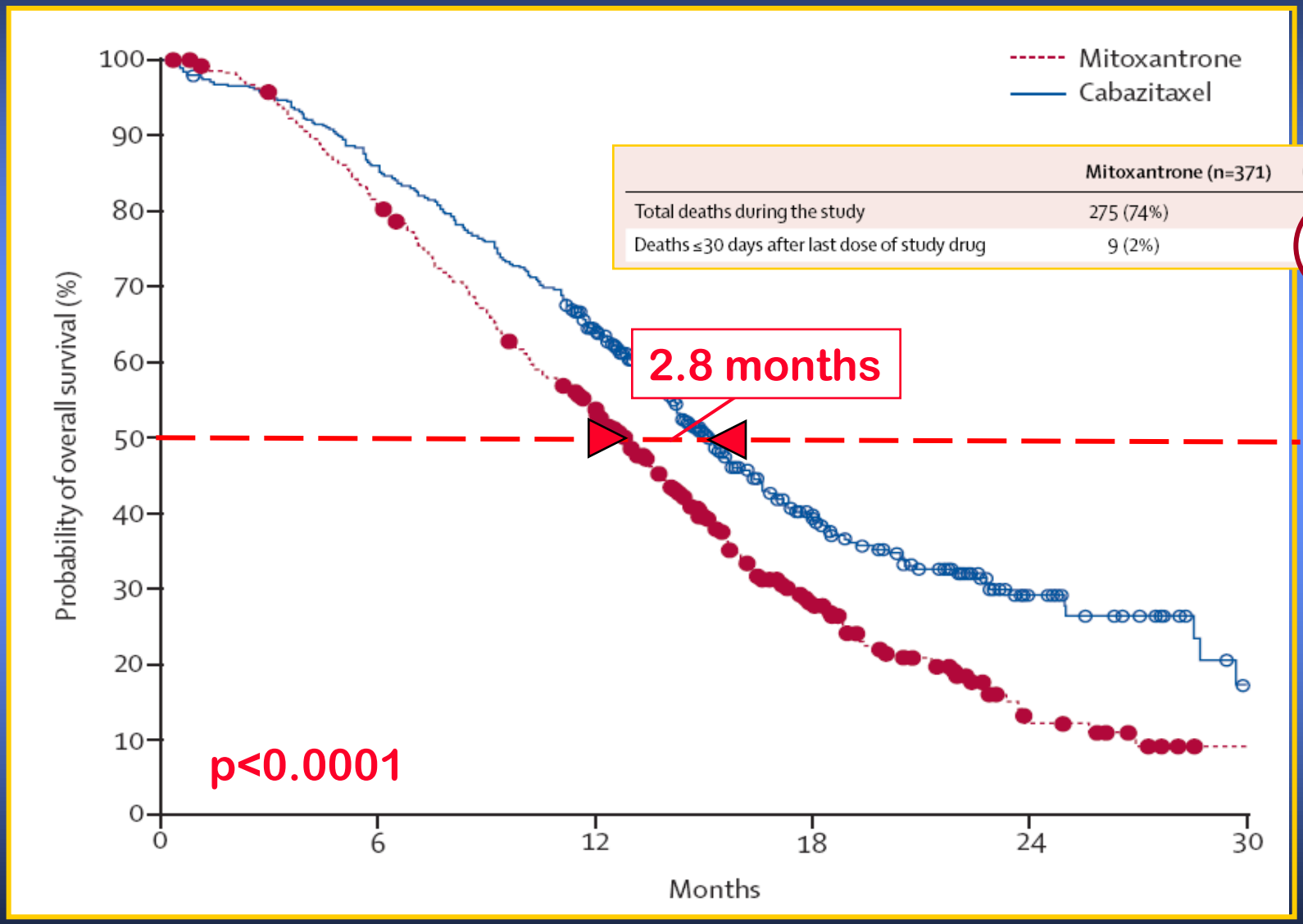
- Castrate level testosterone (<1.7 nmol/L*)
- 3 consecutive PSA rises, 1 week apart, resulting in two 50 % increases over the nadir, PSA >2 ng/mL
- Antiandrogen withdrawal for ≥4 wk (flutamide) and for ≥6 wk (bicalutamide)
- PSA progression despite consecutive hormonal manipulations

European Association of Urology

*Normal: 6.25 - 26.28

Cabazitaxel vs. mitoxantrone *second line* for HRPCA

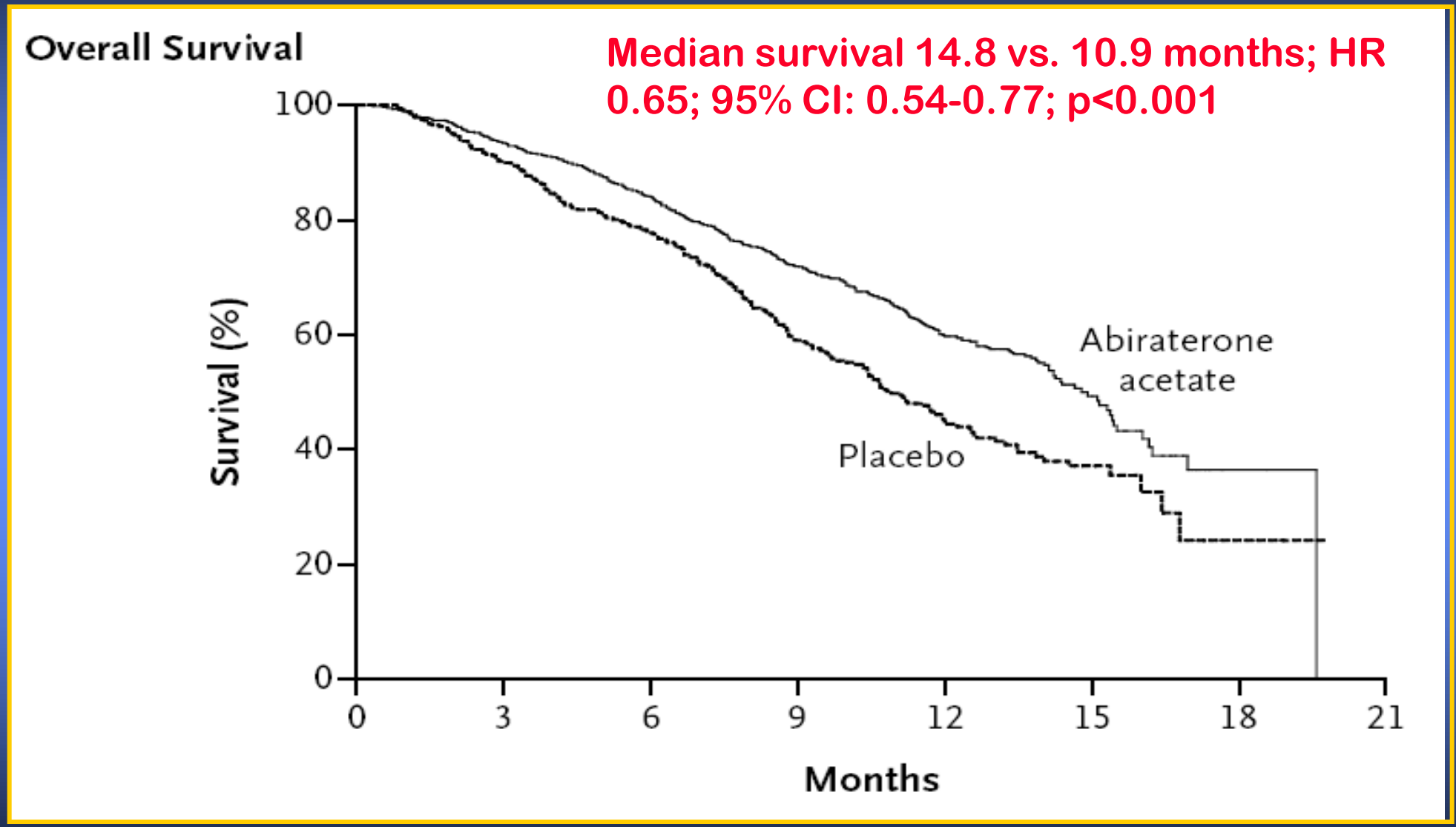
(n=755)



	Mitoxantrone (n=371)	Cabazitaxel (n=371)
Total deaths during the study	275 (74%)	227 (61%)
Deaths ≤30 days after last dose of study drug	9 (2%)	18 (5%)

De Bono et al., Lancet 2010

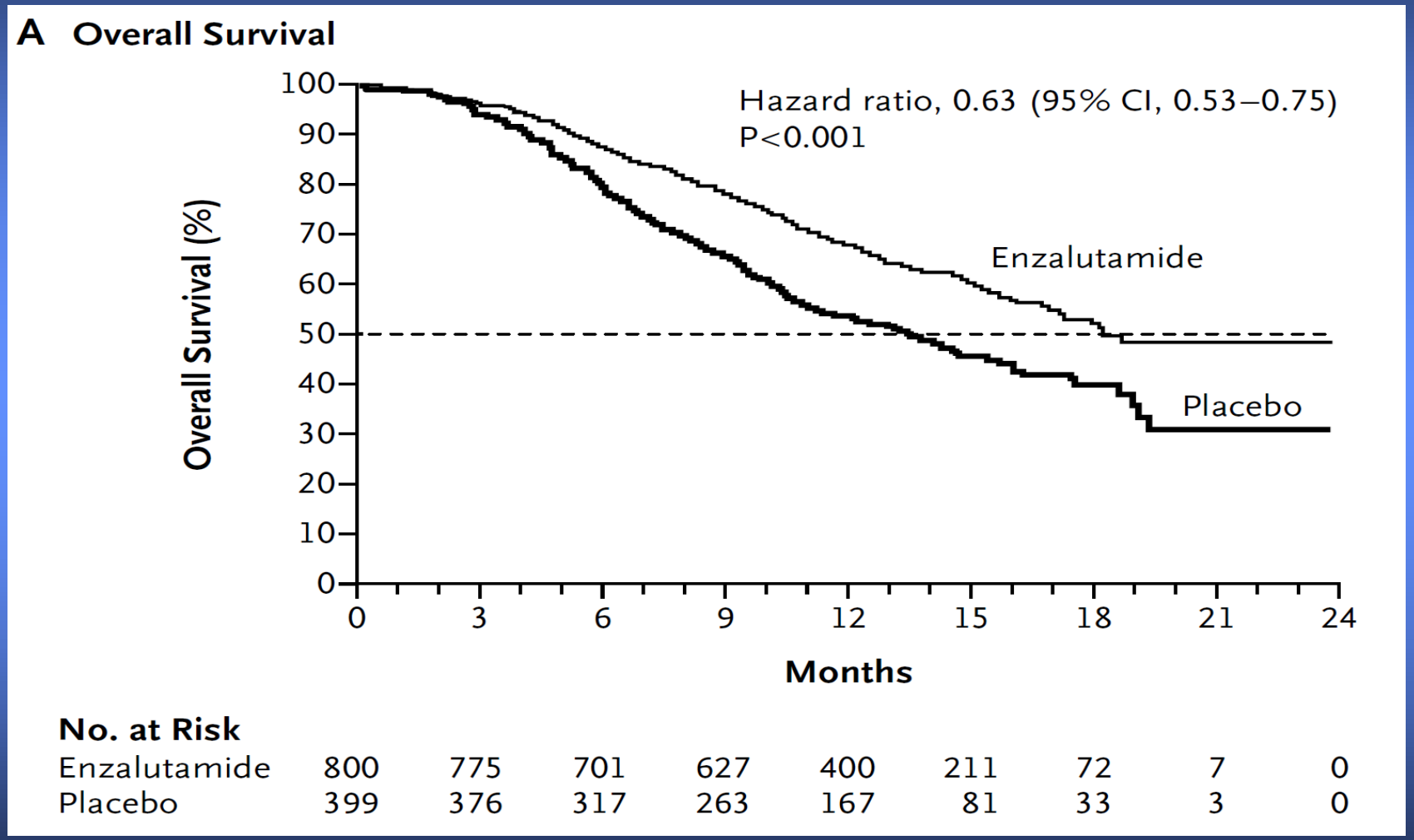
Abiraterone after docetaxel failure (n=1195)



De Bono et al., Lancet 2010

Enzalutamide after docetaxel failure

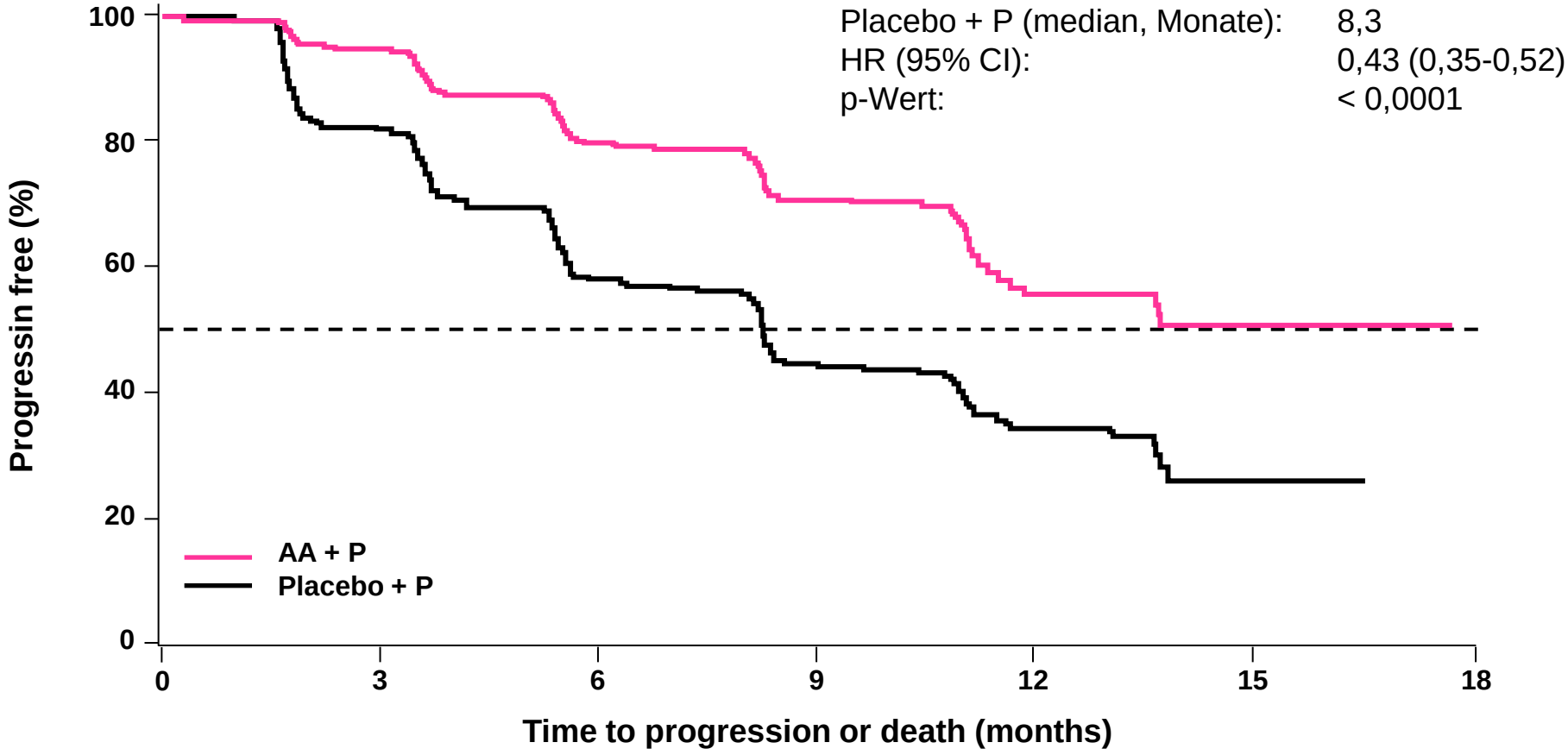
Overall survival 18,4 vs. 13,6 months



Scher et al., NEJM 2012

Abiraterone before chemotherapy

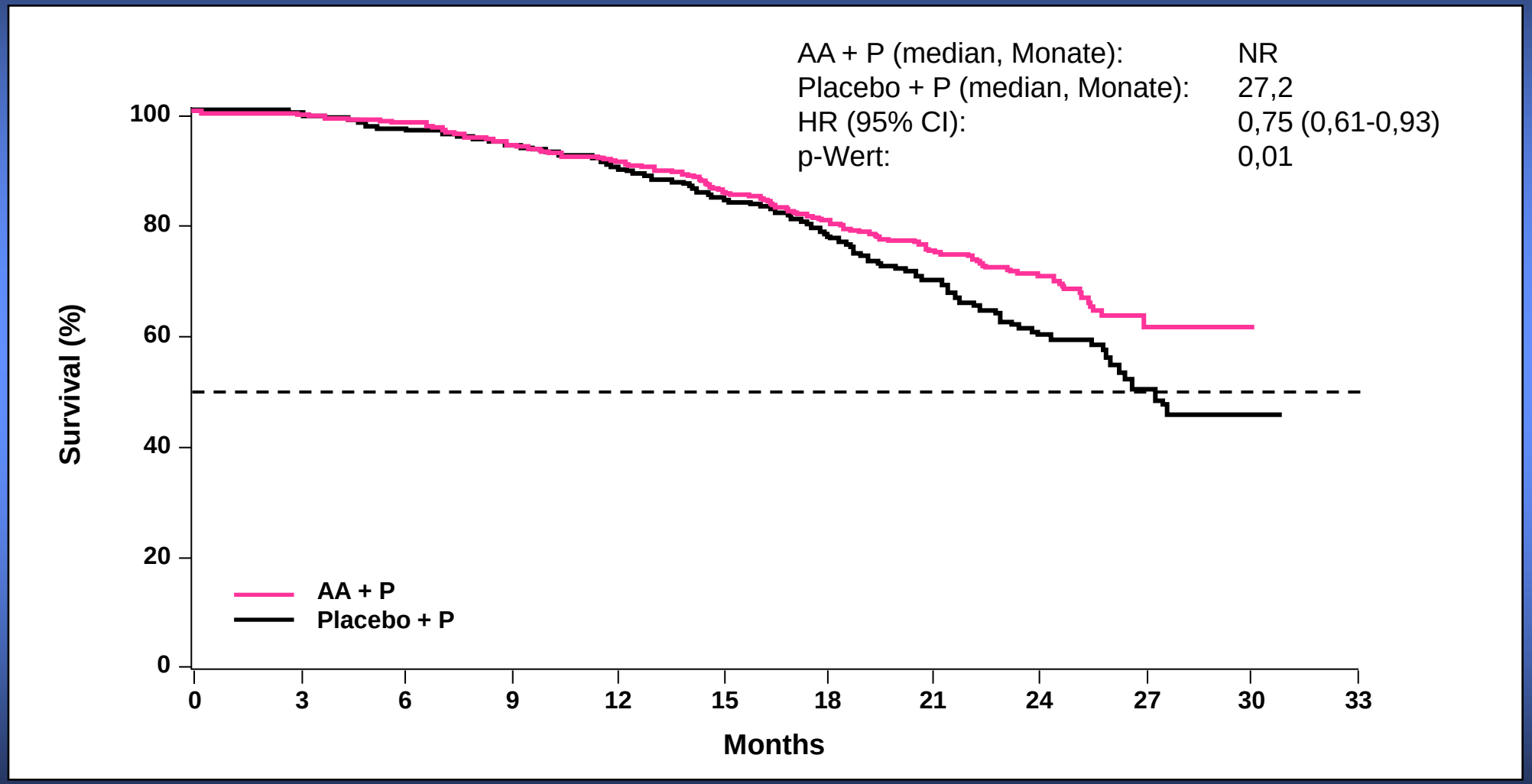
radiological progression free survival



Ryan et al., NEJM 2012

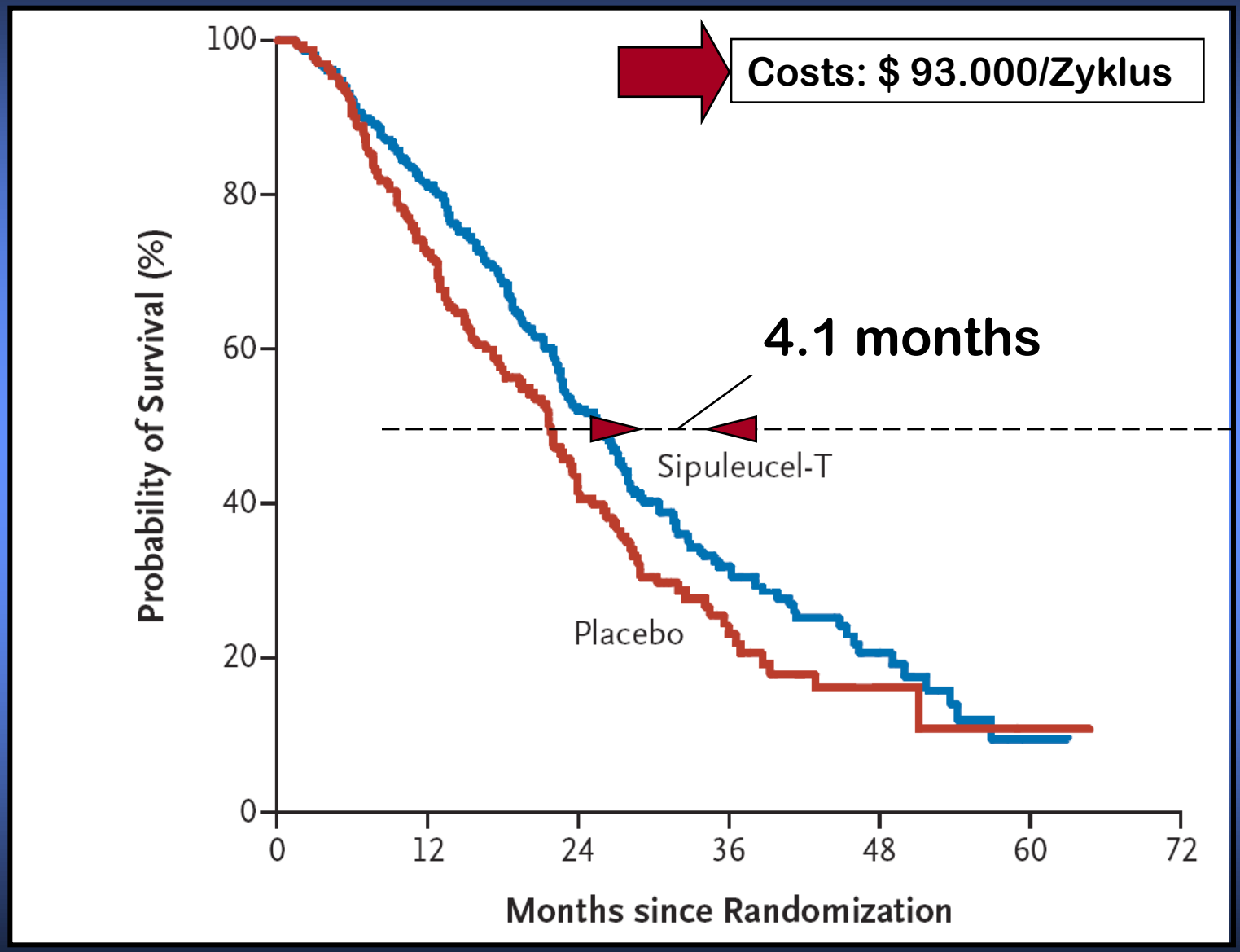
Abiraterone before chemotherapy

Overall survival



Ryan et al., NEJM 2012

Sipuleucel-T (Provenge®) in CRPC (n=512)

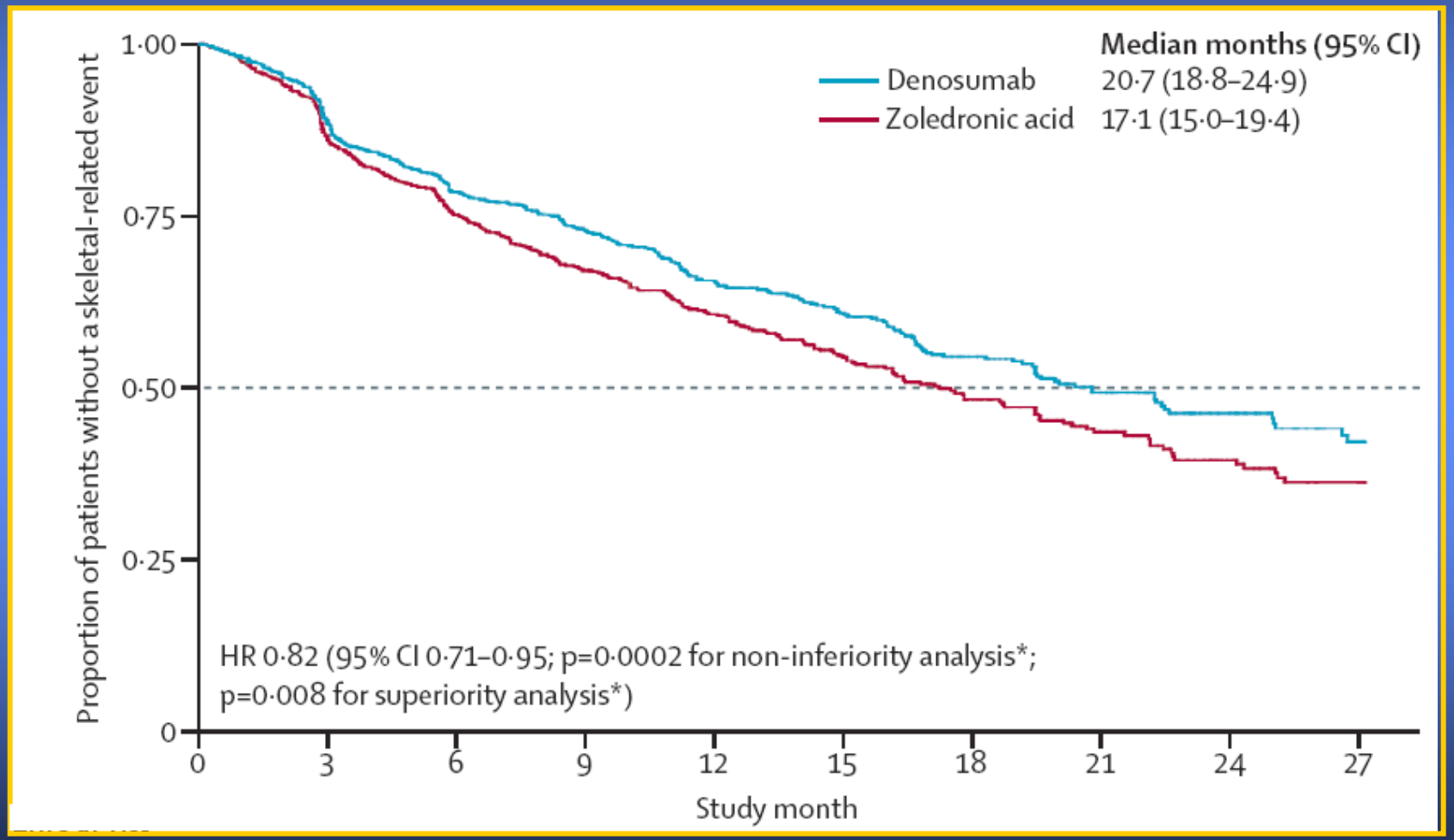


Kantoff et al., NEJM 2010

Treatment of bone metastases

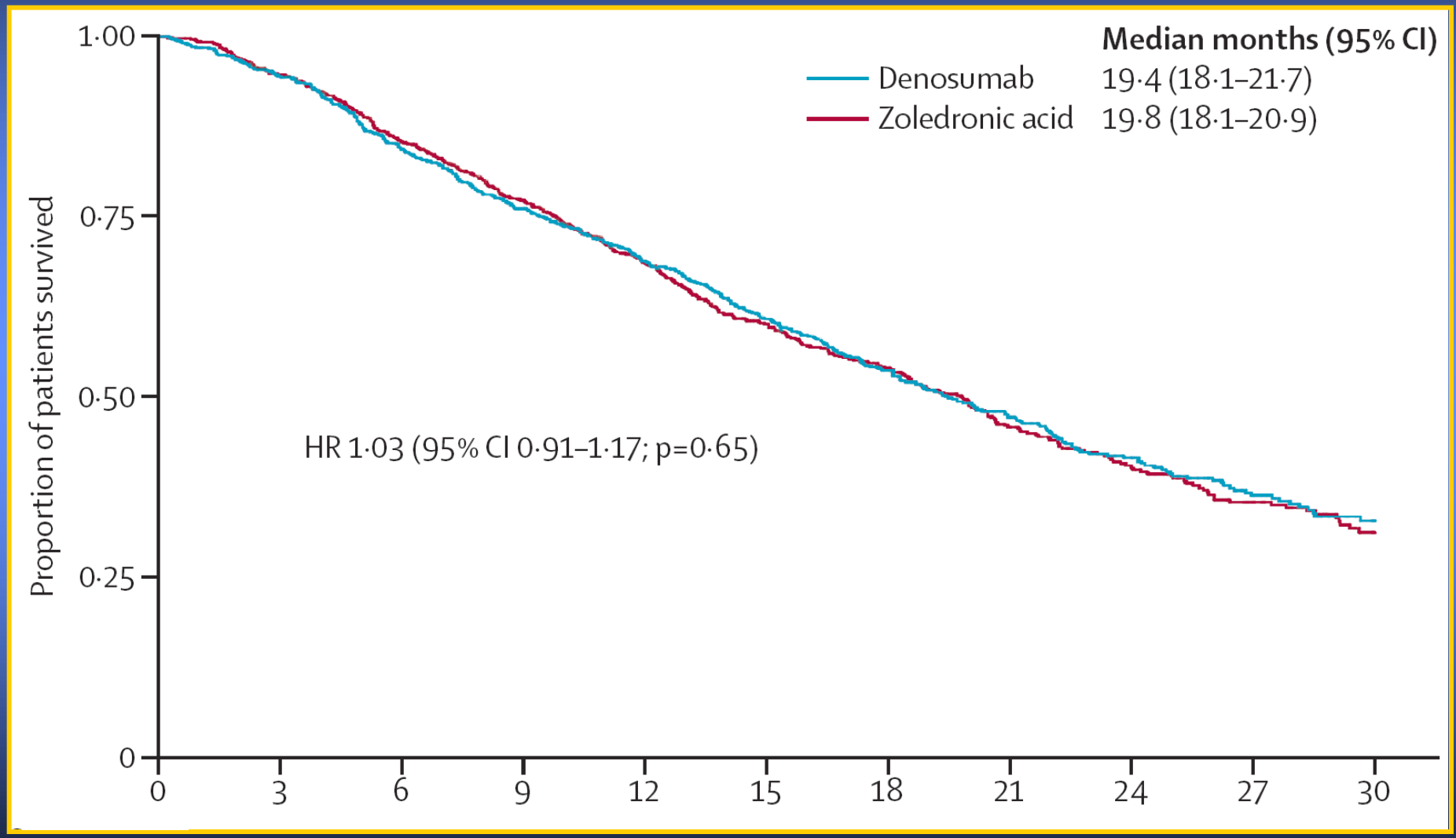
Denosumab added as an additional option.

Denosumab vs. zoledronate to prevent skeleton related events in CRPC (n=1904)



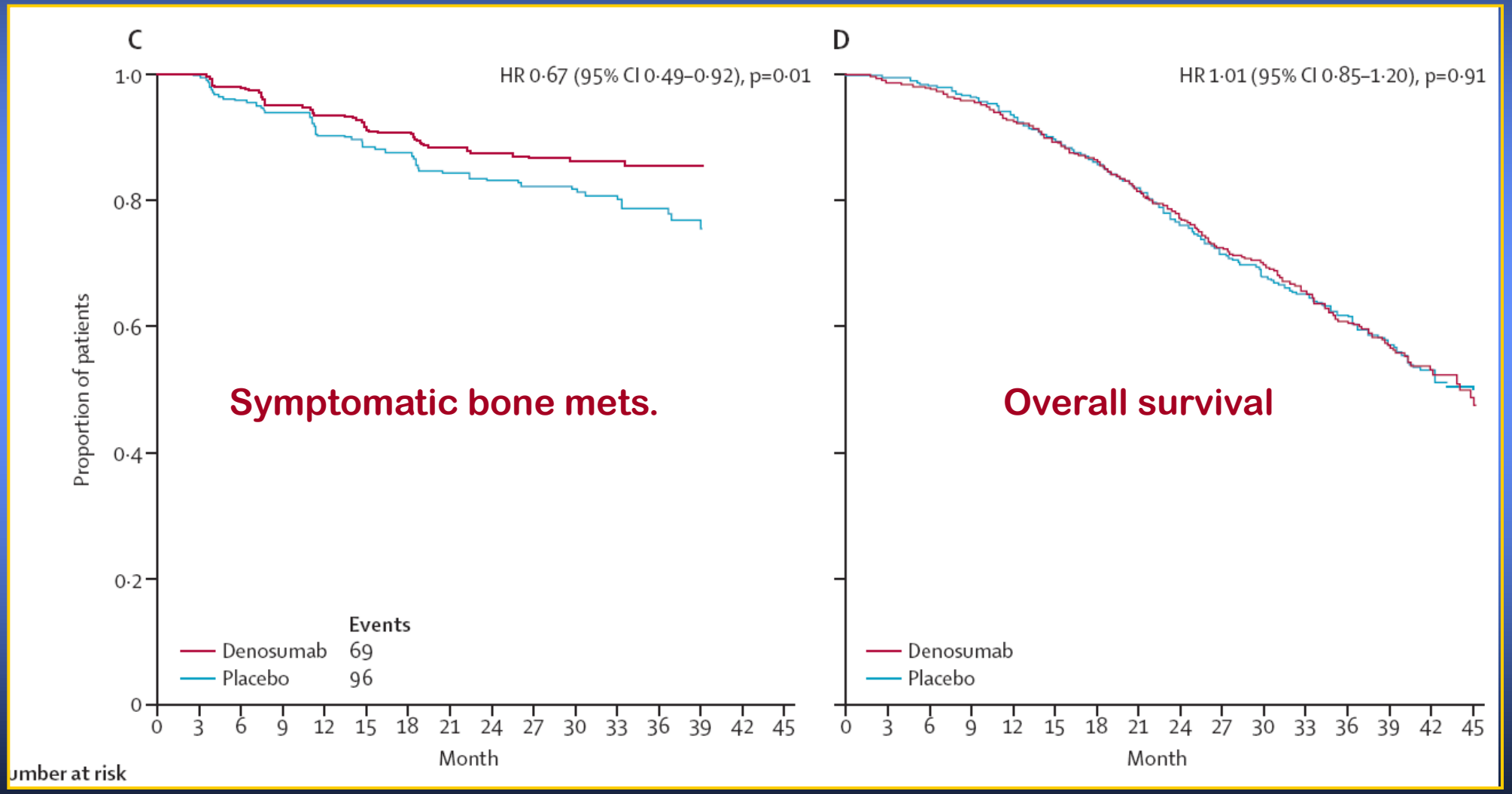
Fizazi et al., Lancet 2011

Denosumab vs. zoledronate in CRPC: survival (n=1904)



Fizazi et al., Lancet 2011

Denosumab vs. placebo to prevent bone metastases in CRPC (n=1432)



Smith et al., Lancet 2012

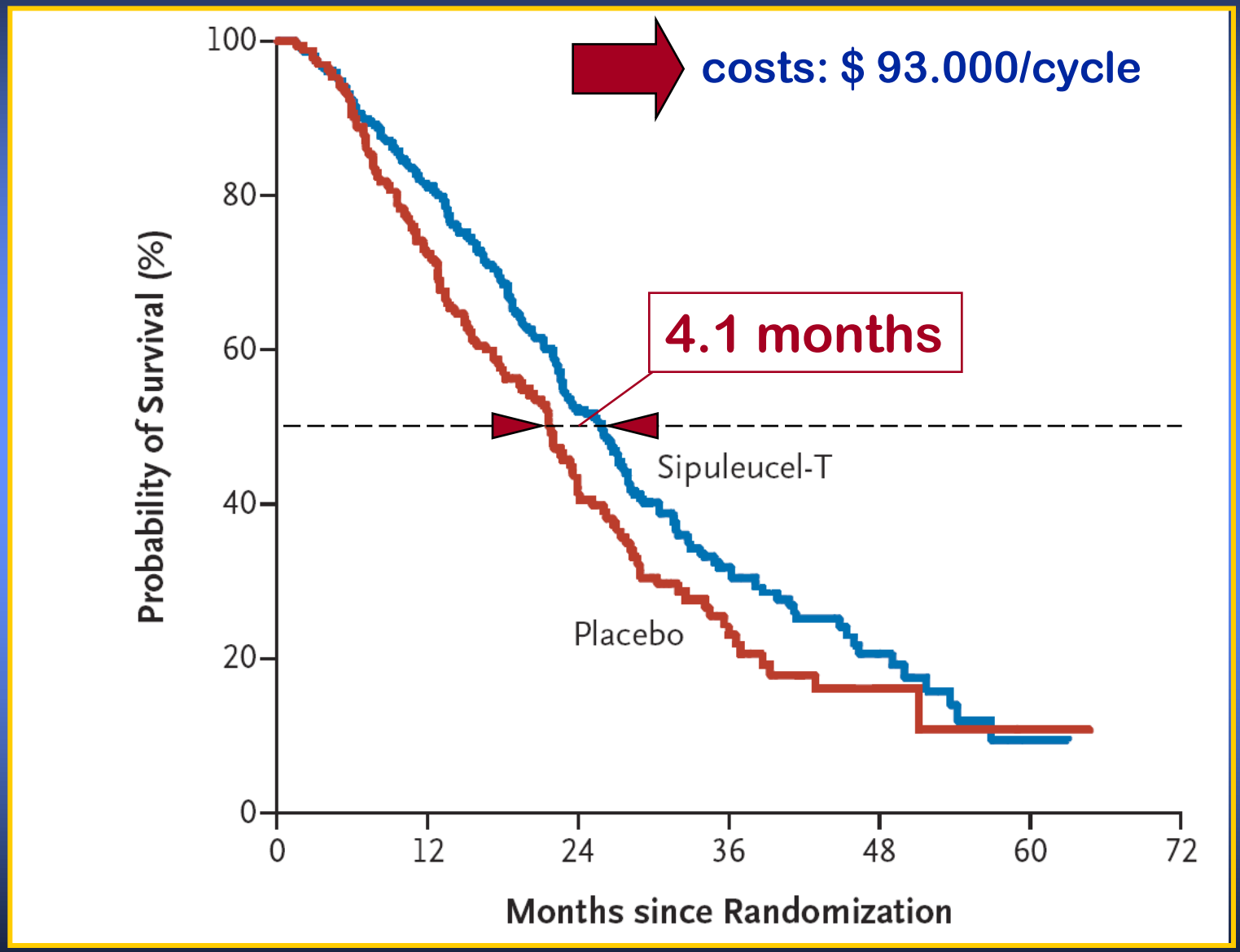
FDA panel votes against Amgen's Xgeva for prostate cancer

February 8, 2012 | 2:36 p.m.

Washington— A panel of cancer experts voted against a new use for Amgen Inc.'s Xgeva in prostate cancer on Wednesday, saying the drug's ability to slow the spread of the disease did not translate into meaningful benefits for patients.

The Food and Drug Administration's cancer drug panel voted 12 to 1 that the benefits of the drug did not outweigh its risks, which included bone disease in about 6% of patients. The FDA is not required to follow the group's advice, although it often does.

Sipuleucel-T (Provenge®) for CRPC (n=512)



Kantoff et al., NEJM 2010

Radium-223 (Alpharadin)

ALSYMPCA trial: design

921 men with CRPC & bone metastases (≥ 2 hot spots)

No known visceral mets.

Post-docetaxel or "unfit"

Randomised: 2:1

Alpharadin 50 kBq/kg bw
6 IV doses

Best supportive care

Placebo 6 IV doses

Best supportive care

Primary endpoint:

- OS

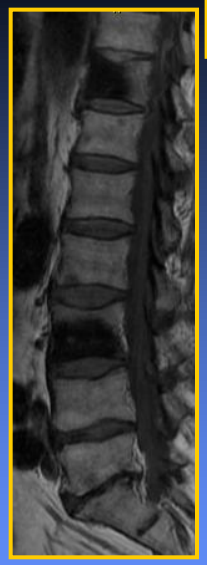
Secondary endpoints:

- TTPP
- TTP in total-ALP
- Safety
- HRQoL

Stratifications:

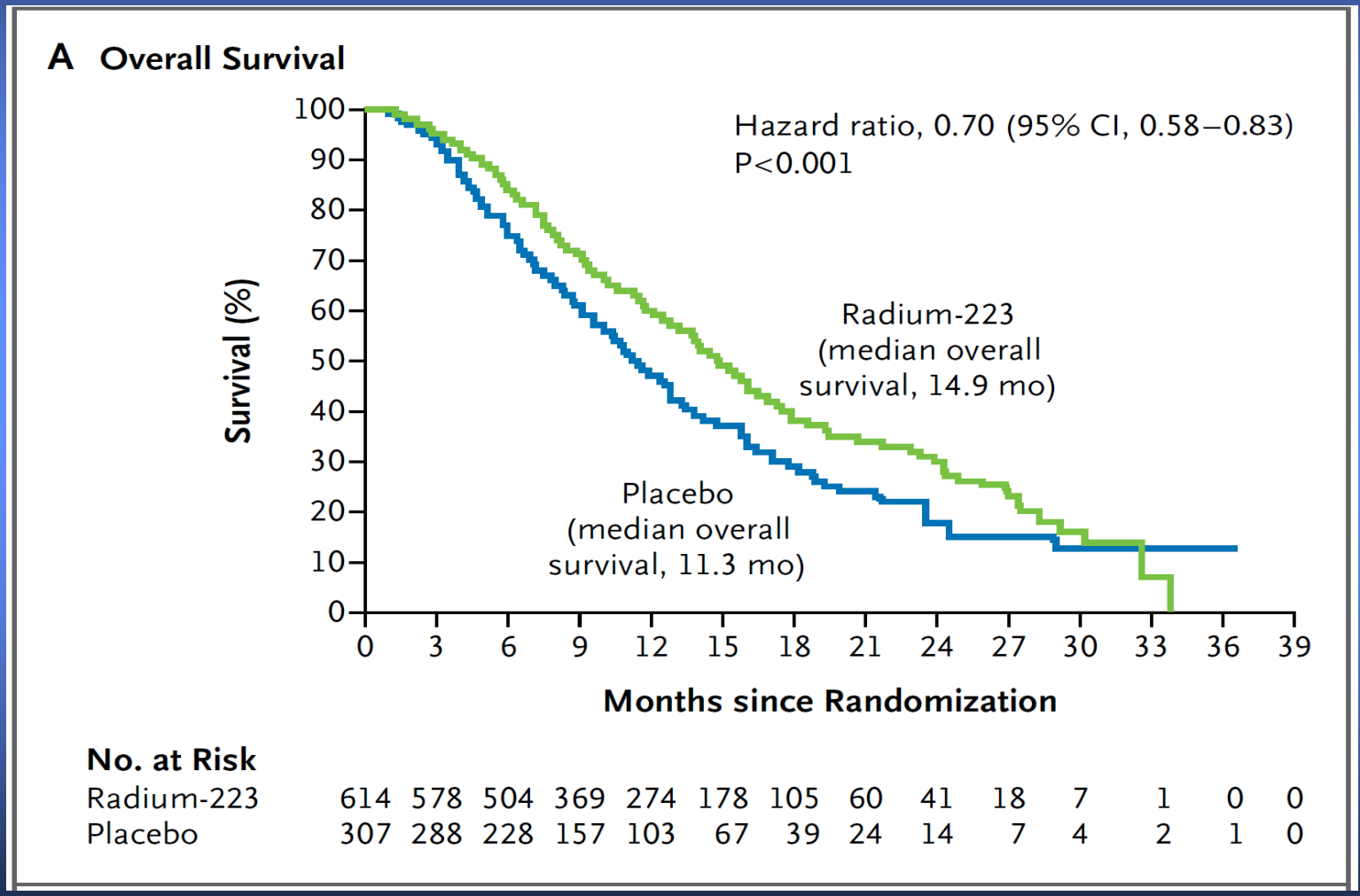
Total ALP:	< 220 U/L vs.≥ 220 U/L
Bisphosphonate use:	Yes vs. No
Prior docetaxel:	Yes vs. No

http://media01.smartcom.no/Microsite/start.aspx?eventid=6325. Accessed November 2011



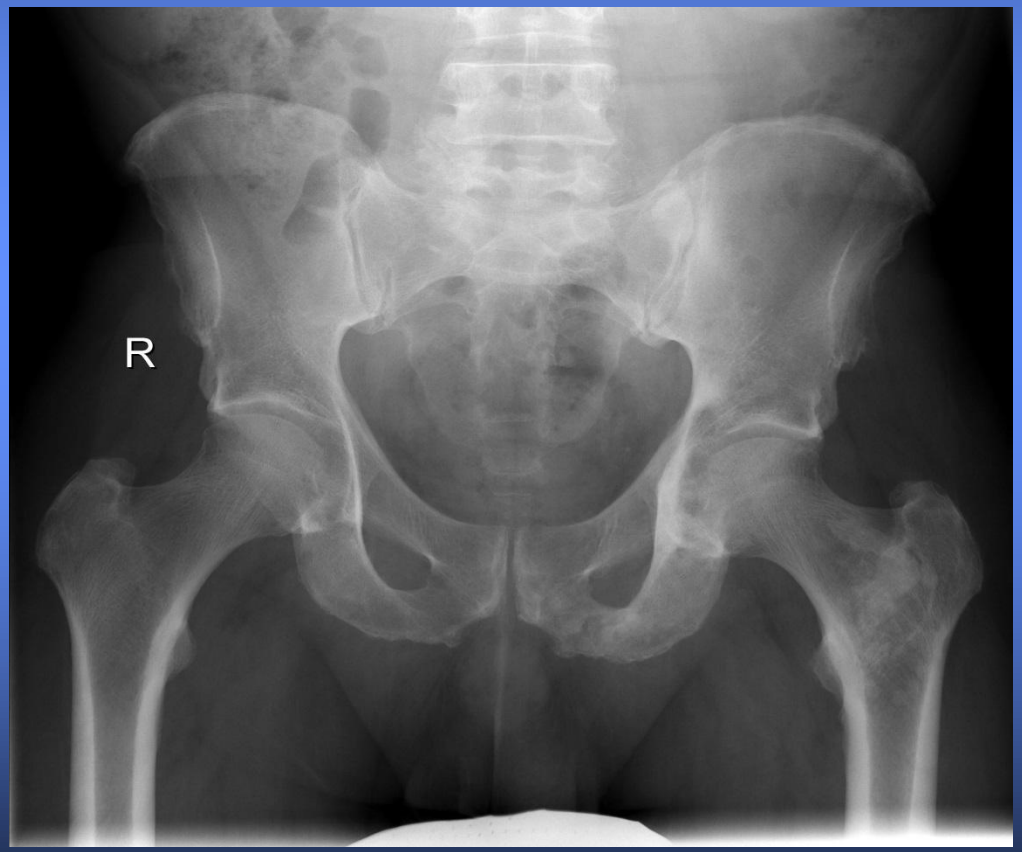
Radium-223 (Alpharadin) vs. placebo for symptomatic bone metastases

ALSYMPCA trial, overall survival (n=921)



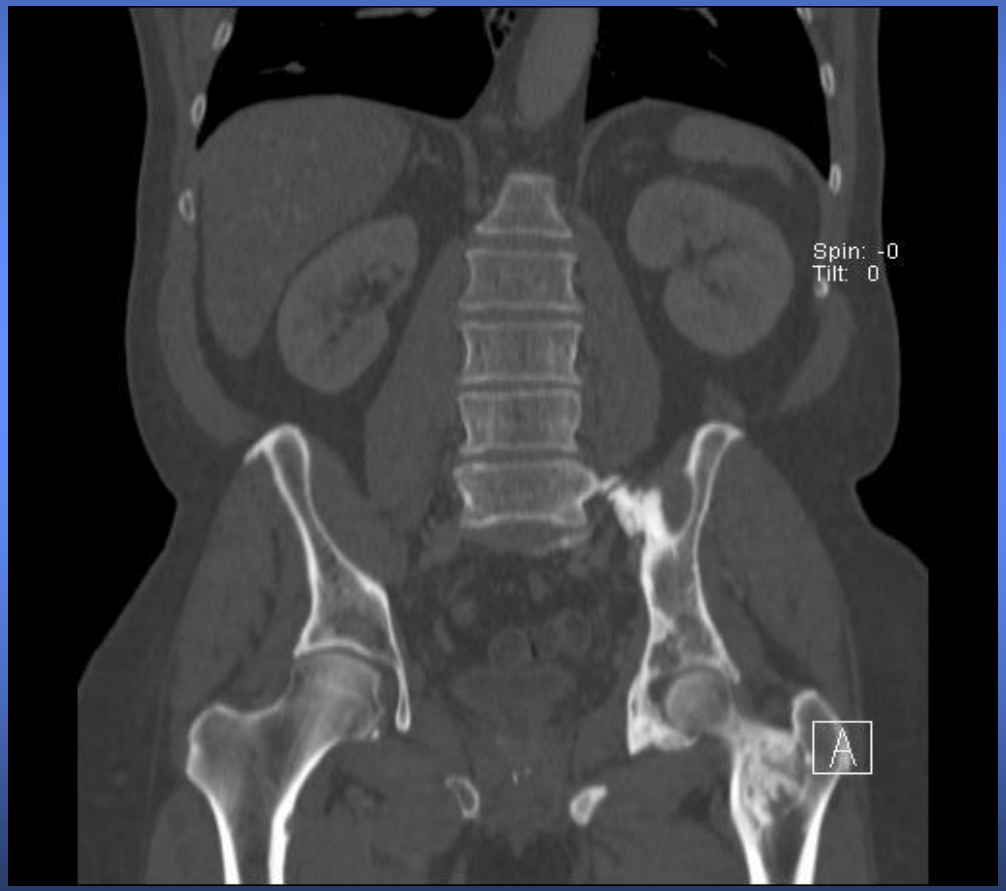
Parker et al., NEJM 2013

62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip



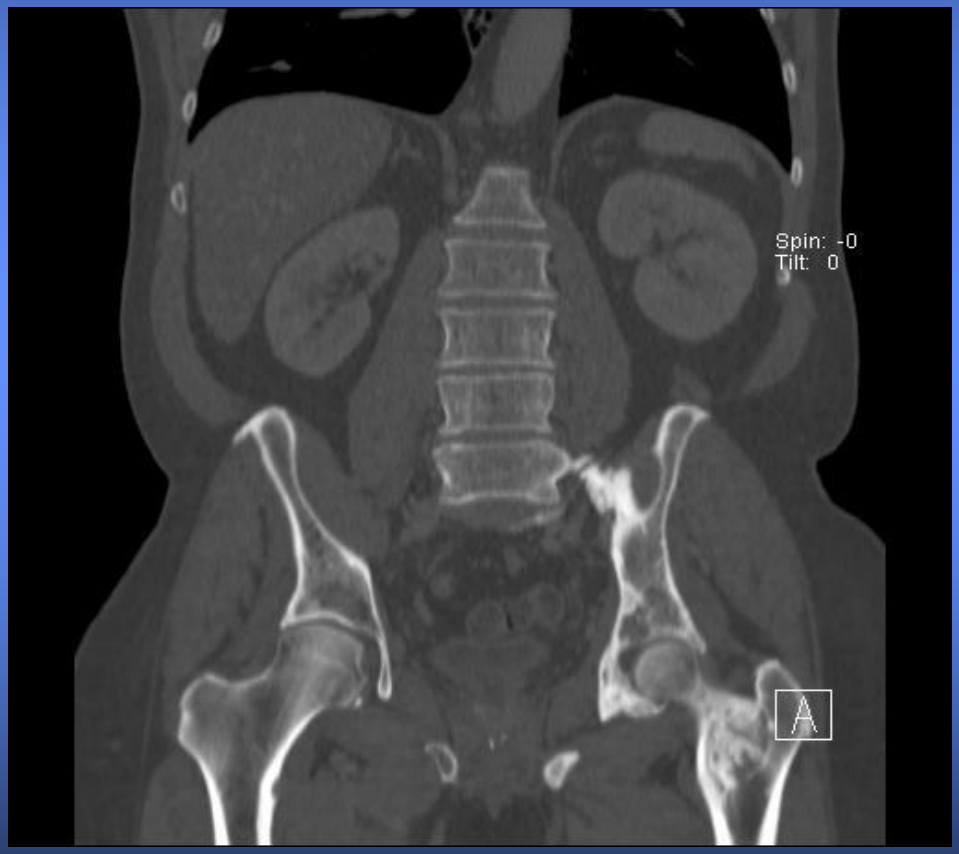
- Start hormonal therapy
- PSA NADIR 31 ng/ml
- from 08/2007 Docetaxel Chemotherapy, 10 cycles until 03/2008
- PSA 01/2008: 11.9 ng/ml
- 02/2010: PSA 63, Start clinical study with antibody against Integrines

62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip



- Study until 11/2010
- consecutive PSA-rise until 282 ng/ml
- no progressive pain, no progressive bone metastasis
- from 01/2011 again therapy with docetaxel
- 9 cycles: PSA 06/2011 83.7 ng/ml
- Stop Chemo, PSA 09/2011, 40 ng/ml (NADIR)

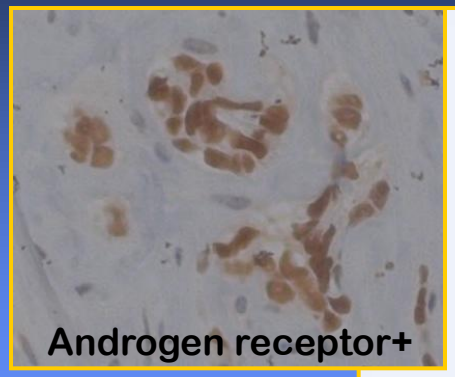
62 years, 08/2006 PCA metastatic to bone, PSA 422 ng/ml, metastasis left hip



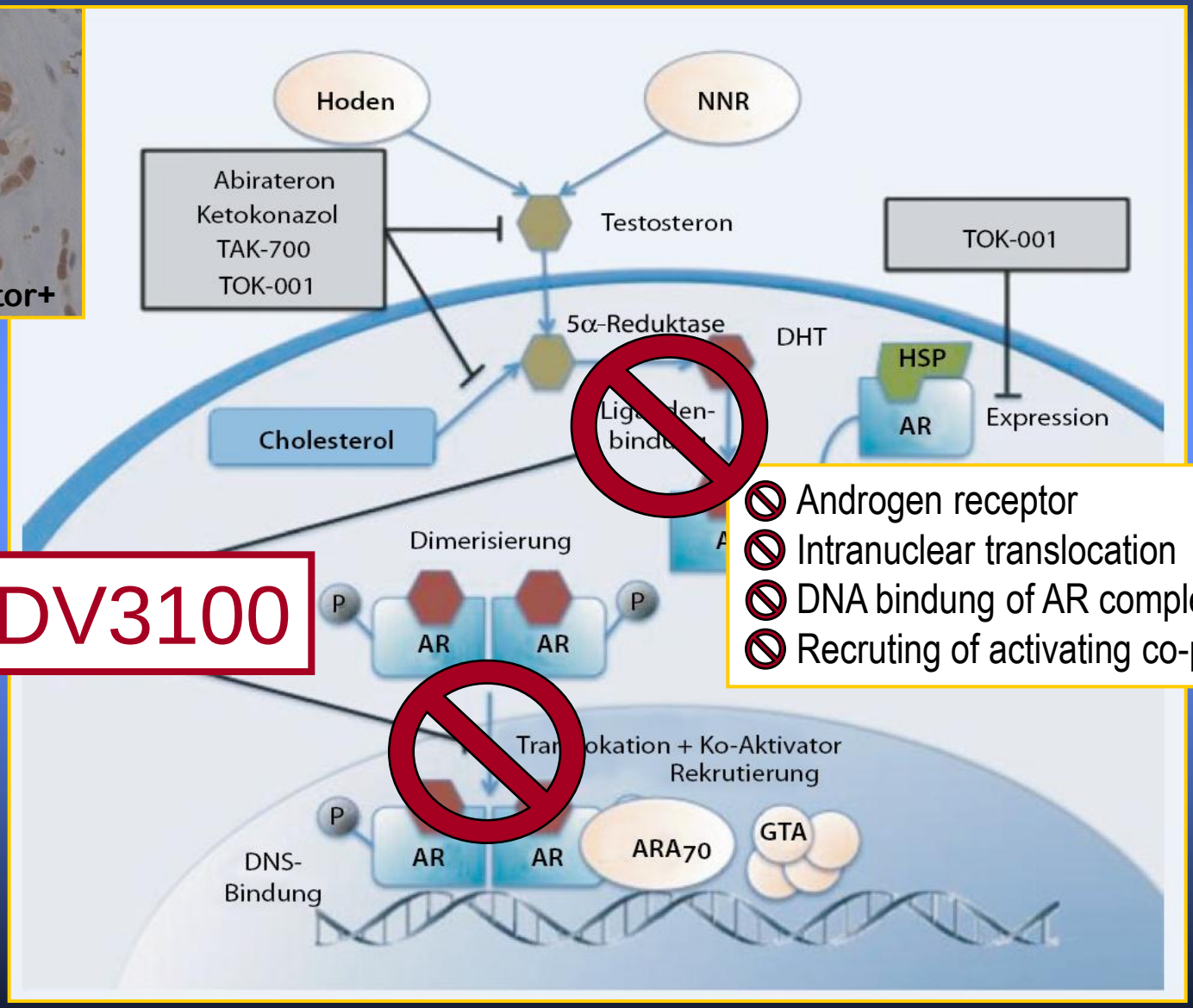
- from 01/2012 Abiraterone with PSA 90 ng/ml
- 04/2012 PSA 171 ng/ml, from 04/2012 Cabazitaxel
- 10 cycles Cabazitaxel until 10/2012
- PSA 11/2012: 19 ng/ml (NADIR)
- PSA 04/2013 127 ng/ml
- Bone scan: progressive bone metastases
- Start Enzalutamide 03/2014

Future developments: new drugs

Testosterone metabolism, androgen receptor signalling and interaction of MDV3100



© Dr. M. Sergon, UKD



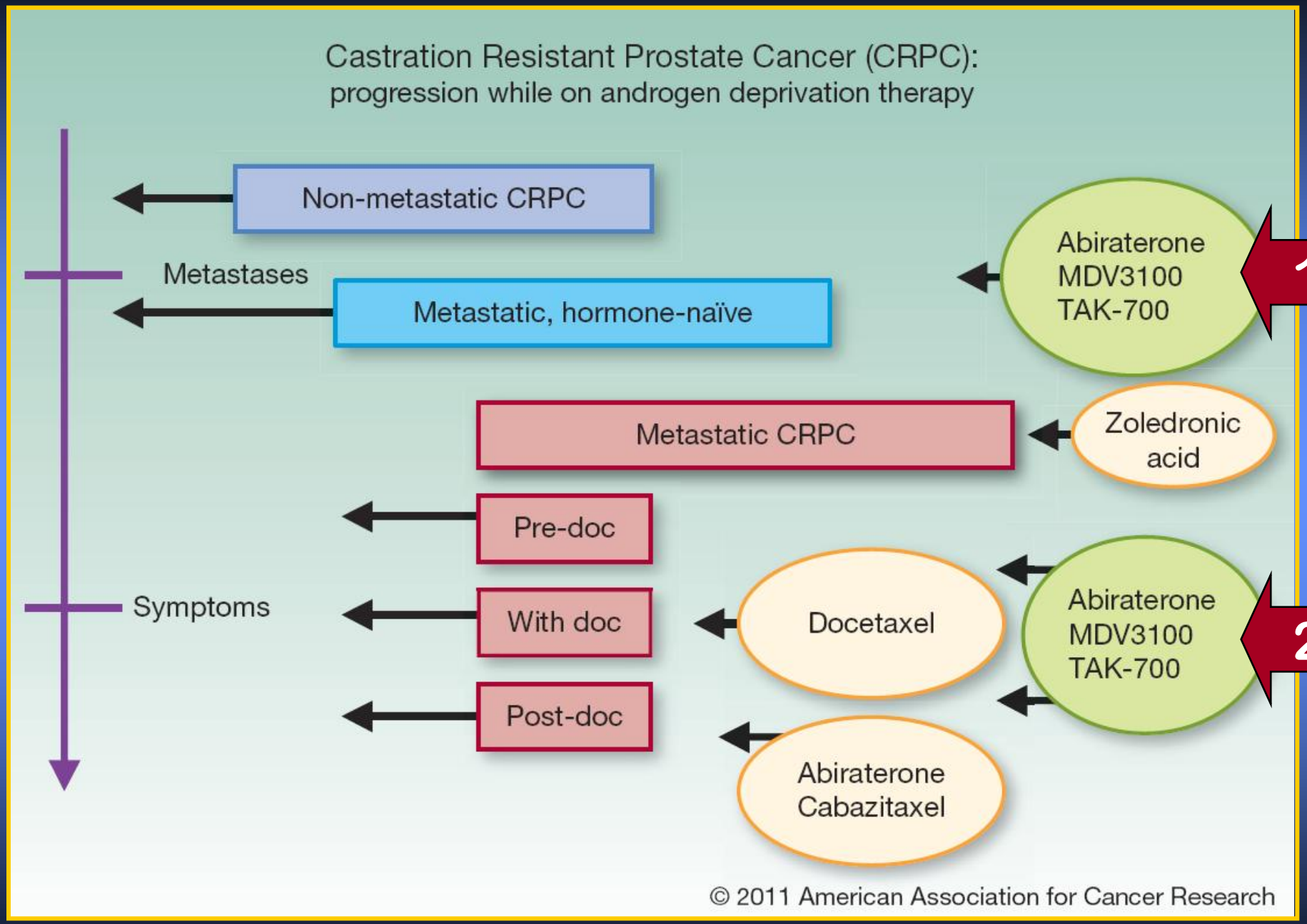
MDV3100

Tran et al., Science 2009

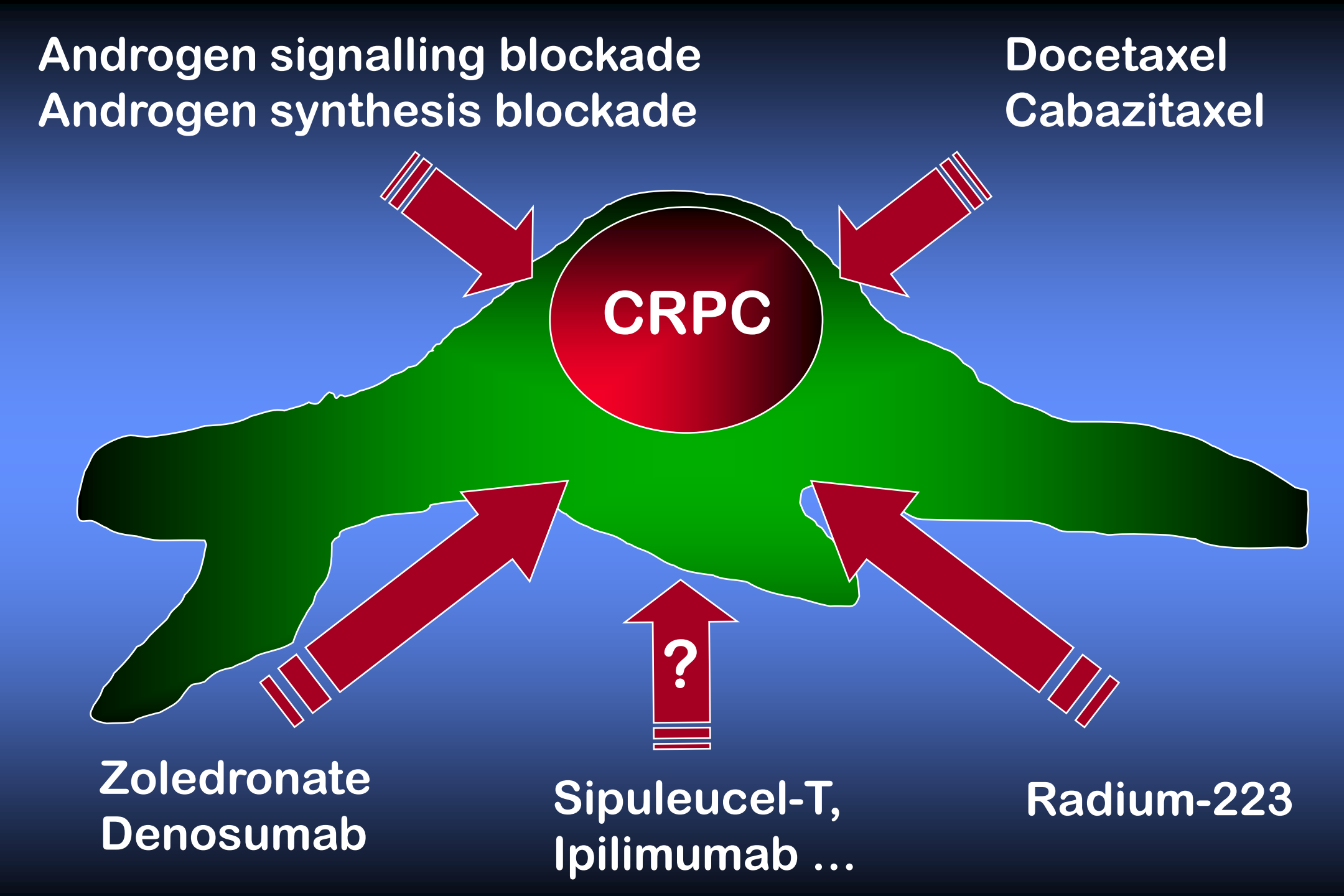
- Androgen receptor
- Intranuclear translocation
- DNA bindung of AR complex
- Recruting of activating co-proteins

Ohlmann et al., Urologe 2011

Future developments: earlier treatment



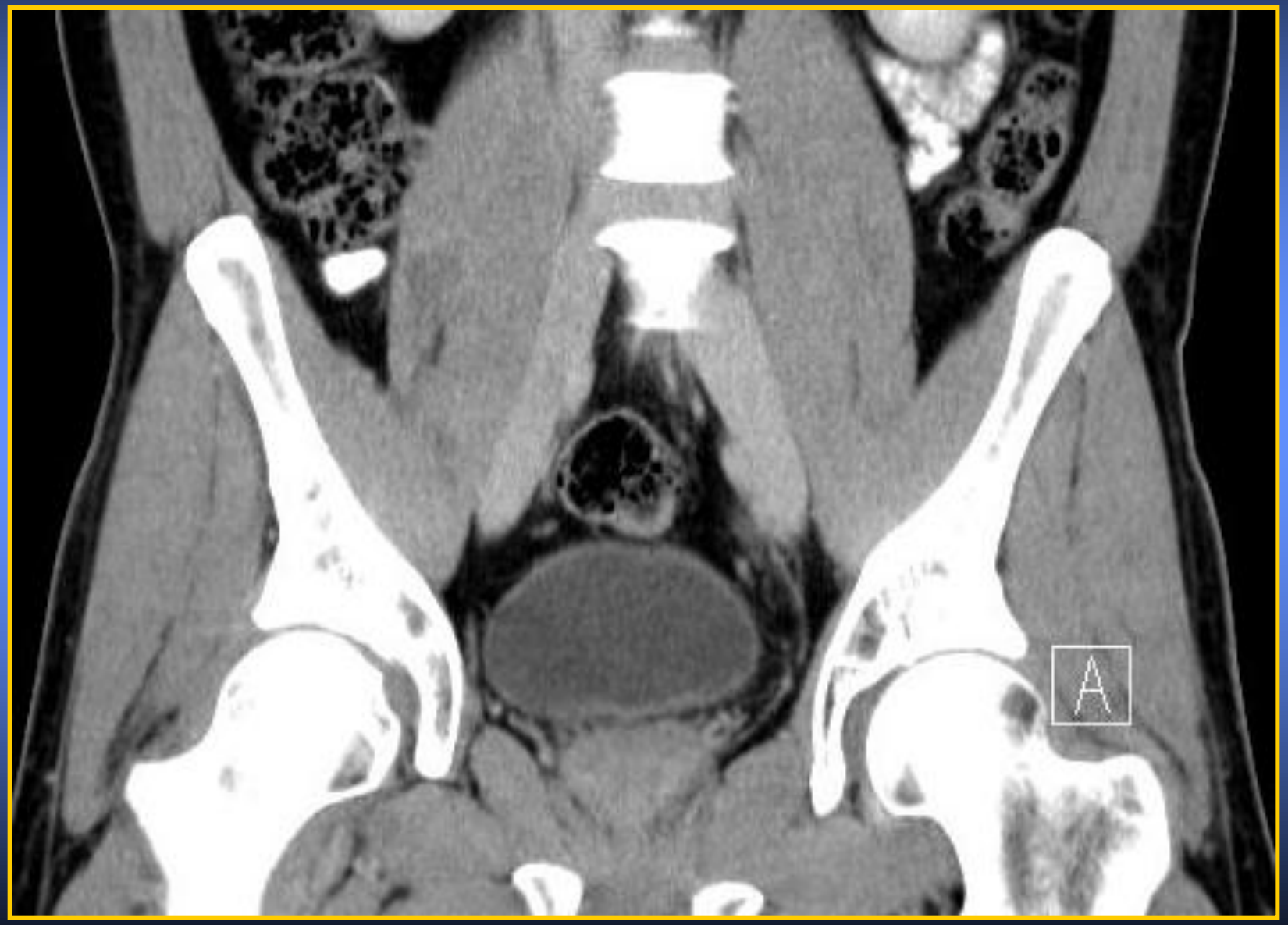
Massard and Fizazi, Clin Cancer Res 2011


Androgen signalling blockade
Androgen synthesis blockade
Docetaxel
Cabazitaxel
CRPC
?
Zoledronate
Denosumab
Sipuleucel-T,
Ipilimumab …
Radium-223

Patient history

- 42 y, academic
- 2/10 Zyl. Gleason 3+4=7, cT1c,
  PSA 7.9 ng/ml
- Reference pathologist: Gleason 3+5=8
- No comorbidity

CT: normal



Options

a) Nerve- sparing RPE
b) EBRTX
c) Brachytherapy
d) Active Surveillance

Current Model

Extent of Disease Probability		
Indolent Cancer		N/A
Organ Confined Disease		54%
Extracapsular Extension		38%
Seminal Vesicle Invasion		9%
Lymph Node Involvement		5.0%
Primary Treatment Outcome		
Progression Free Probability after Radical Prostatectomy	5 Year	92%
	10 Year	88%
Probability of Cancer-Specific Survival	10 Year	99%
	15 Year	99%

Historical Model

Extent of Disease Probability		
Indolent Cancer		N/A
Organ Confined Disease		37%
Extracapsular Extension		40%
Seminal Vesicle Invasion		15%
Lymph Node Involvement		8%
Primary Treatment Outcome		
Progression Free Probability after Radical Prostatectomy	5 Year	80%
	10 Year	N/A

Memorial Sloan Kettering Cancer Center

mskcc.org
PREDICTION TOOLS

Therapieempfehlung

Ihr Tumor hat ein geringes Progressionsrisiko, wenn man von der qualitativen Einschätzung des Gleason Score absieht. Allerdings erfüllt der Tumor mit einer Ausdehnung von 70% in einem Zylinder nicht mehr die idealen Bedingungen einer Active Surveillance Strategie. Trotzdem sollte für Sie die Devise gelten: „Tee trinken und warten". Sie haben Zeit bis zu einer Entscheidung über die zu wählenden Therapiestrategie. Diesen Zeitraum möchte ich durch aktive Überwachung möglichst weit gefasst sehen. Lassen Sie dreimonatlich die PSA-Werte und den Tastbefund kontrollieren.

!


118852
Julius
Hackethal
Keine Angst
vor Krebs

?

1 year later

- 3/12 Zyl. Gleason 3+4=7, cT1c,
- PSA 12.3 ng/ml

Current Model

Extent of Disease Probability		
Indolent Cancer		N/A
Organ Confined Disease		47%
Extracapsular Extension		44%
Seminal Vesicle Invasion		15%
Lymph Node Involvement		6.7%
Primary Treatment Outcome		
Progression Free Probability after Radical Prostatectomy	5 Year	90%
	10 Year	85%
Probability of Cancer-Specific Survival	10 Year	99%
	15 Year	99%

Historical Model

Extent of Disease Probability		
Indolent Cancer		N/A
Organ Confined Disease		23%
Extracapsular Extension		40%
Seminal Vesicle Invasion		20%
Lymph Node Involvement		16%
Primary Treatment Outcome		
Progression Free Probability after Radical Prostatectomy	5 Year	69%
	10 Year	N/A

Memorial Sloan Kettering Cancer Center

mskcc.org
PREDICTION TOOLS

Radium 223 case studies part 4: combination therapy

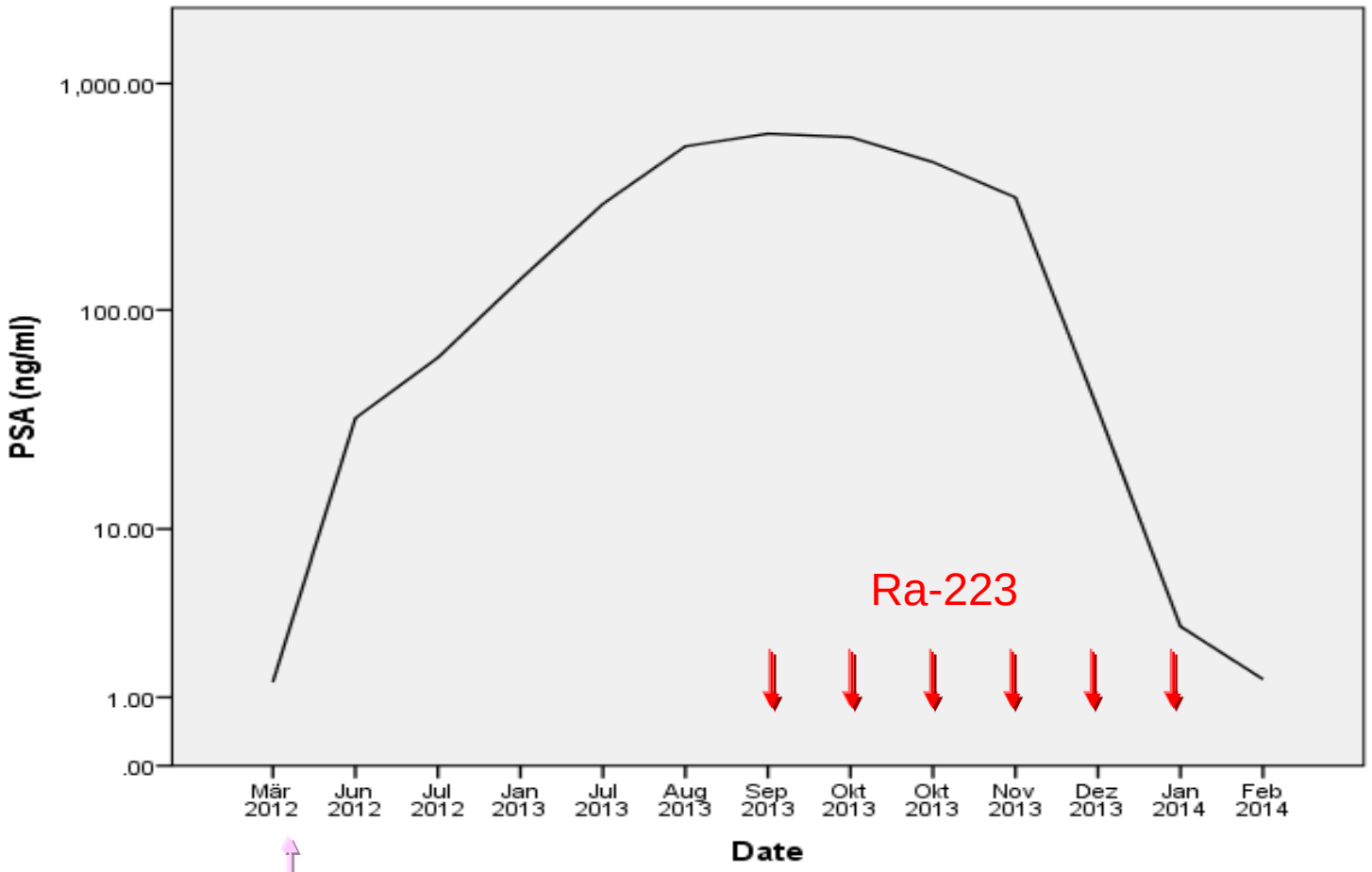
Manfred Wirth

University Hospital Carl Gustav Carus Dresden and
Technical University of Dresden,
Dresden, Germany

Case

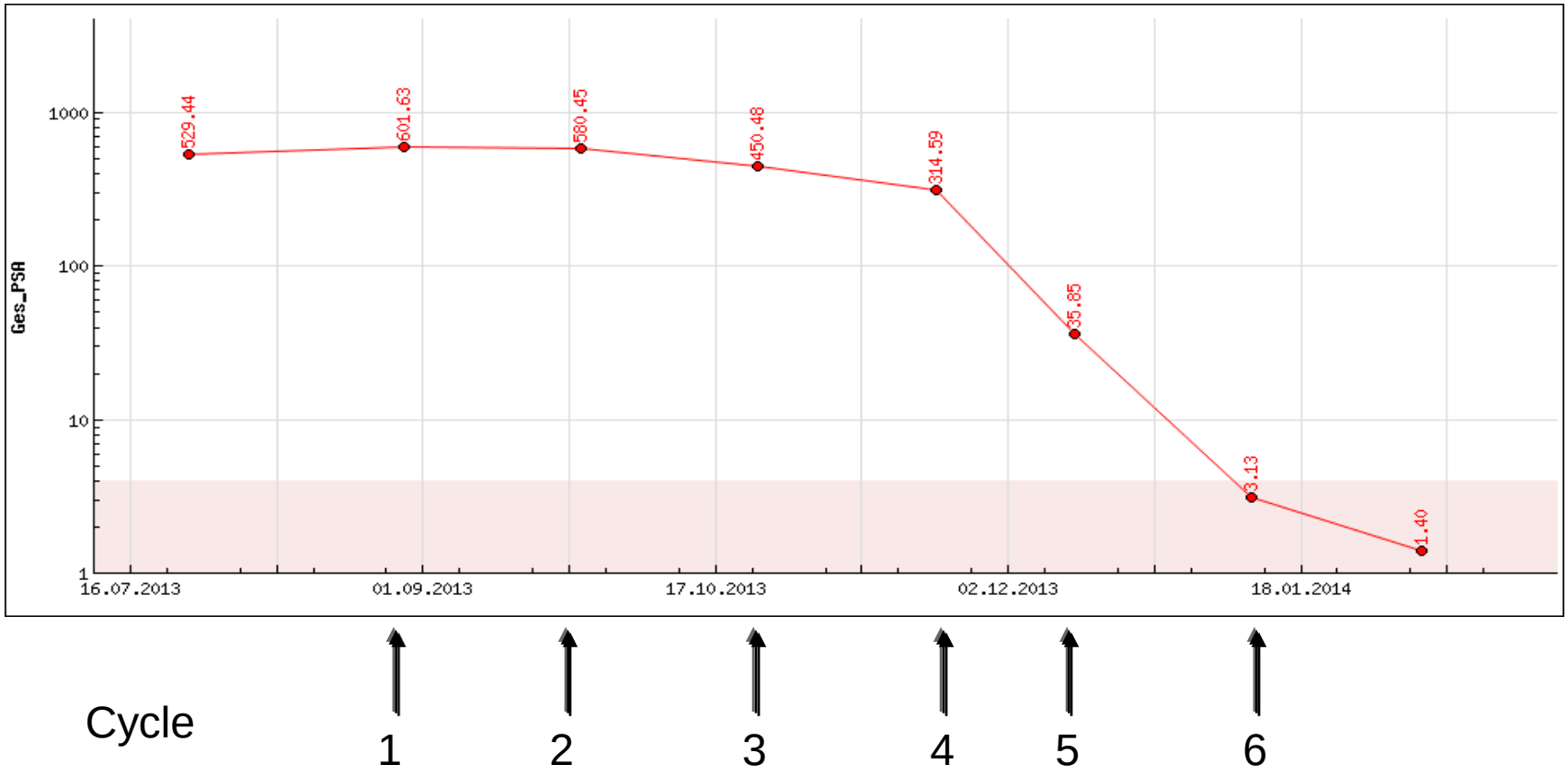
- 78 year old male
- Diagnosis of PCA metastatic to bone 06/2011
- Gleason score 4+5=9
- Since 06/2011 complete androgen blockade with Busereline and Bicalutamide
- Since 08/2011 Zoledronic acid 4 weekly
- After progression to castrate resistance 4 cycles of Docetaxel 1012/2012
- Since 01/2013 Abiraterone 1000 mg daily
- 10/2013 stop Bicalutamide

Overall PSA - Kinetics



Case – PSA during Ra-223

- PSA after start of Ra-223 parallel to Abiraterone:



Case II – Ra-223 and Abiraterone

- No significant AE‘s
- No progressive pain
- No opioid medication

- No liver toxicity, no bone marrow toxicity

- Conclusion: In this case no AE‘s with both medications
- Therapy oncologically effective regarding PSA response and Performance status

Radium 223 case studies part 4: combination therapy

Manfred Wirth

University Hospital Carl Gustav Carus Dresden and
Technical University of Dresden,
Dresden, Germany

Case

- 65 year old male at diagnosis
- 11/2011: PSA 65 ng/ml, Gleason 5+5=10
- Androgen deprivation therapy
  - 05/2012: PSA Nadir 0.34 ng/ml
- CRPC
  - 09/2012: PSA 20.5 ng/ml
  - Na-F-PET 10/2012: multiple bone metastases
- Initiation of Docetaxel 12 cycles until 05/2013
  - PSA Nadir 1.6 ng/ml
  - PSA 05/2013: 14.9 ng/ml

Case

- Docetaxel-therapy and further course:

- 07/2013: PSA 34.5 ng/ml
- Pain lumbar spine
- Planning of Ra-223
- First dose 30/09/2013

Case – PSA, Medication and LFT

Date	PSA (ng/ml)	Ra 223	Abiraterone (mg/24h)	ASAT (µmol/s*l)	ALAT (µmol/s*l)
30/09/2013	83.02	yes	-	0.43	0.35
30/10/2013	196.84	yes	-	0.35	0.46
27/11/2013	440.33	yes	1000	0.45	0.43
30/12/2013	1201.9	yes	1000	0.44	0.35
29/01/2014	2291.25	yes	1000	0.88	0.35
27/02/2014	3443.16	-	1000	0.37	0.5

Adverse events

Cycle	AE 1 (Treatment)	AE 2 (Treatment)	AE 3 (Treatment)	AE 4 (Treatment)
1	-			
2	Pain right hip (Metamizol, Tilidine)			
3	-			
4	Fatigue	Flu/ Cold		
5	Fatigue	Pain/ cramps both thighs	Weight loss 4kg	

Serious Adverse Events

- 30/01/2014 – 05/02/2014
- Fever
- Exsiccosis
- Hypokalemia
- Anemia – Transfusion, 2 Units of Packed red blood cells

- 17/02/2014 – 22/02/2014
- Fever
- Exsiccosis
- Borderline Hypokalemia

Case – PSA, Medication, Hb and Potassium

Date	PSA (ng/ml)	Ra 223	Abiraterone (mg/24h)	Hb (mmol/l)	Potassium (mmol/l)
30/09/2013	83.02	yes	-	7.5	4.05
30/10/2013	196.84	yes	-	7.6	
27/11/2013	440.33	yes	1000	7.0	4.5
30/12/2013	1201.9	yes	1000	7.0	4.8
29/01/2014	2291.25	yes	1000	6.1	4.5
30/01/2014 (SAE)		-	1000	4.9	2.92
17/02/2014 (SAE)	2539.33	-	1000	6.5	3.51
27/02/2014	3443.16	-	1000	6.0	3.51

Phase 3 ALSYMPCA: adverse events

	All grades		Grades 3 or 4	
	Radium 223 (n=600)	Placebo (n=301)	Radium 223 (n=600)	Placebo (n=301)
Haematological				
Anaemia	187 (31)	92 (31)	76 (13)	39 (13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	69 (12)	17 (6)	38 (6)	6 (2)
Non-haematological				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhoea	151 (25)	45 (15)	9 (2)	5 (2)
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (18)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

Data are n (%)

Parker C et al. N Engl J Med 2013;369:213–23

Summary

- Combination therapy feasible
- No additional significant adverse events than expected
- Liver function stable
- Notable: Serious adverse events
  - Hypokalemia: probably related to Abiraterone, could have been aggravated by Ra 223 though no typical side effects of Ra 223
  - Anemia: caused by progressive tumor in bone, but possibly related to Ra 223
- Oncologic efficacy of combination Ra 223 with abiraterone in this case not convincing
  - PSA rise
  - Deterioration of clinical state
- More data needed, observational studies?

Thank you for your attention!

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