

# mCRPC – aktuelle Therapieansätze

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**AKS-Sommerschule, Bregenz 07/15**

# Prostatakarzinom ist ein signifikantes und langfristiges Gesundheitsproblem in Europa/Nordamerika

In 2012, prostate cancer was the most commonly diagnosed cancer in men in Europe

- Over 436,000 new cases reported
- Predicted to rise to ~590,000 cases by 2030

In 2012, prostate cancer was the third leading cause of cancer death in Europe

- Over 101,400 deaths reported
- Predicted to rise to 142,430 deaths in 2030



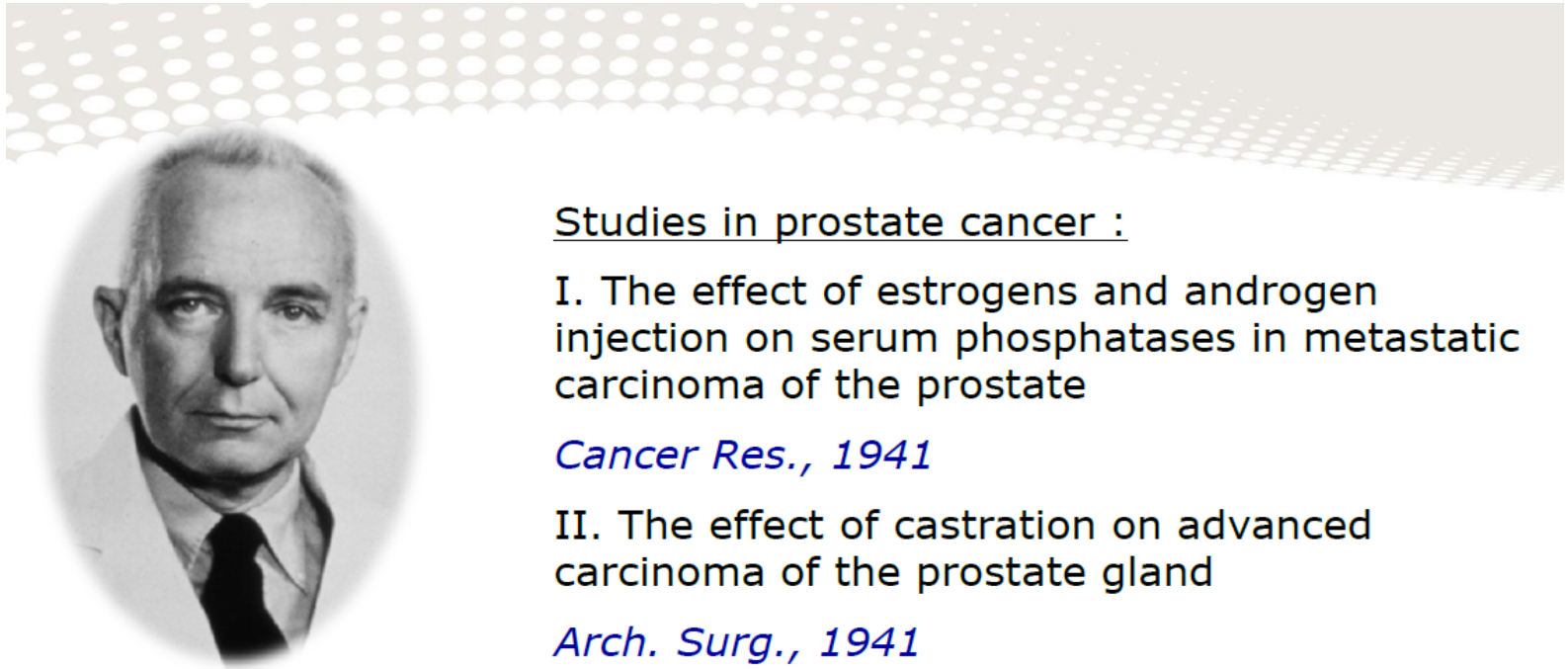
# Tumorlast bei mCRPC

- **PC** ist ein signifikantes + langfristiges Gesundheitsproblem in Europa und USA
- Bis zu **40%** der **PC** entwickeln metastatische Erkrankungen <sup>2</sup>
- Letztlich werden die meisten **PC** trotz **ADT** progredient → kastrationsrefraktär <sup>3,4</sup>
- Reaktivierung des **AR**-signalweges ist der sog. „key driver“ bei der Progression in das CRPC-Stadium <sup>5,6</sup>
  - Verschiedene molekulare Mechanismen **AR**-überexpression inkludierend <sup>5,6</sup>
- **AR** ist der logische Zielpunkt in der Behandlung des CRPC

ADT=androgen-deprivation therapy; AR=androgen receptor; CRPC=castration-resistant prostate cancer; mCRPC=metastatic CRPC.

1. GLOBOCAN Cancer Fact Sheet 2012: Incidence and Mortality Rates All Cancer in Europe. Available at <http://globocan.iarc.fr>. Last accessed: April 2014.
2. Beltran H, et al. *Eur Urol* 2011;60:279–90.
3. Hou X, Flaig TW. *Adv Urol* 2012;2012:978351.
4. Ryan CJ, Tindall DJ. *J Clin Oncol* 2011;29:3651–8.
5. Hu R, et al. *Expert Rev Endocrinol Metab* 2010;5:753–64.
6. Heinlein CA, Chang C. *Endocr Rev* 2004;25:276–308.

# Charles Huggins, der Vater der Hormontherapie



**Charles HUGGINS**  
1901 – 1955  
Winner of 1966 Nobel Prize

## Studies in prostate cancer :

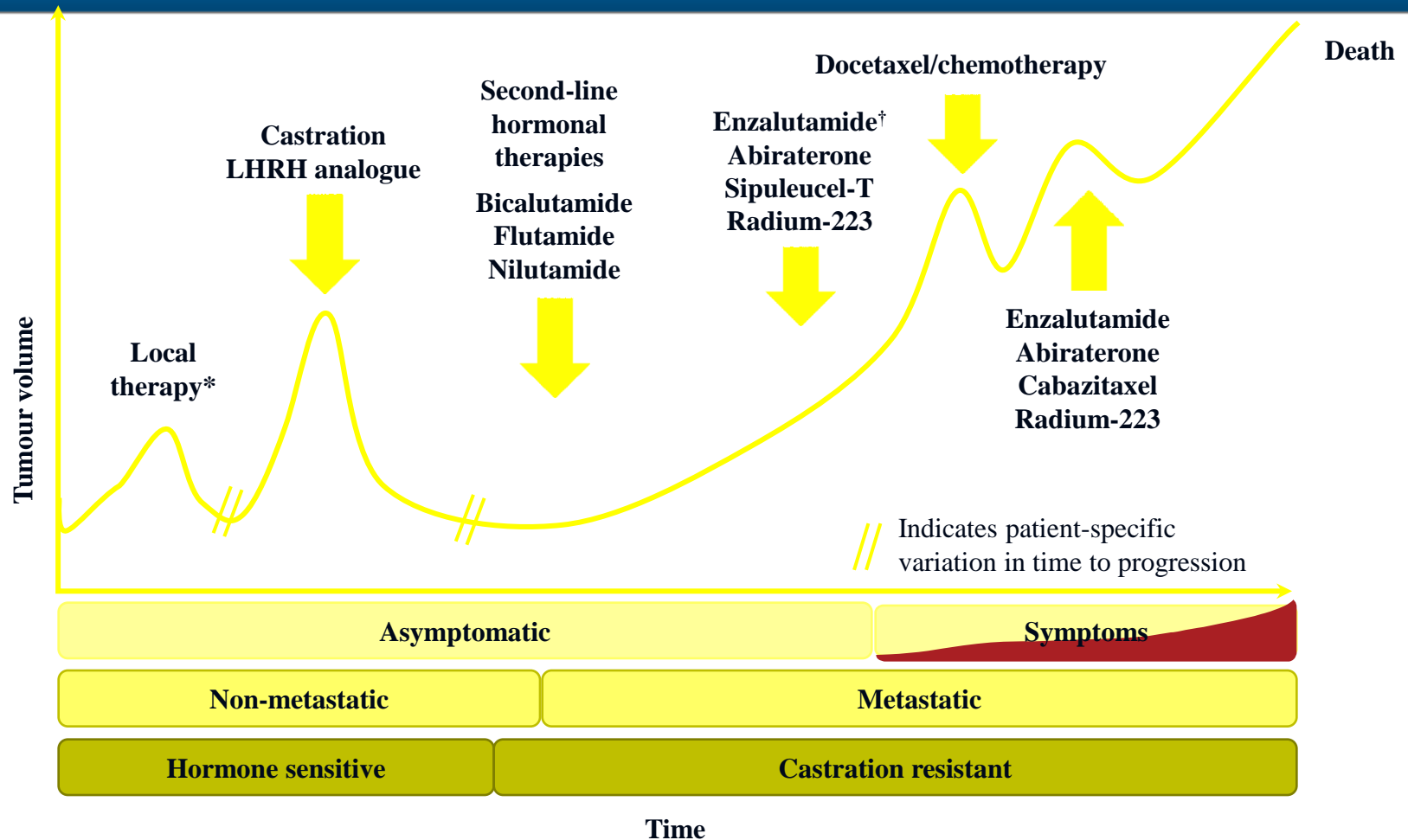
I. The effect of estrogens and androgen injection on serum phosphatases in metastatic carcinoma of the prostate

*Cancer Res., 1941*

II. The effect of castration on advanced carcinoma of the prostate gland

*Arch. Surg., 1941*

# PC ist ein Kontinuum verschiedener Erkrankungsstadien



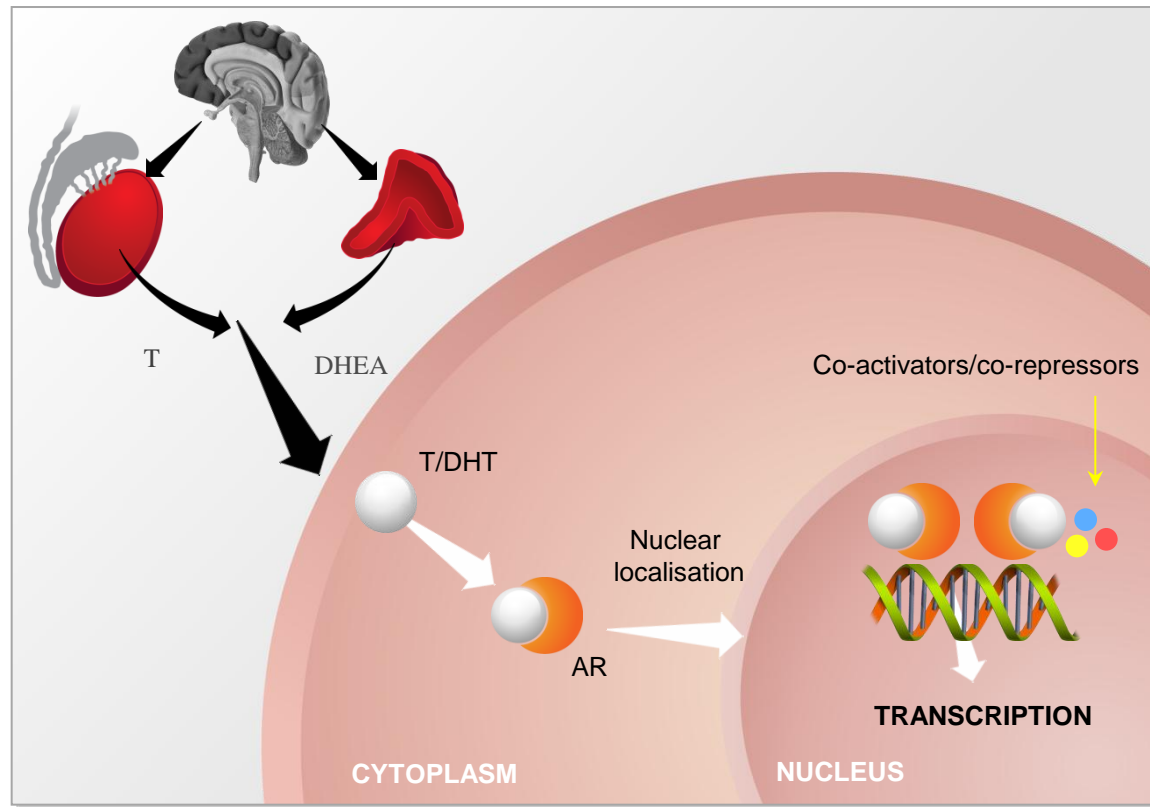
\*For example surgery, radiotherapy. †Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients.

LHRH=luteinising hormone-releasing hormone.

Adapted from George D. *Urology – The Gold Journal* 2013; Available at <http://education.goldjournal.net/path.php?1396:0:Media:title:bxvc:bxvcs> Last accessed June 2014

# Der biologische Effekt der Androgene wird über den AR-signalweg gesteuert<sup>1</sup>

- Both the normal prostate and prostate tumour cells rely on the AR signalling pathway for maintenance and growth<sup>2</sup>



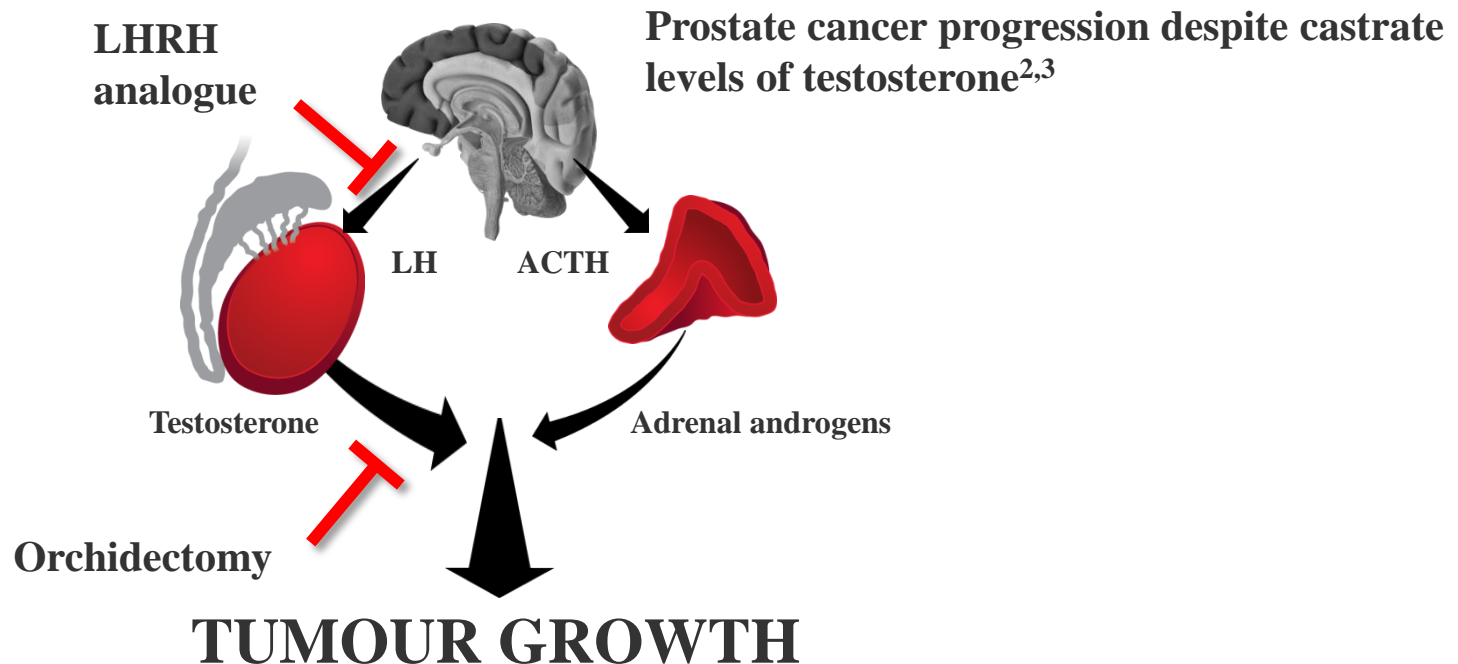
AR=androgen receptor; DHEA=dehydroepiandrosterone; DHT=dihydrotestosterone; T=testosterone.

1. Heinlein CA, Chang C. *Endocr Rev* 2004;25:276–308.

2. Hou X, Flaig TW. *Adv Urol* 2012;2012:978351.

# Die meisten PC zeigen trotz ADT eine Progression zu CRPC<sup>1,2</sup>

- CRPC is defined as disease progression despite castrate levels of testosterone ( $\leq 50$  ng/dL)<sup>2,3</sup>



ACTH=adrenocorticotrophic hormone; ADT=androgen-deprivation therapy; CRPC=castration-resistant prostate cancer; LH=luteinising hormone; LHRH=luteinising hormone-releasing hormone.

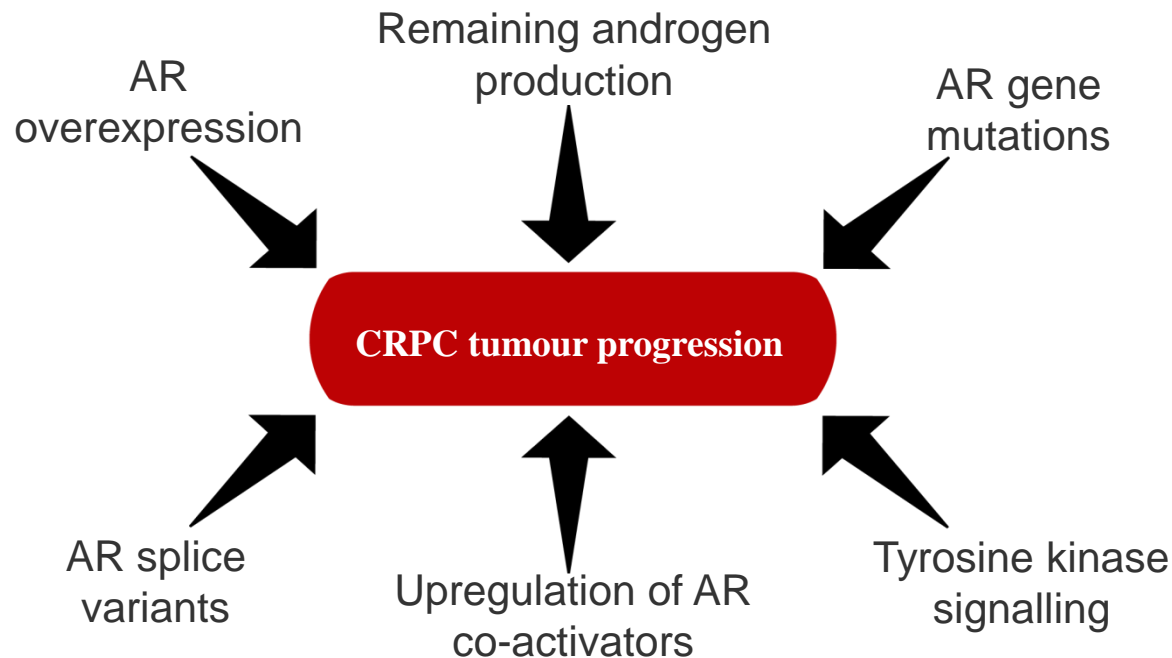
1. Hou X, Flaig TW. *Adv Urol* 2012;2012:978351.

2. Ryan CJ, Tindall DJ. *J Clin Oncol* 2011;29:3651–8.

3. Heidenreich A, *et al.* Available at <http://www.uroweb.org/guidelines/online-guidelines/>. Last accessed: April 2014.

# Der AR-signalweg ist der “key driver” bei der Progression zur CRPC

- Fehlendes Ansprechen von ADT aufgrund aufrechter AR-signal trotz Testosteron im Kastrationsbereich<sup>1–3</sup>
- Bei CRPC, wird AR-signalweg durch Veränderung der Biologie der PC-zellen reaktiviert<sup>3</sup>

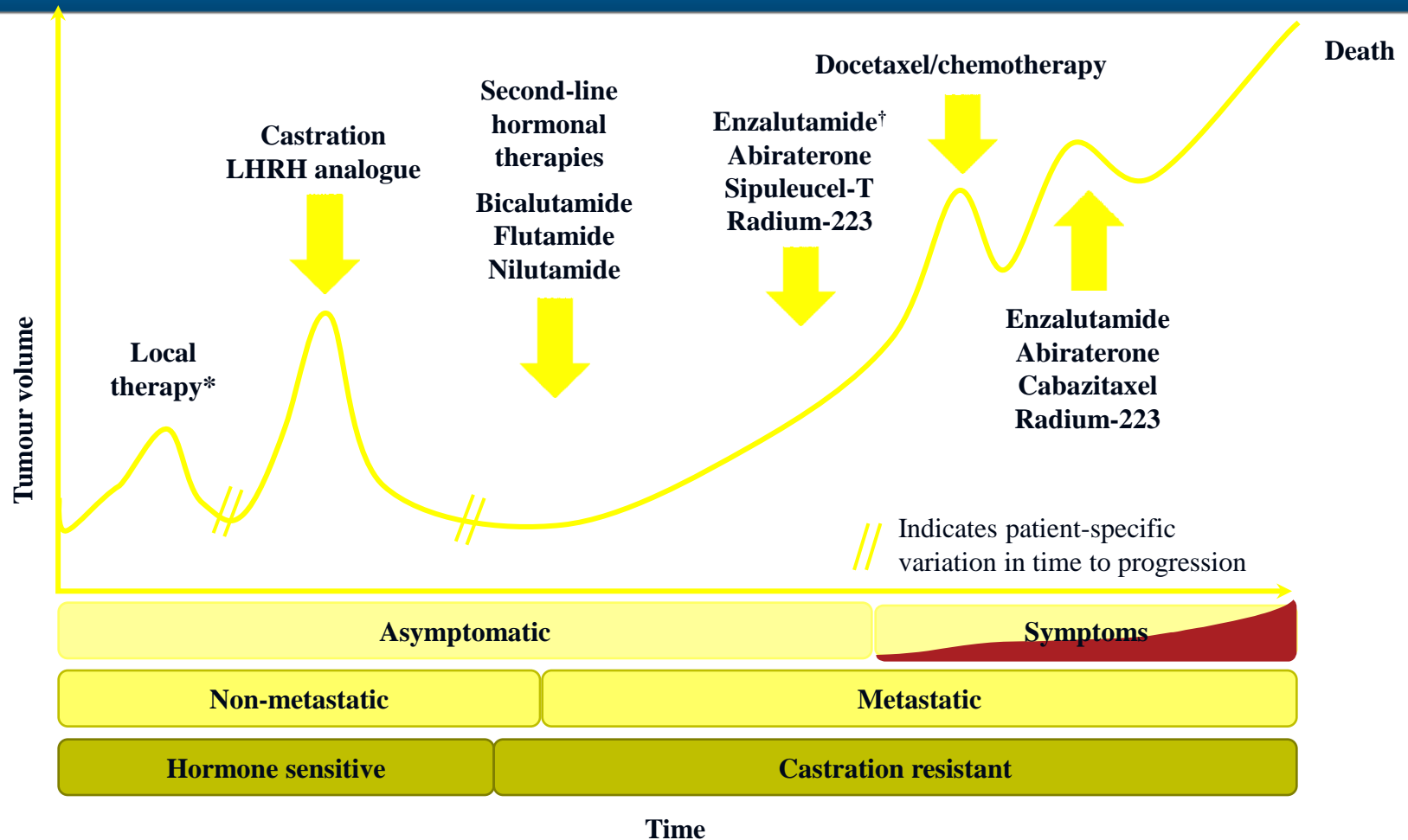


ADT=androgen-deprivation therapy; AR=androgen receptor; CRPC=castration-resistant prostate cancer.

1. Chen Y, *et al. Lancet Oncol* 2009;10:981–91.
2. Hu R, *et al. Expert Rev Endocrinol Metab* 2010;5:753–64.
3. Heinlein CA, Chang C. *Endocr Rev* 2004;25:276–308.



# PC ist ein Kontinuum verschiedener Erkrankungsstadien



\*For example surgery, radiotherapy. †Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients.

LHRH=luteinising hormone-releasing hormone.

Adapted from George D. *Urology – The Gold Journal* 2013; Available at <http://education.goldjournal.net/path.php?1396:0:Media:title:bxvc:bxvcs> Last accessed June 2014

# Erweitertes Armamentarium für mCRPC

- **Standardchemotherapie: Taxotere**
- 
- **Abiraterone Acetat** (COU-AA-301; COU-AA-302)
  - **Enzalutamid** (AFFIRM, PREVAIL)
  - **Chemohormonale Therapie** (CHAARTED)
  - Radium-223
  - 2.Linien-Chemotherapie: Cabazitaxel
  - Immunotherapy: Sipuleucel-T (IMPACT), Ipilimumab

# AR- antagonisten 3.Generation:Abirateron + Enzalutamid

- AR- Überexpression ist:
  - Eine häufige molekulare Veränderung bei progressivem CRPC<sup>1,2</sup>
- Wenn ARs überexprimiert sind:
  - Zeigen die gängigen Antiandrogene agonistische Fähigkeit<sup>3</sup>

**Ziel:Identifizierung AR antagonisten der 3.Gen.mit günstigen Eigenschaften:Fehlen von AR- agonismus + antagonismus in Zellen mit überexpr.AR**

AR=androgen receptor; CRPC=castration-resistant prostate cancer.

1. Visakorpi T, *et al. Nat Gen* 1995;9:401–6.
2. Holzbeierlein J, *et al. Am J Path* 2004;164:217–27.
3. Chen Y, *et al. Lancet Oncol* 2009;10:981–91.

# ABIRATERON – (ACETAT)

- Androgen-Biosynthese-Hemmer
- ABI hemmt Cytochrome P450 17A1 (CYP17A1)
- CYP17A1 schwächt das AR-signal durch Entziehen adrenaler + intratumoralen Androgene

# COU-AA-301 Study Design

Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study  
(147 sites in 13 countries; USA, Europe, Australia, Canada)

- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel
- Randomized 2:1
- Stratification by:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)

Abiraterone acetate  
1000 mg daily

Prednisone 5mg twice daily

Placebo daily

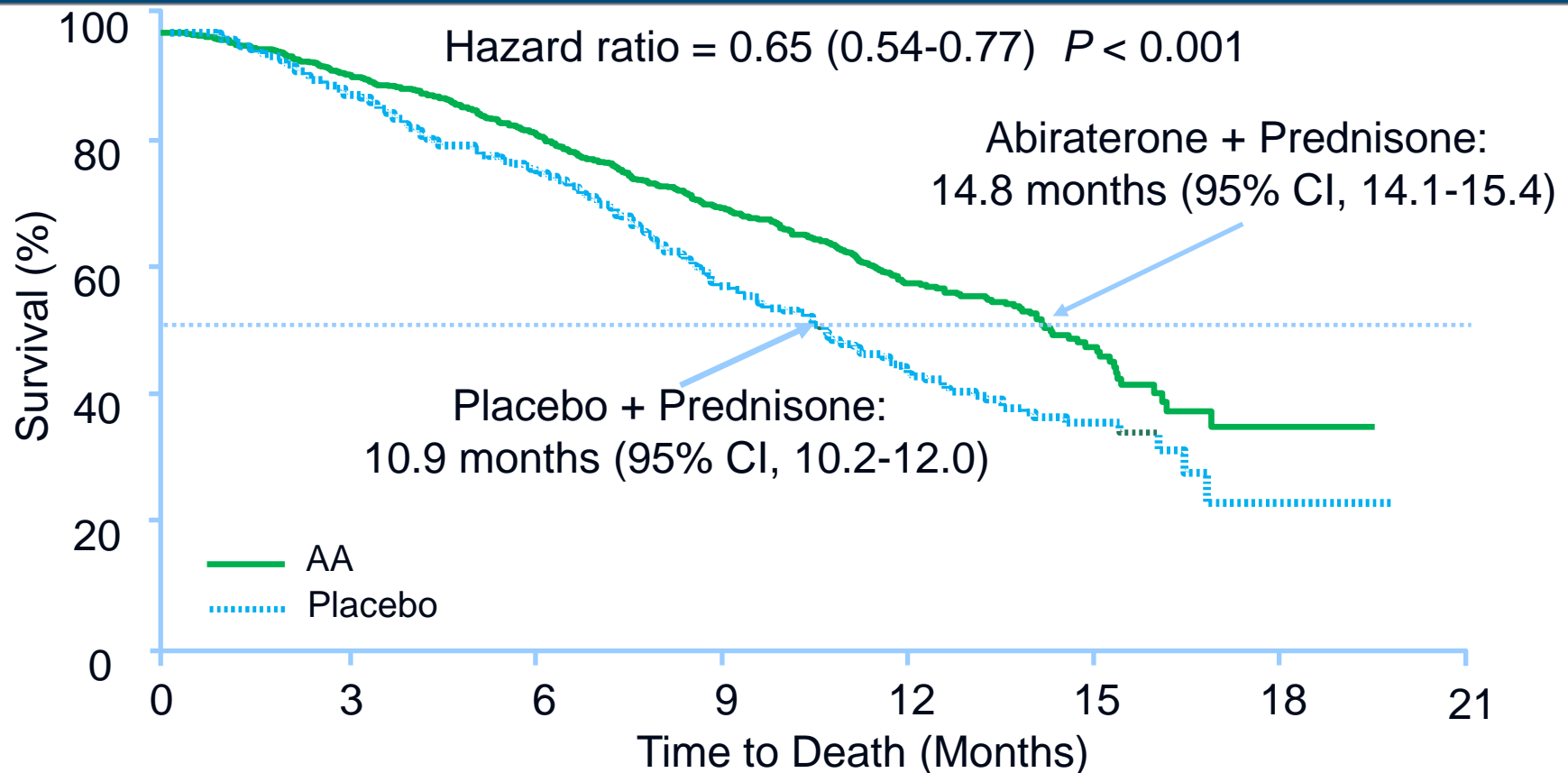
Prednisone 5mg twice daily

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Primary endpoint:

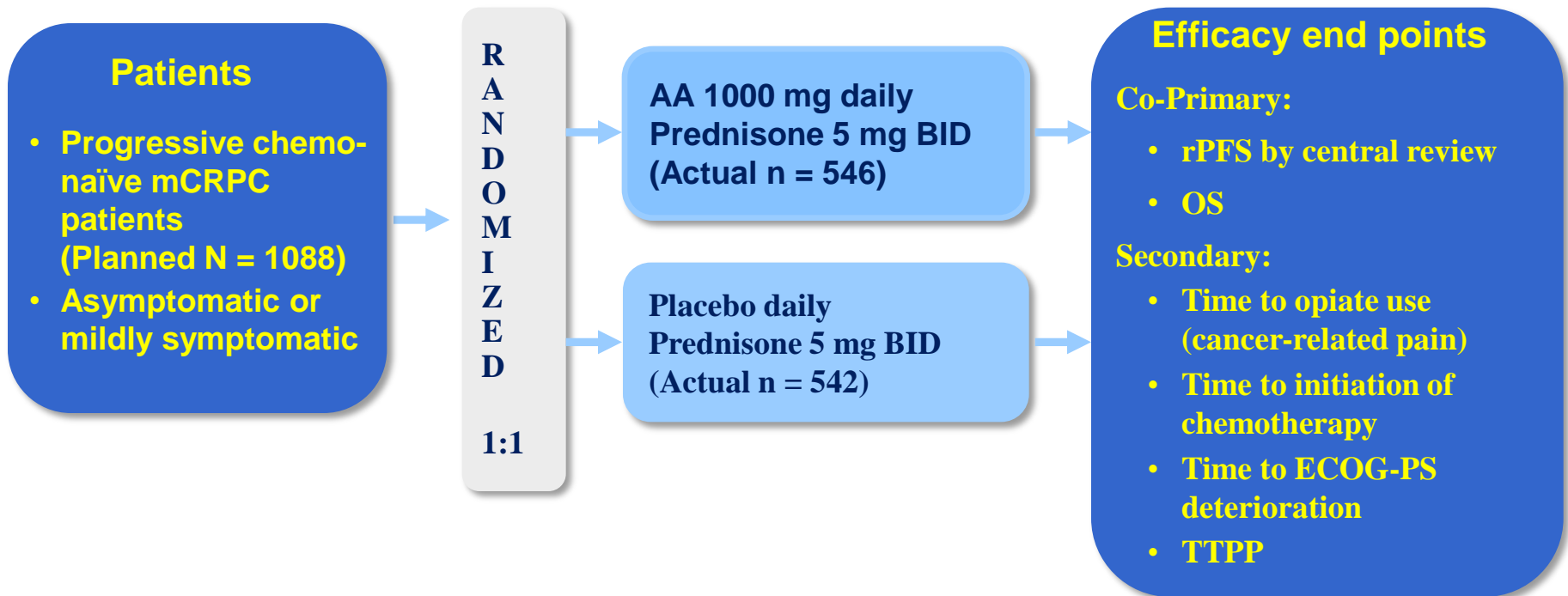
OS (25% improvement; HR 0.8)

# Overall Survival – Analysis



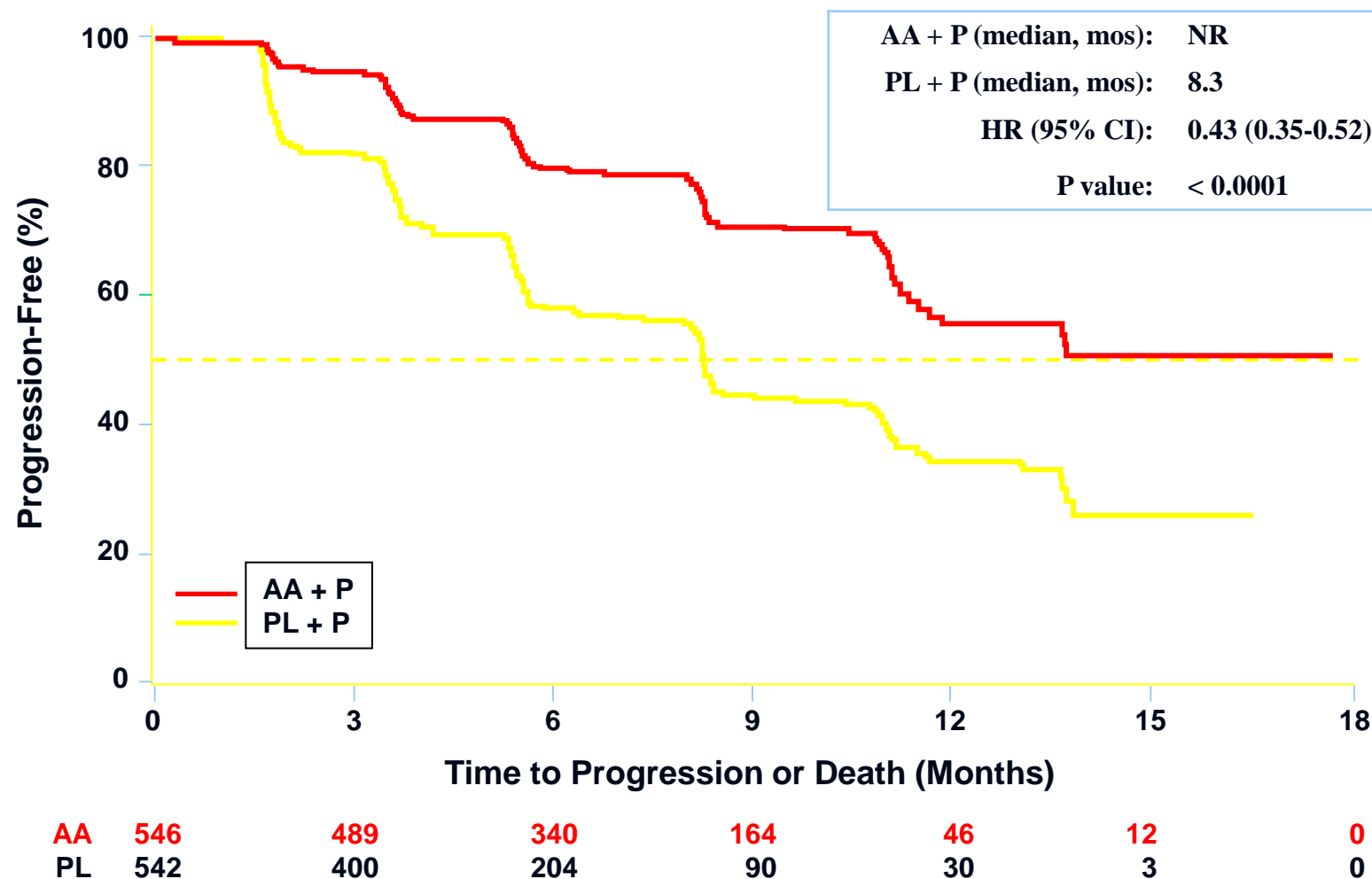
AA	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

# Overall Study Design of COU-AA-302



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

# Statistisch signifikante Verbesserung des rPFS

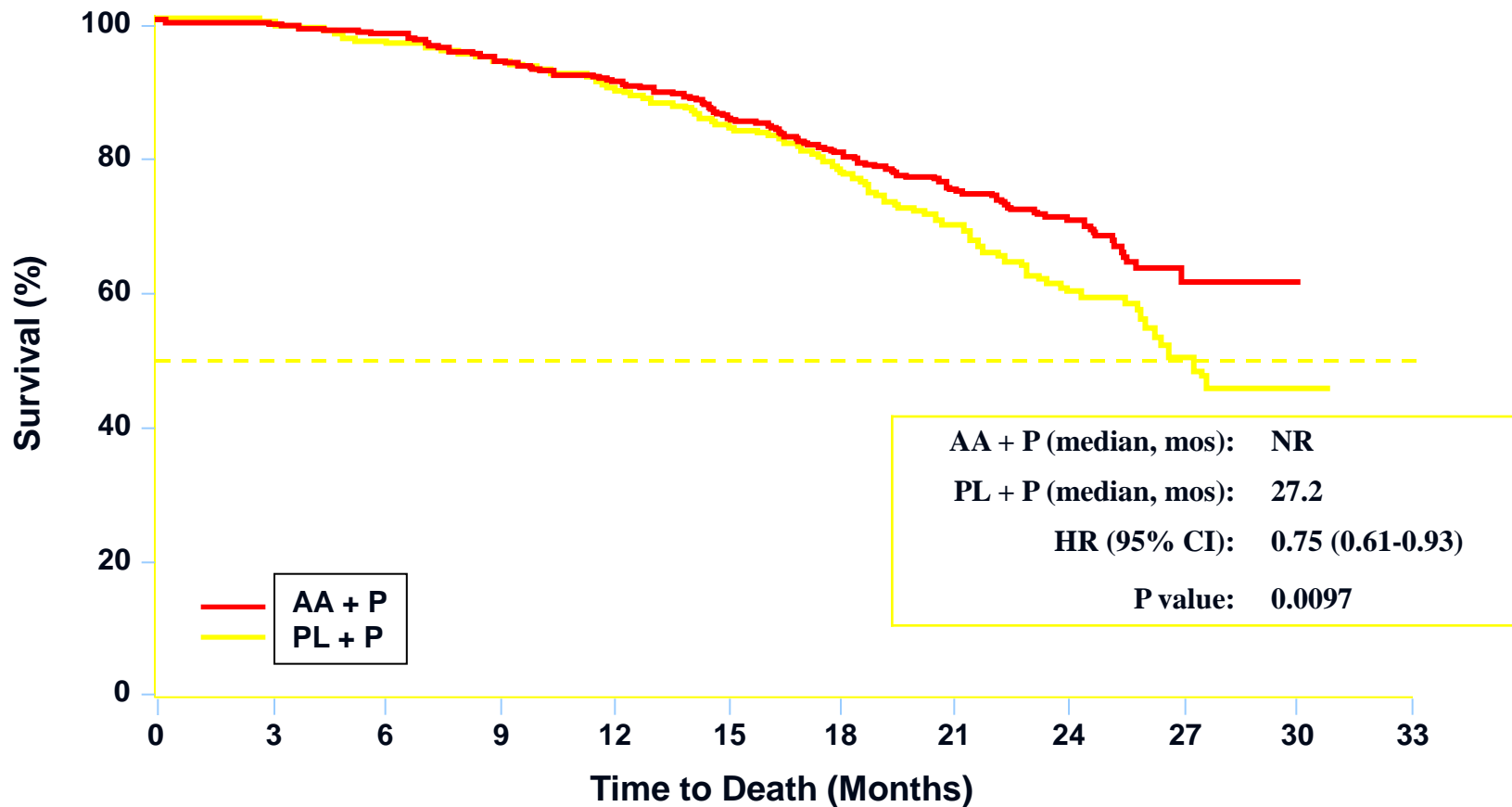


Data cutoff 20/12/2010

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



# Starker Trend : Verlängerung des Gesamtüberlebens



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

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

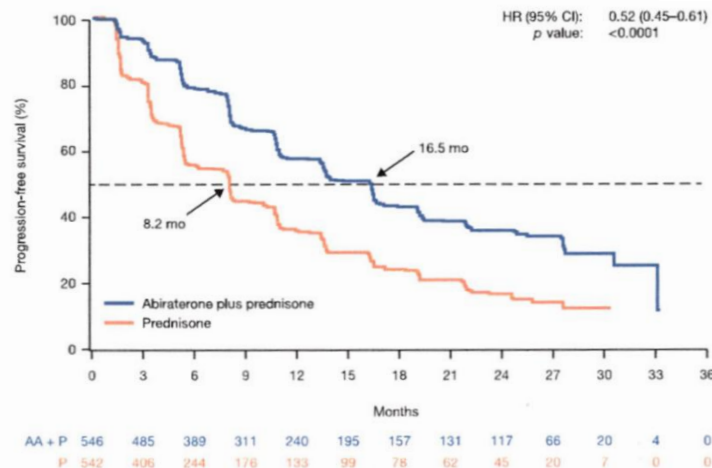
Data cutoff 20/12/2011

# Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302)

Dana E. Rathkopf<sup>a,\*</sup>, Matthew R. Smith<sup>b</sup>, Johann S. de Bono<sup>c</sup>, Christopher J. Logothetis<sup>d</sup>, Neal D. Shore<sup>e</sup>, Paul de Souza<sup>f</sup>, Karim Fizazi<sup>g</sup>, Peter F.A. Mulders<sup>h</sup>, Paul Mainwaring<sup>i</sup>, John D. Hainsworth<sup>j</sup>, Tomasz M. Beer<sup>k</sup>, Scott North<sup>l</sup>, Yves Fradet<sup>m</sup>, Hendrik Van Poppel<sup>n</sup>, Joan Carles<sup>o</sup>, Thomas W. Flaig<sup>p</sup>, Eleni Efstathiou<sup>d</sup>, Evan Y. Yu<sup>q</sup>, Celestia S. Higano<sup>q</sup>, Mary-Ellen Taplin<sup>r</sup>, Thomas W. Griffin<sup>s</sup>, Mary B. Todd<sup>t</sup>, Margaret K. Yu<sup>s</sup>, Youn C. Park<sup>t</sup>, Thian Kheoh<sup>s</sup>, Eric J. Small<sup>u</sup>, Howard I. Scher<sup>a</sup>, Arturo Molina<sup>v</sup>, Charles J. Ryan<sup>u</sup>, Fred Saad<sup>w</sup>

EUROPEAN UROLOGY 66 (2014) 815–825

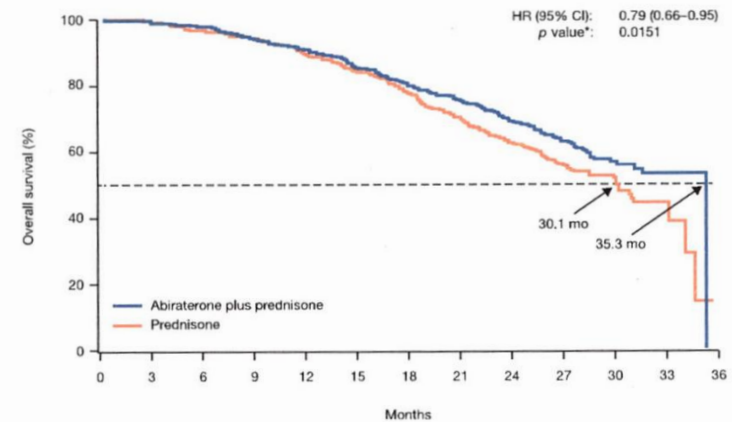
(A)



(B)

Favours  
abiraterone plus prednisone ← → Favours  
prednisone

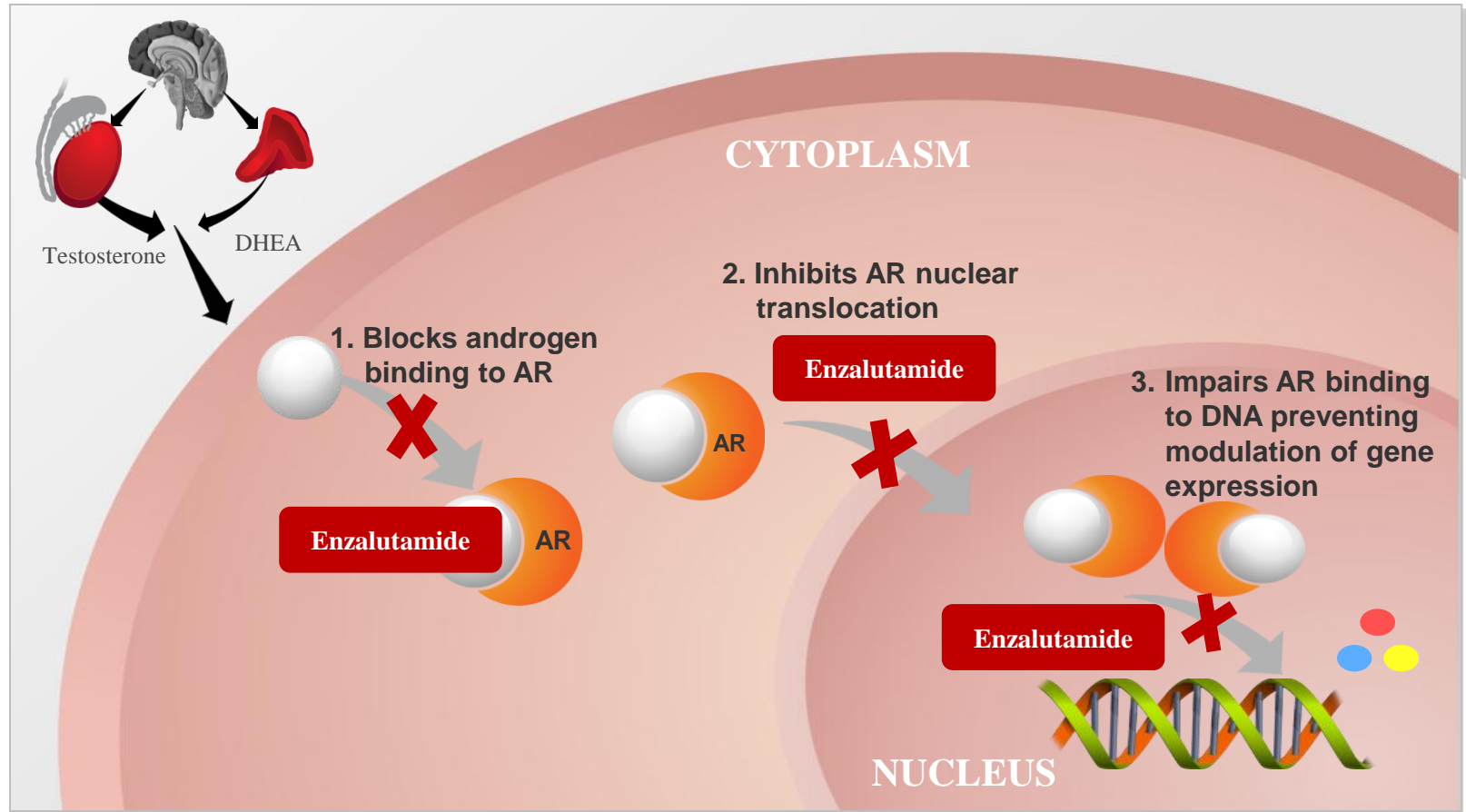
(A)



(B)

Favours  
abiraterone plus prednisone ← → Favours  
prednisone

# Enzalutamid zielt direkt auf 3 Schlüsselpositionen des AR-signalweges <sup>1,2</sup>



AR=androgen receptor; DHEA=dehydroepiandrosterone.

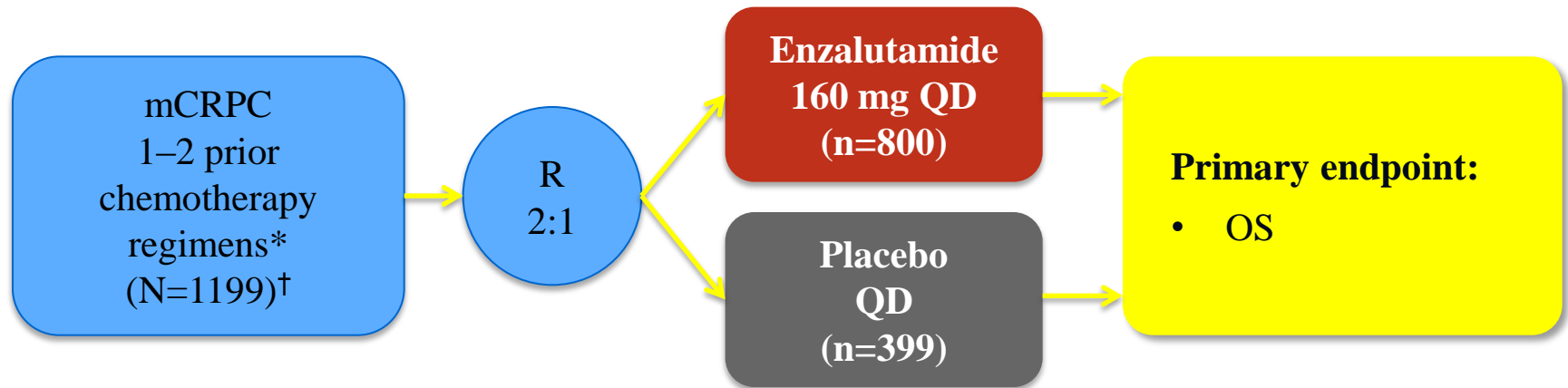
1. Tran C, *et al. Science* 2009;324:787–90;

2. Hu R, *et al. Expert Rev Endocrinol Metab* 2010;5:753–64.

# Enzalutamid bei mCRPC

## Post-chemotherapie

- AFFIRM is a Phase 3 randomised, double-blind, placebo-controlled trial evaluating the safety and efficacy of enzalutamide in patients with mCRPC after chemotherapy



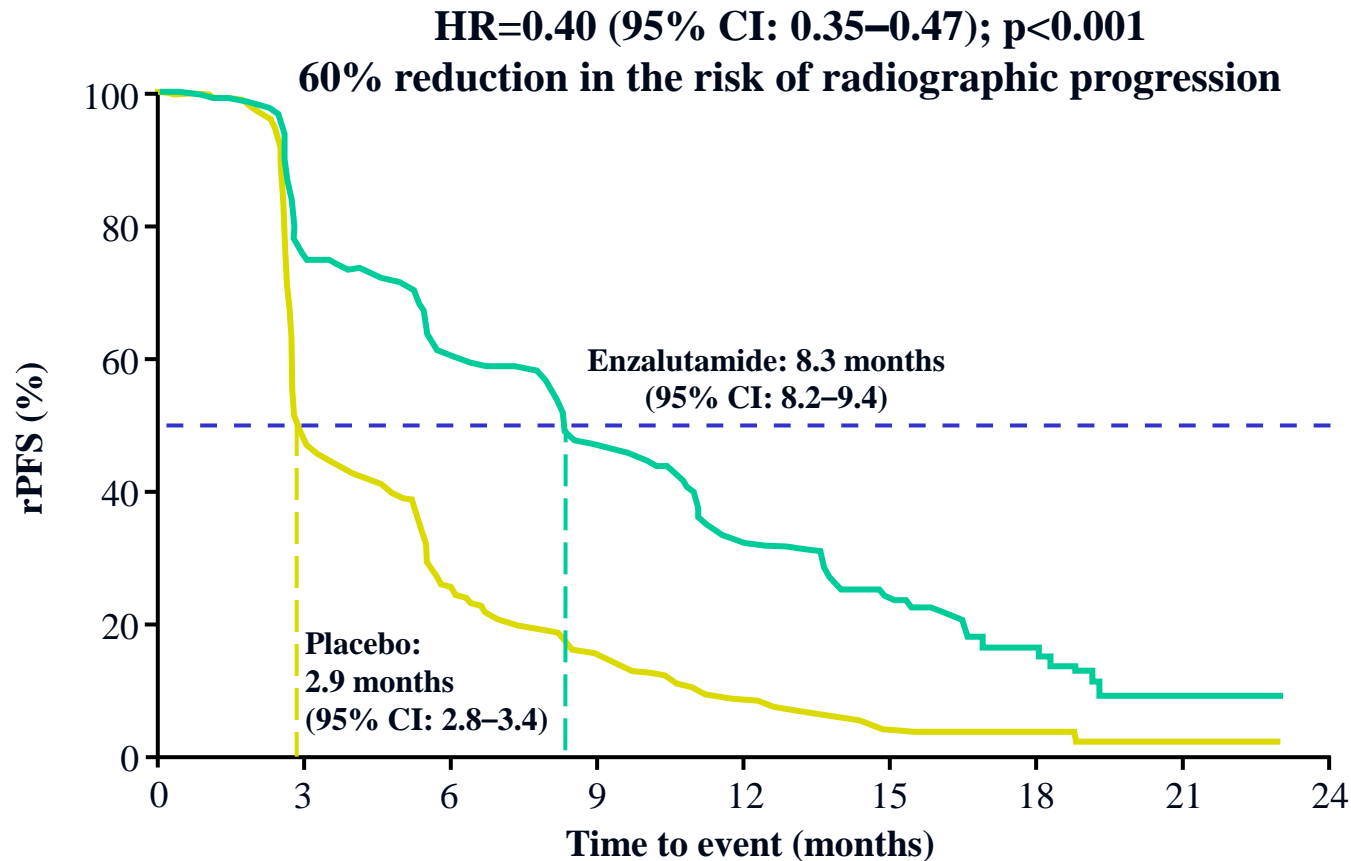
\*At least one cycle of docetaxel (glucocorticoids were allowed but not required); †Patients were excluded from the trial if they had brain metastases, a history of seizure or any condition that may pre-dispose to seizure.

Recruitment in 156 centres from 15 countries across five continents between September 2009 and November 2010.

mCRPC=metastatic castrate-resistant prostate cancer; QD=once daily; R=randomisation.

Scher HI, *et al. N Engl J Med* 2012;367:1187–97.

# Enzalutamid verlängert signifikant rPFS vgl.mit Placebo



Enzalutamide, n	800	583	447	287	140	58	13	1	0
Placebo, n	399	176	86	46	20	7	3	0	0

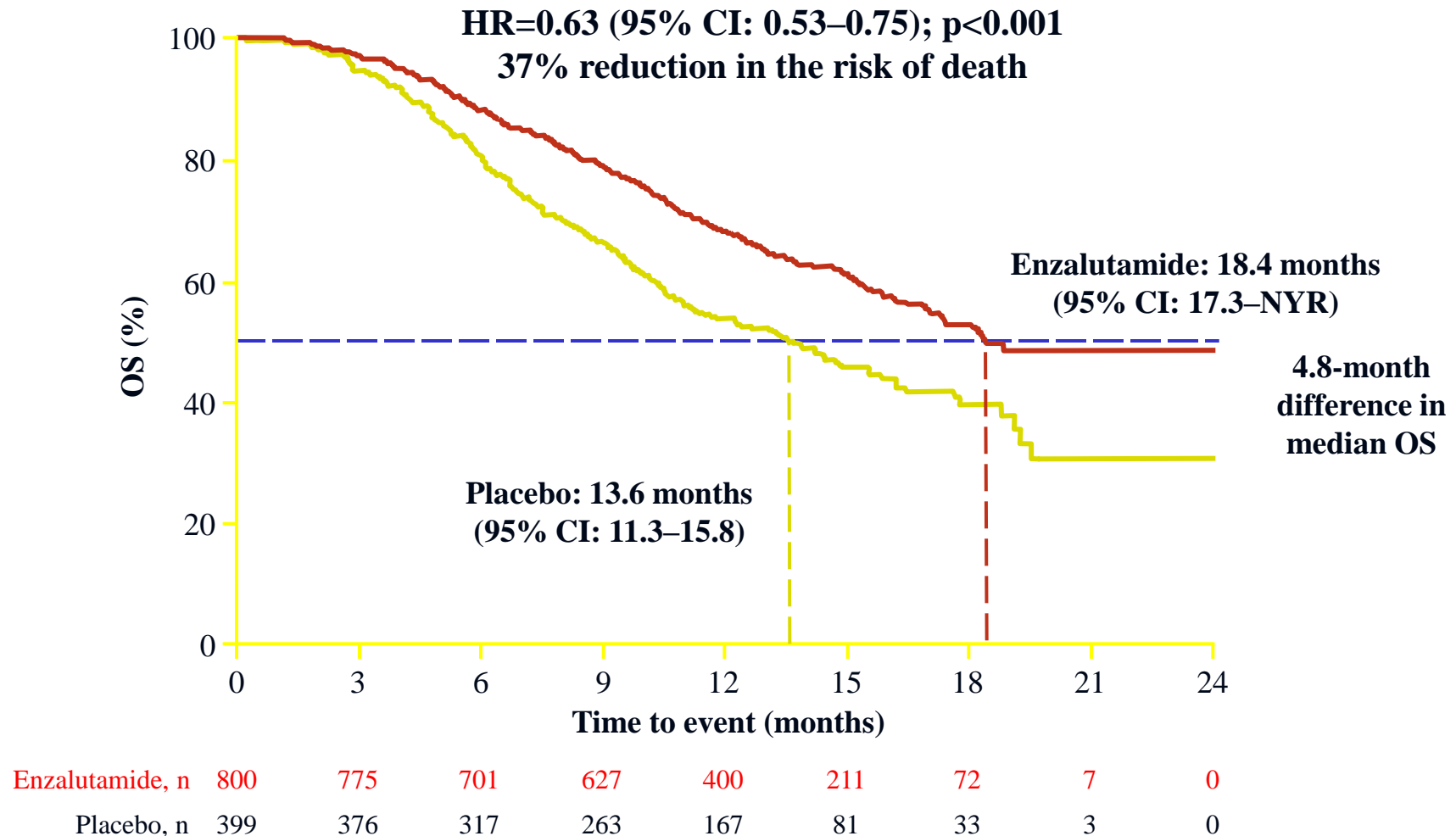
rPFS defined by RECIST 1.1 for soft tissue and PCWG2 for bone disease.

CI=confidence interval; HR=hazard ratio; PCWG2=Prostate Cancer Working Group; RECIST=Response Evaluation Criteria in Solid Tumours;

rPFS=radiographic progression-free survival.

Scher HI, et al. *N Engl J Med* 2012;367:1187–97.

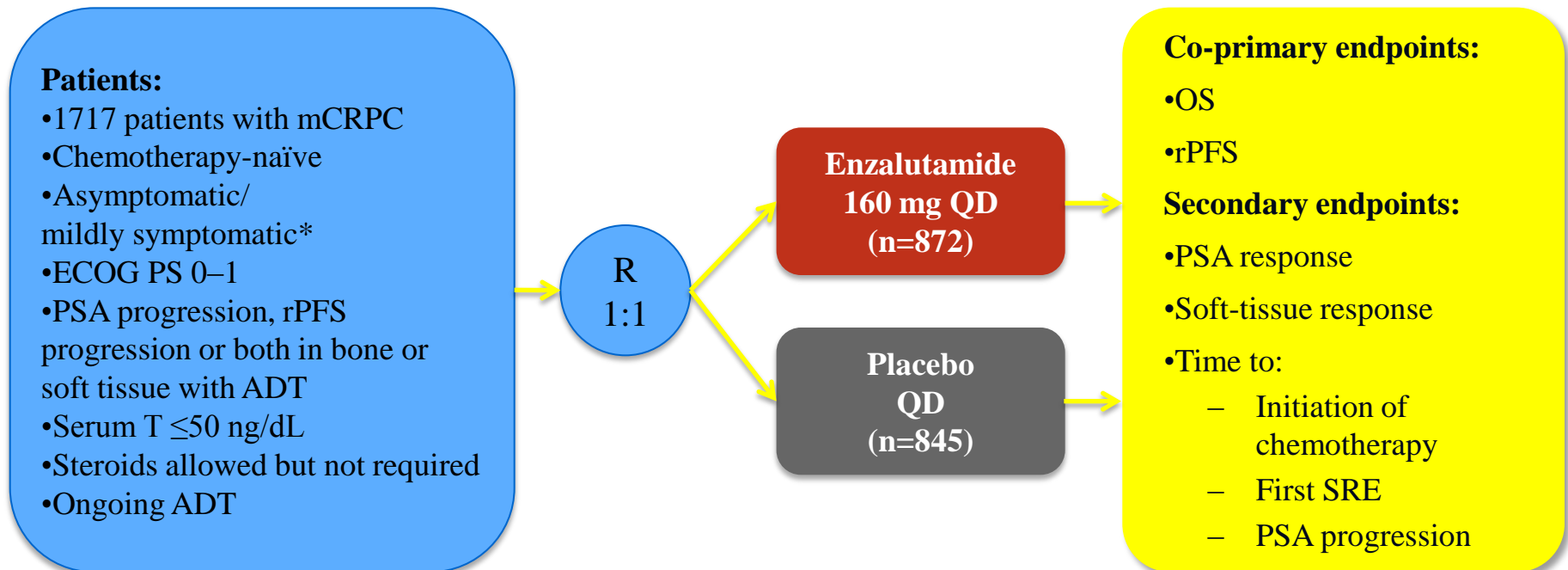
# Enzalutamid zeigt signifikanten Gesamtüberlebensvorteil vgl. mit Placebo



# Enzalutamid bei chemotherapie-naïven mCRPC

## Pat.: Studiendesign

- PREVAIL is a Phase 3 randomised, double-blind, placebo-controlled trial evaluating the safety and efficacy of enzalutamide in chemotherapy-naïve patients with mCRPC



Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients. \*Patient scored less than four on BPI-SF-Q3.

Recruitment in 207 centres from 22 countries across four continents between September 2010 and September 2012.

ADT=androgen-deprivation therapy; BPI-SF=Brief Pain Inventory-Short Form; ECOG PS=Eastern Cooperative Oncology Group performance status;

mCRPC=metastatic castration-resistant prostate cancer; OS=overall survival; QD=once daily; rPFS=radiographic progression-free survival; T=testosterone.

Beer TM, et al. *N Engl J Med* 2014; DOI: 10.1056/NEJMoa1405095. [Epub ahead of print].

# PREVAIL wurde gestoppt und entblindet

- The IDMC reviewed the data after 540 deaths\*
- The IDMC reported **statistically significant benefits in OS and rPFS**
  - The PREVAIL study was halted and unblinded
  - Patients from the placebo arm are being offered treatment with enzalutamide

Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients.

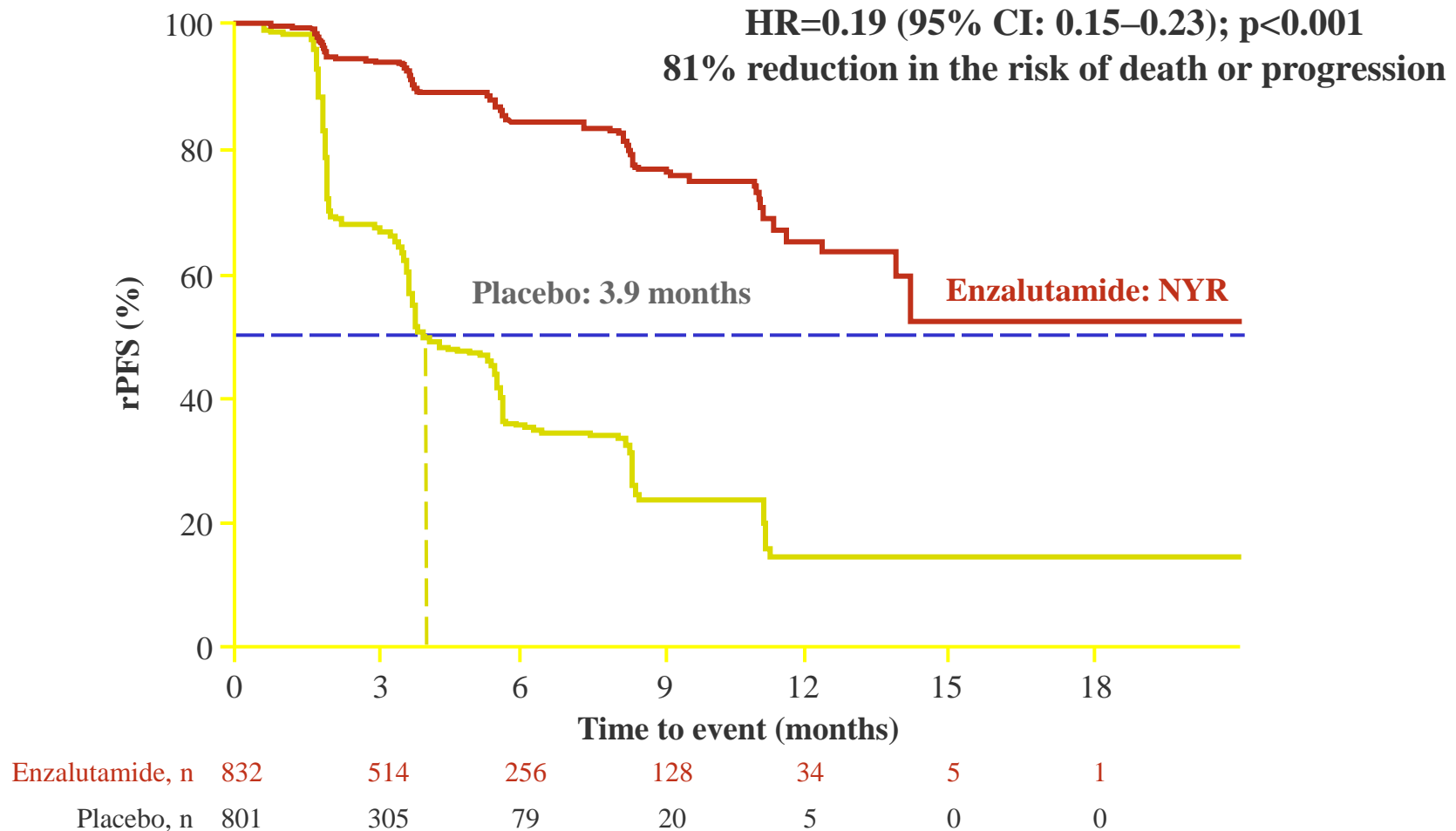
\*Data cut-off date: 16 September 2013.

IDMC=Independent Data Monitoring Committee; OS=overall survival; rPFS=radiographic progression-free survival.

Beer TM, *et al. N Engl J Med* 2014; DOI: 10.1056/NEJMoa1405095. [Epub ahead of print].

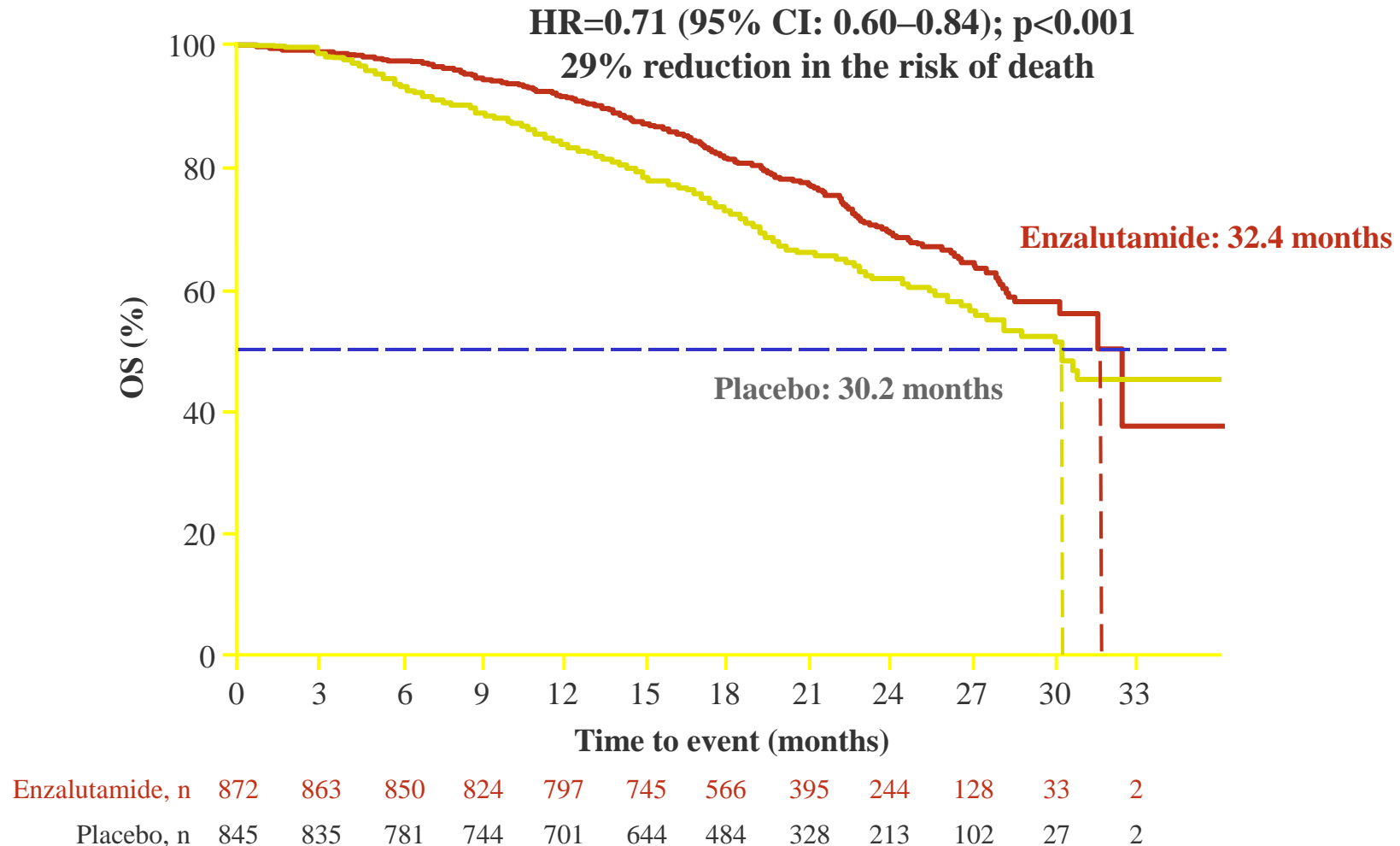


# Enzalutamide verlängert rPFS:\*



Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients. \*Radiographic disease progression was evaluated using the PCWG2 guidelines for bone disease and RECIST 1.1 for soft tissue disease. CI=confidence interval; HR=hazard ratio; NYR=not yet reported; PCWG=Prostate Cancer Working Group; RECIST=Response Evaluation Criteria in Solid Tumours; rPFS=radiographic progression-free survival.

# Enzalutamid zeigte einen signifikanten Gesamtüberlebensvorteil verglichen mit Placebo



Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients. Date of analysis: 16 September 2013.

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

Beer TM, et al. *N Engl J Med* 2014; DOI: 10.1056/NEJMoa1405095. [Epub ahead of print].

# Zusammenfassung

- **Die Abirateron- und Enzalutamidstudien:**
  - Zeigten signifikante Effektivität verglichen mit Placebo im Postchemotherapie Setting und bei Chemotherapie-naïven mCRPC:<sup>1</sup>
    - Reduzieren das Todesrisiko bis zu 29% ( $p<0.001$ )
    - Verzögern die Progression der metastat. Erkrankung bis zu 81% ( $p<0.001$ )
  - Verbesserten signifikant alle sek. Endpunkte vergl. mit Placebo<sup>1</sup>
    - Delayed time to first SRE ( $p<0.001$ )
    - Soft-tissue response in 59% of patients ( $p<0.001$ )
    - Delayed time to chemotherapy by 17 months ( $p<0.001$ )
    - Improved PSA response
    - Delayed time to PSA progression ( $p<0.001$ )
    - Delayed time to QoL deterioration ( $p<0.001$ )
    - Improved FACT-P Total ( $p<0.0001$ ) and subscale scores ( $p\leq 0.0025$ )<sup>2</sup>
  - Waren generell gut verträglich

Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients.

FACT-P=Functional Assessment of Cancer Therapy – Prostate; mCRPC=metastatic castration-resistant prostate cancer; PSA=prostate-specific antigen; QoL=quality of life; SRE=skeletal-related event.

1. Beer TM, *et al.* *N Engl J Med* 2014; DOI: 10.1056/NEJMoa1405095. [Epub ahead of print].

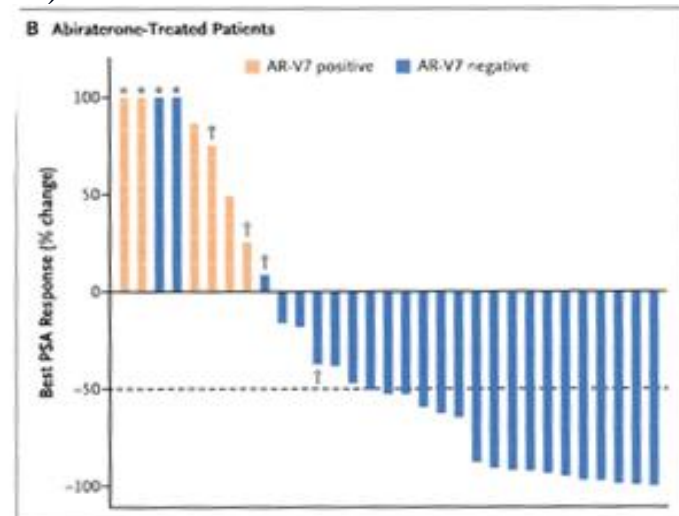
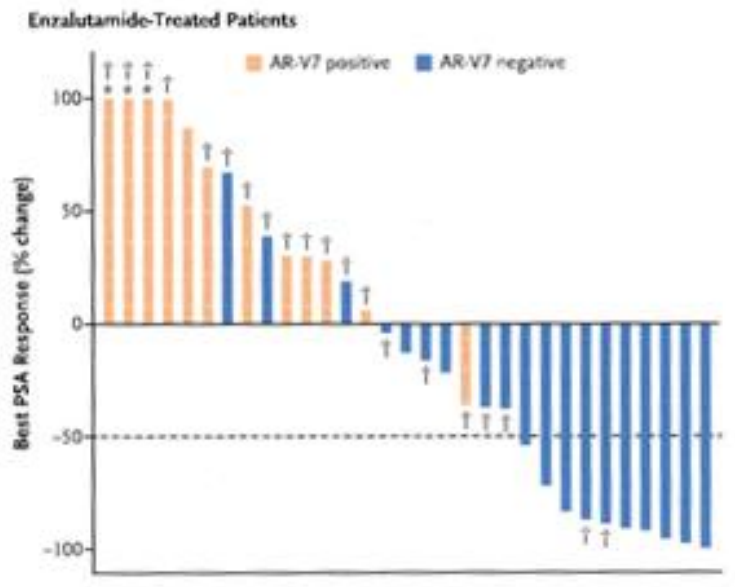
2. Armstrong AJ, *et al.* ASCO 2014. Oral presentation. Abstract 5007.

# AR-V7 und Resistenz gegen ABI und ENZA

## Genom- Veränderungen: PTEN, AR

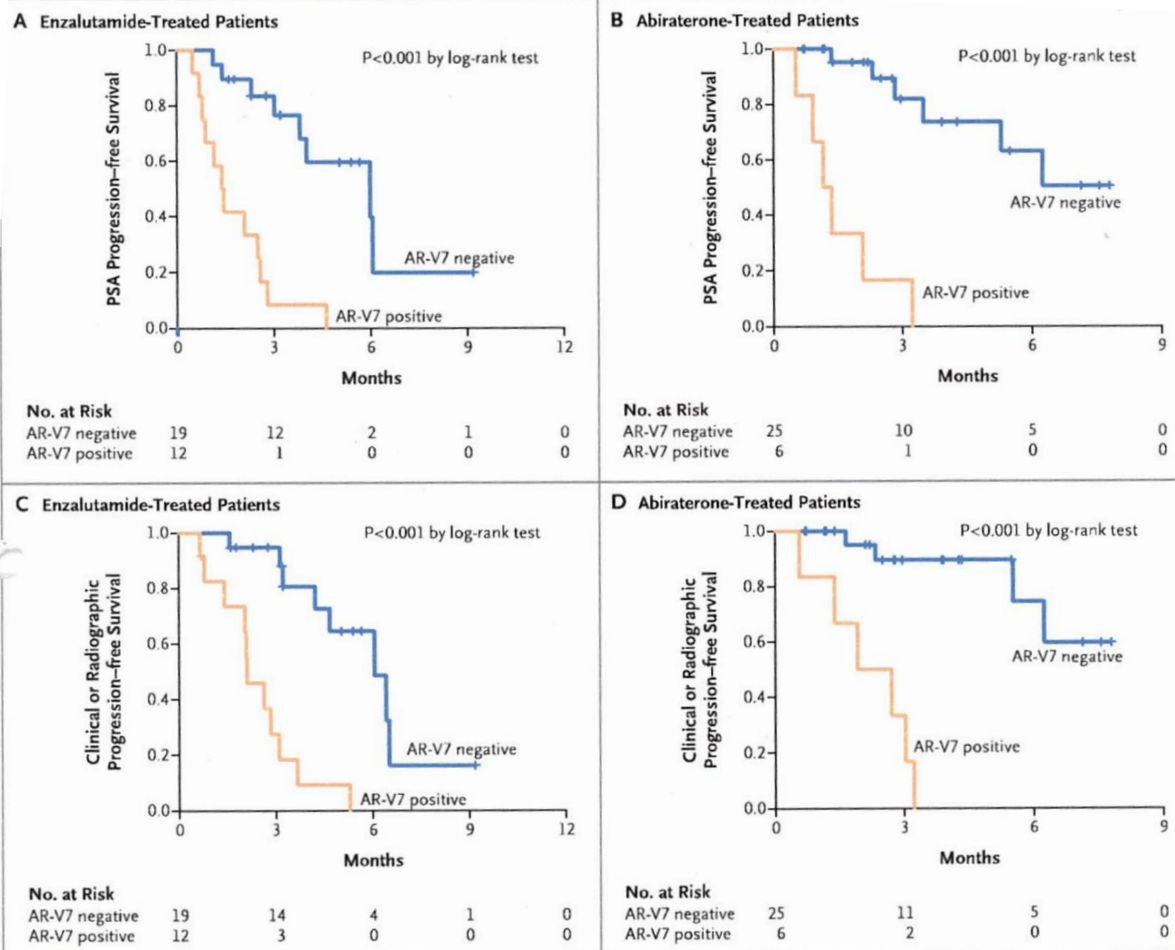
Androgen-receptor isoform entschlüsselt durch splice variant 7 messenger RNA (AR-V7) fehlt die „ligand-binding domain“ (ther.Ziel) aber bleibt aktiv als transcription factor!

Entdeckung in zirkulierenden Tu-zellen (CTCs)



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

Panel A shows the 31 enzalutamide-treated patients, and Panel B the 31 abiraterone-treated patients. The dotted line shows the threshold for defining a PSA response ( $\geq 50\%$  reduction in PSA level from baseline). Asterisks indicate an increase of more than 100% in best PSA response. Daggers indicate patients in the enzalutamide cohort who had previously received abiraterone and patients in the abiraterone cohort who had previously received enzalutamide.



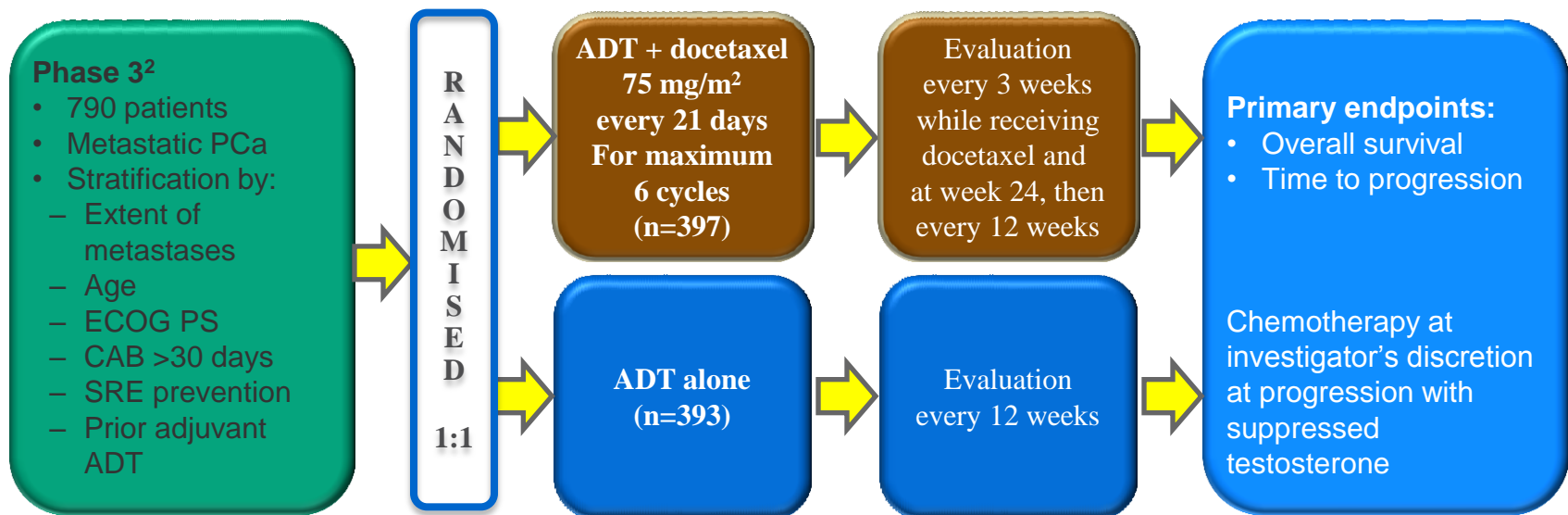
**Figure 3. Kaplan-Meier Analysis of PSA Progression-free Survival and Clinical or Radiographic Progression-free Survival According to AR-V7 Status.**

The median PSA progression-free survival in enzalutamide-treated patients (Panel A) was 1.4 months (95% CI, 0.9 to not reached) in AR-V7-positive patients and 6.0 months (95% CI, 3.8 to not reached) in AR-V7-negative patients (hazard ratio for PSA progression with AR-V7 positivity, 7.4; 95% CI, 2.7 to 20.6;  $P<0.001$  by the log-rank test). The median PSA progression-free survival in abiraterone-treated patients (Panel B) was 1.3 months (95% CI, 0.9 to not reached) in AR-V7-positive patients and more than 5.3 months (95% CI, 5.3 to not reached) in AR-V7-negative patients (hazard ratio for PSA progression with AR-V7 positivity, 16.1; 95% CI, 3.9 to 66.0;  $P<0.001$  by the log-rank test). The median clinical or radiographic progression-free survival in enzalutamide-treated patients (Panel C) was 2.1 months (95% CI, 2.0 to not reached) in AR-V7-positive patients and 6.1 months (95% CI, 4.7 to not reached) in AR-V7-negative patients (hazard ratio for clinical or radiographic progression with AR-V7 positivity, 8.5; 95% CI, 2.8 to 25.5;  $P<0.001$  by the log-rank test). The median clinical or radiographic progression-free survival in abiraterone-treated patients (Panel D) was 2.3 months (95% CI, 1.4 to not reached) in AR-V7-positive patients and more than 6.3 months (95% CI, 6.3 to not reached) in AR-V7-negative patients (hazard ratio for clinical or radiographic progression with AR-V7 positivity, 16.5; 95% CI, 3.3 to 82.9;  $P<0.001$  by the log-rank test).

# CHAARTED: Studiendesign

Phase 3 randomised, open-label trial<sup>1</sup>

Objective: To investigate the benefit of combining ADT and chemotherapy compared to ADT alone in men with metastatic prostate cancer<sup>1</sup>



ADT=androgen deprivation therapy; CAB=complete androgen blockage; ECOG PS=Eastern Cooperative Oncology Group performance status; PCa=prostate cancer; SRE=skeletal-related event.

1. NCT00309985. Available at <http://clinicaltrials.gov>. Last accessed September 2014.

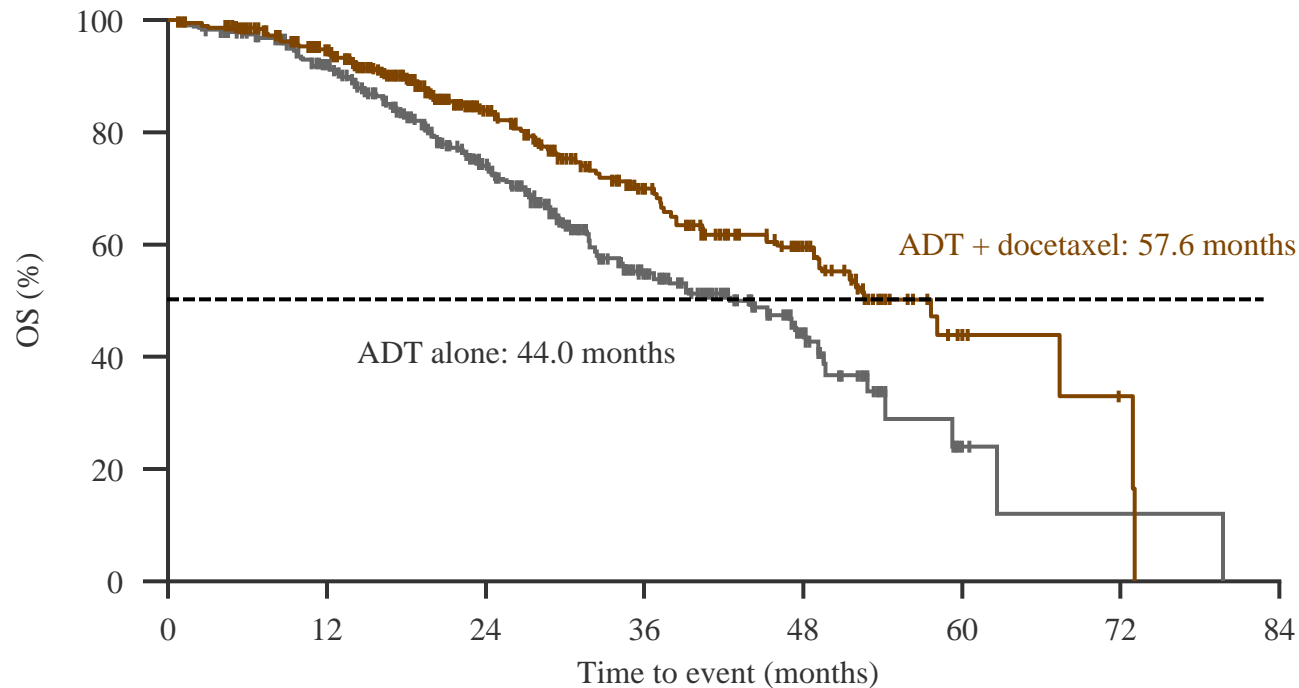
2. Sweeney C, *et al.* ASCO 2014; Oral presentation E3805.

# CHAARTED:Analyse

- 790 Männer rekrutiert zw. 28 Juli 2006 and 21 November 2012
  - Planned interim analysis at 53% information, pre-specified criteria for significance and release of data met in October 2013
  - 16 January 2014 median follow-up of 29 months
    - 136 deaths in ADT alone group versus 101 deaths in ADT + docetaxel group

# CHAARTED: Gesamtüberleben

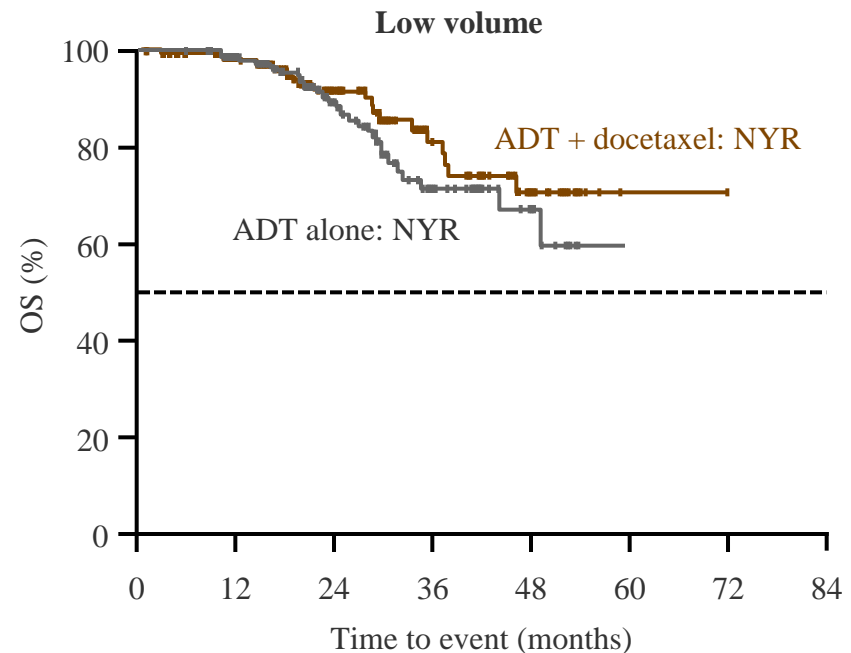
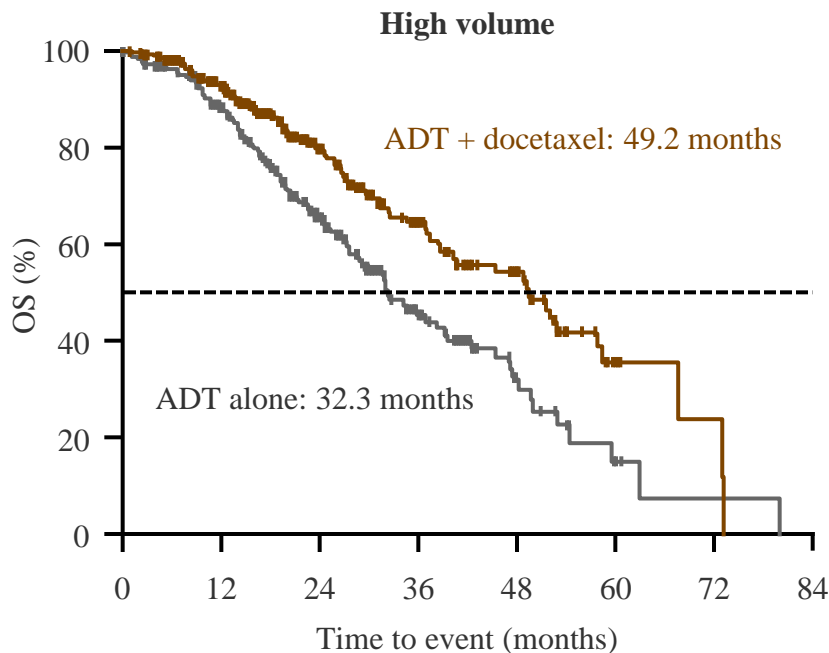
Docetaxel in combination with ADT significantly improved OS compared with ADT alone  
Median OS for docetaxel + ADT was 57.6 months compared with 44.0 months for ADT alone (HR=0.61, 95% CI: 0.47–0.80; p=0.0003)



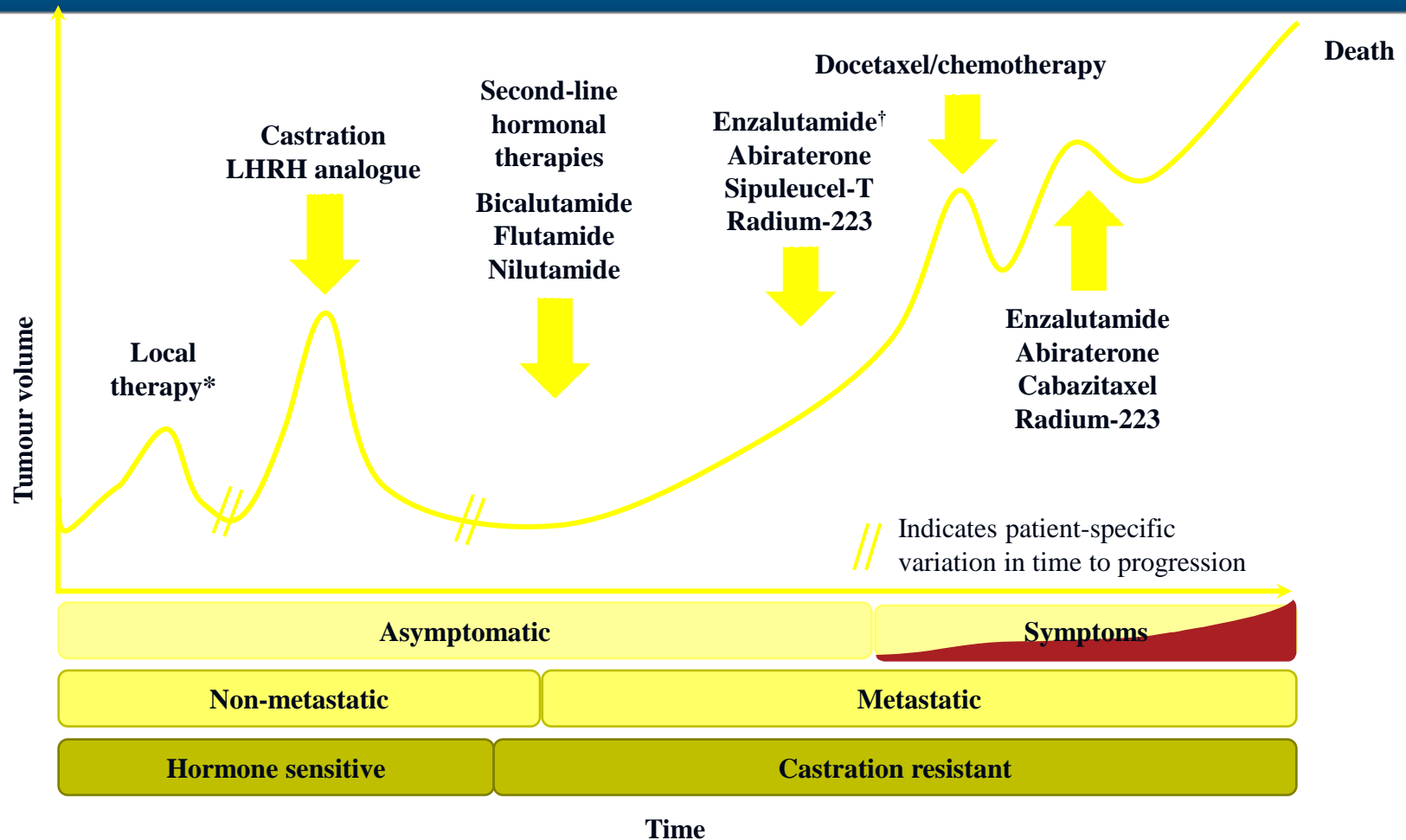


# CHAARTED: Gesamtüberleben bei unterschiedlichem Ausmaß der M+erkrankung

- In patients with high-volume metastatic disease, ADT + early docetaxel improves median OS by 17 months compared with ADT alone
  - Median OS for docetaxel + ADT was 49.2 months compared with 32.3 months for ADT alone (HR=0.60, 95% CI: 0.45–0.81; p=0.0006)
  - Median OS was NYR for both treatment groups in patients with low volume of metastatic disease (HR=0.63, 95% CI: 0.34–1.17; p=0.1398)



# PC ist ein Kontinuum verschiedener Erkrankungsstadien



\*For example surgery, radiotherapy. <sup>†</sup>Enzalutamide is not approved for use in chemotherapy-naïve mCRPC patients.

LHRH=luteinising hormone-releasing hormone.

Adapted from George D. *Urology – The Gold Journal* 2013; Available at

<http://education.goldjournal.net/path.php?1396:0:Media:title:bxvc:bxvcs> Last accessed June 2014

Vielen Dank...

# STAMPEDE Trial

- **Größte prospektiv, randomisierte Studie für die Behandlung des Prostatakarzinoms**
- **(> 6000 Pat. seit 2005)**
- **Neues Design (multistage / multiarm) mit nachträglichen Modifizierungsmöglichkeiten**
- **Studie noch laufend**

# STAMPEDE

## Setting and hypothesis

---

- Setting
  - Hormone therapy the mainstay of treatment since 1940s
  - Addition of radiotherapy to N0M0 disease improves outcomes
- Hypothesis
  - Early use of active therapies may give a larger absolute benefit in overall survival

## Inclusion criteria

### Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- $\geq 2$  of: Stage T3/4  
PSA  $\geq 40$  ng/ml  
Gleason 8-10

### Relapsing after previous RP or RT with $\geq 1$ of:

- PSA  $\geq 4$  ng/ml and rising with doubling time  $< 6$  m
- PSA  $\geq 20$  ng/ml
- Node-positive
- Metastatic

### All patients

Fit for all protocol treatment

Fit for follow-up

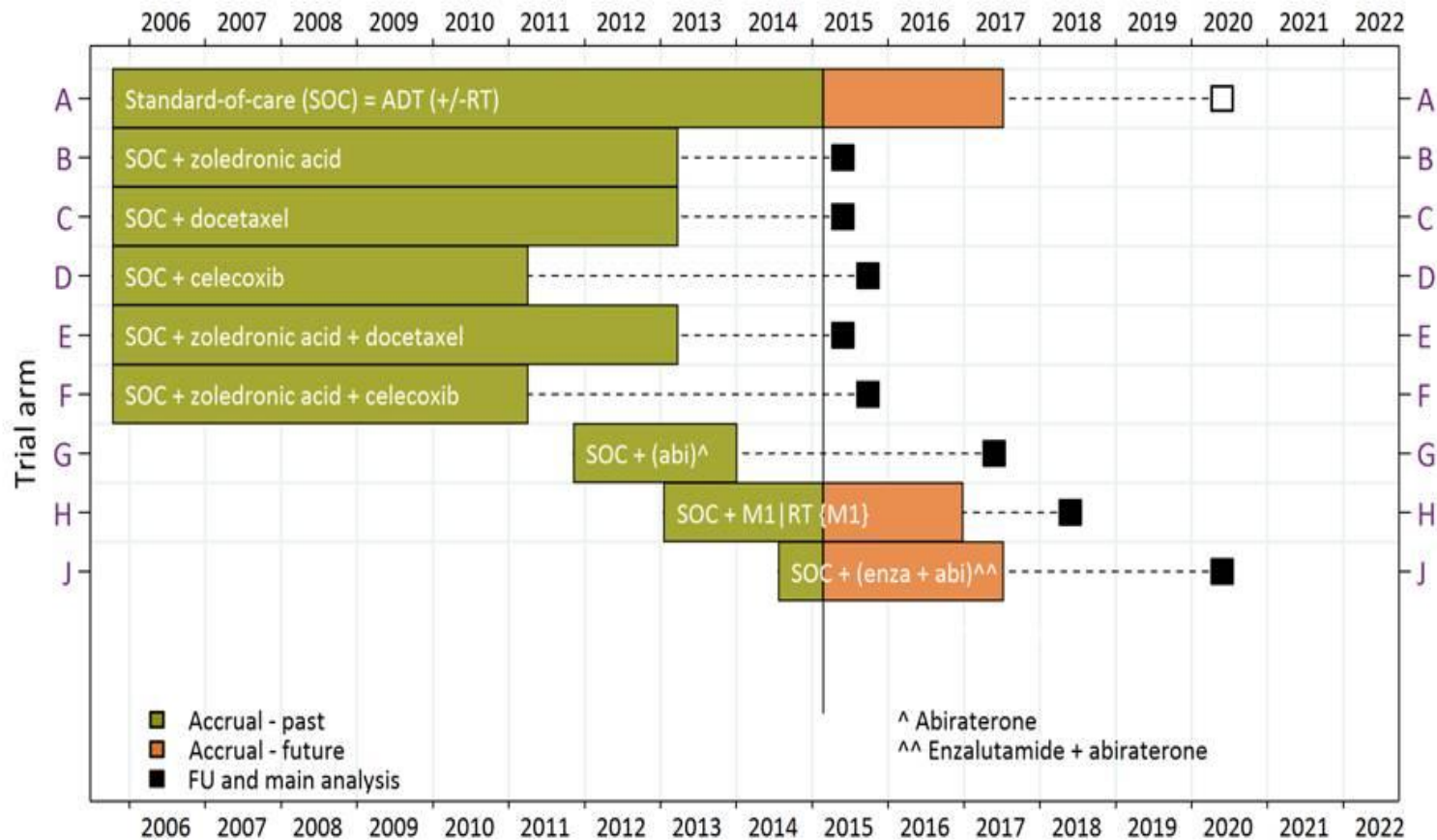
WHO performance status 0-2

Written informed consent

### Full criteria

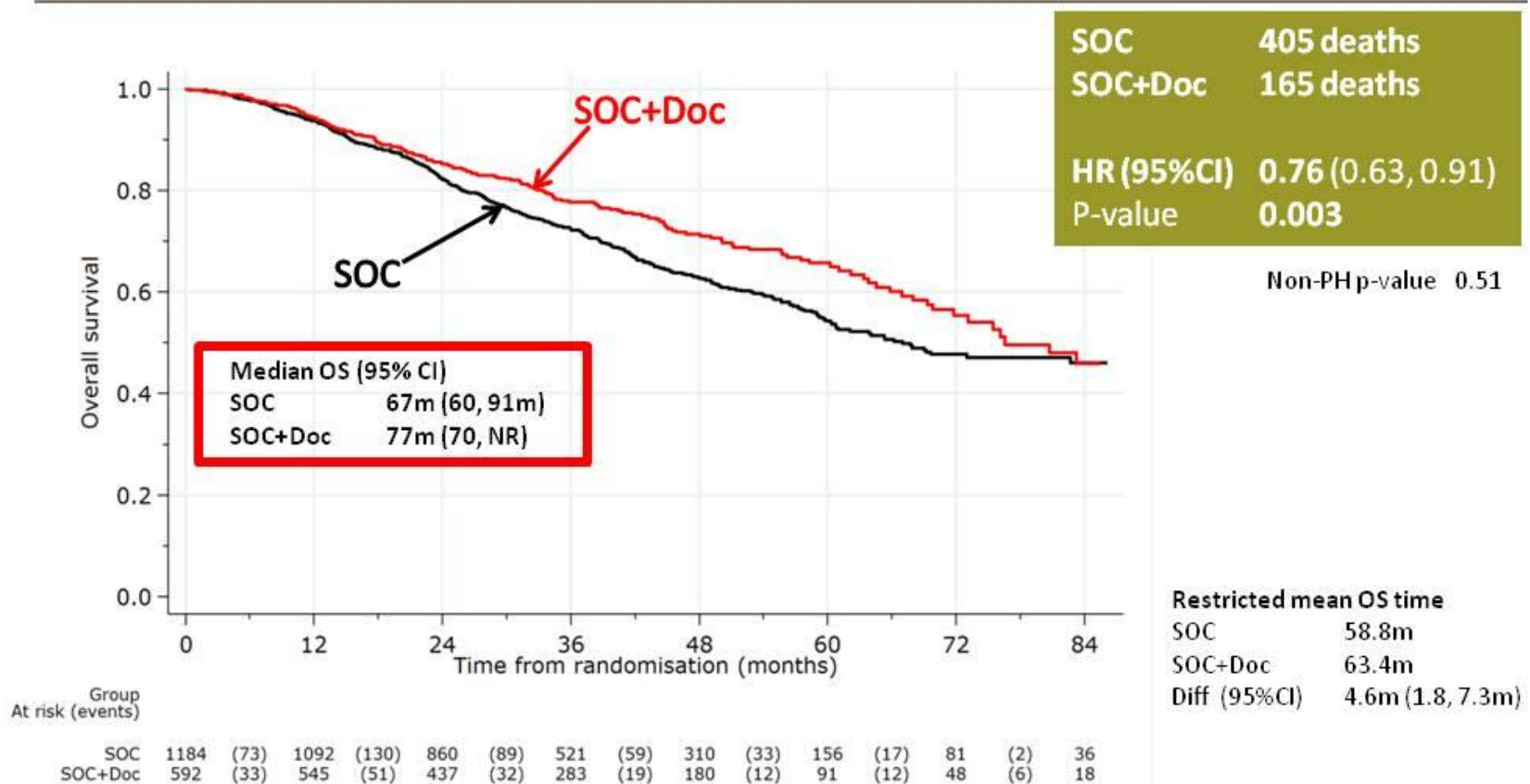
[www.stampededtrial.org](http://www.stampededtrial.org)

# STAMPEDE: date set for release of results for original comparisons



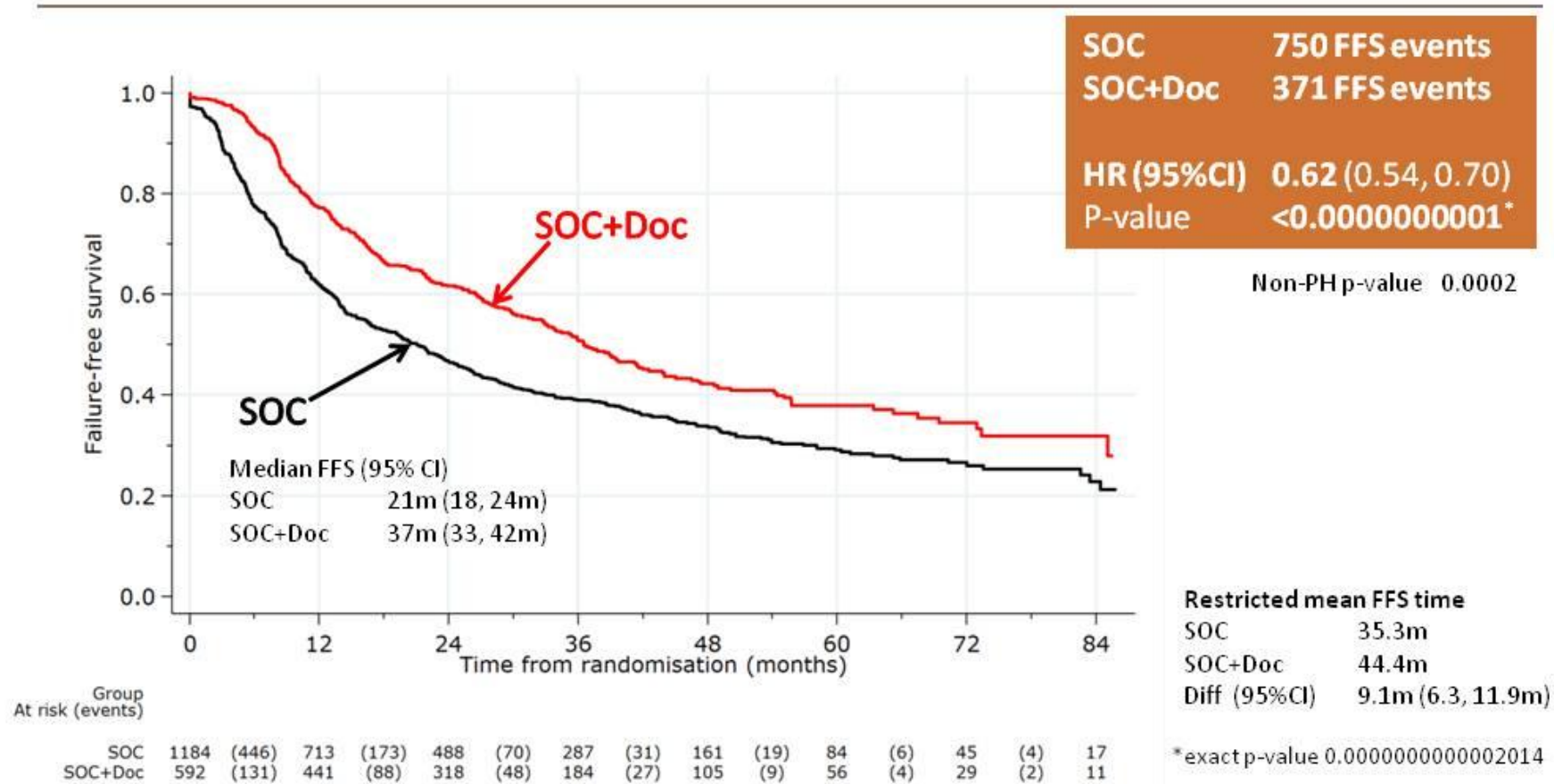


# Docetaxel: Survival





# Docetaxel: Failure-free survival



## Cause of Death\*

	AS+RT (n=59)	AS+RT+CT (n=43)
Death due to cancer under study	23	16
Death due to protocol treatment	0	2
Death due to other cause	24	16
Death due to second primary	12	5
Unknown cause of death	0	4

**\*Based on central review blinded to treatment arm**

## Conclusions

- **For the first time, improvement in overall survival observed with (tolerable) adjuvant chemotherapy for localized, high-risk, hormone-sensitive prostate cancer.**
  - Cumulative incidence of DM reduced
- **The potential role of docetaxel in hormone-sensitive prostate cancer is consistent with and supported by our data and other studies, such as STAMPEDE and CHAARTED.**
- **This analysis is relatively early and additional follow-up will likely be enlightening.**

# **Characterization of Neuro-endocrine Prostate Cancer in Patients with mCRPC Cancer to Abiraterone or Enzalutamide**

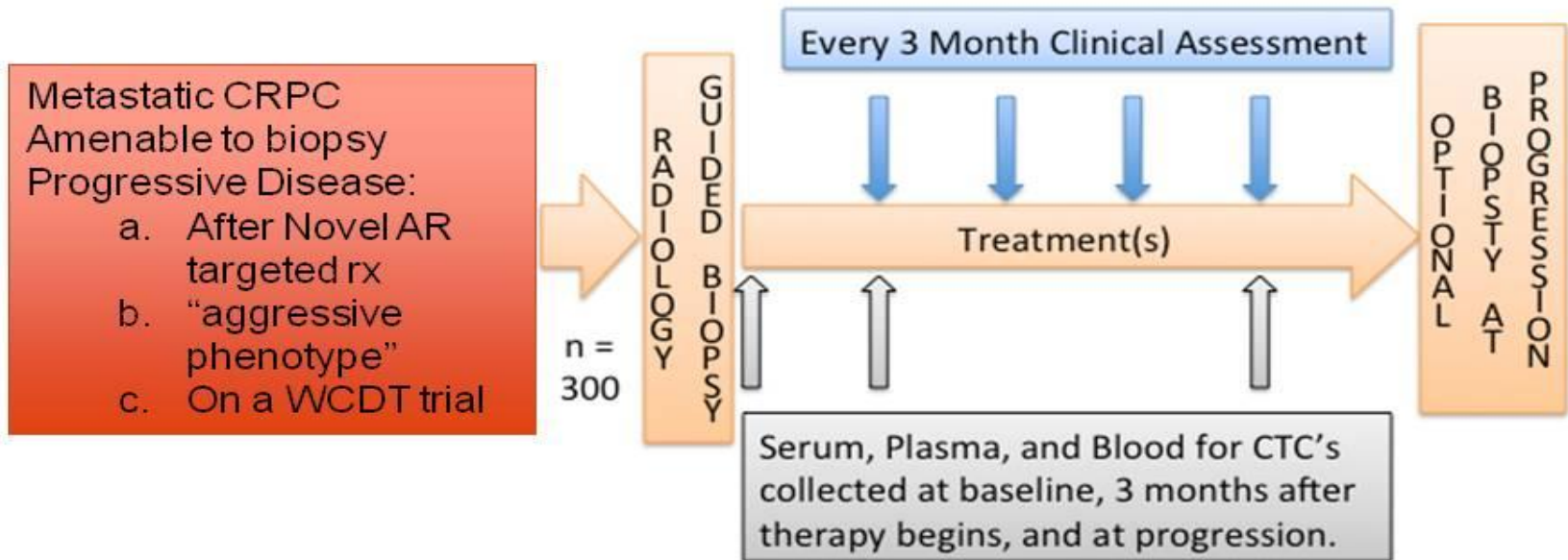
## **Preliminary Results from the SU2C/PCF/AACR West Coast Prostate Cancer Dream Team**

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

PRESENTED AT:  **Annual '15  
Meeting**



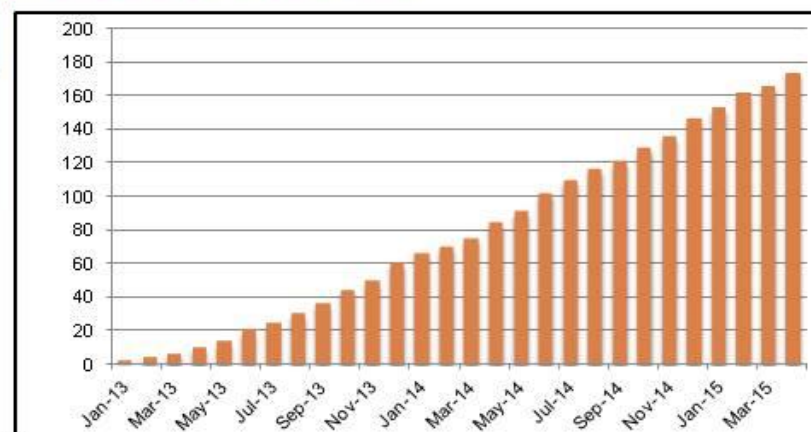
# Dream Team Biopsy Trial





## Patient Demographics and Accrual

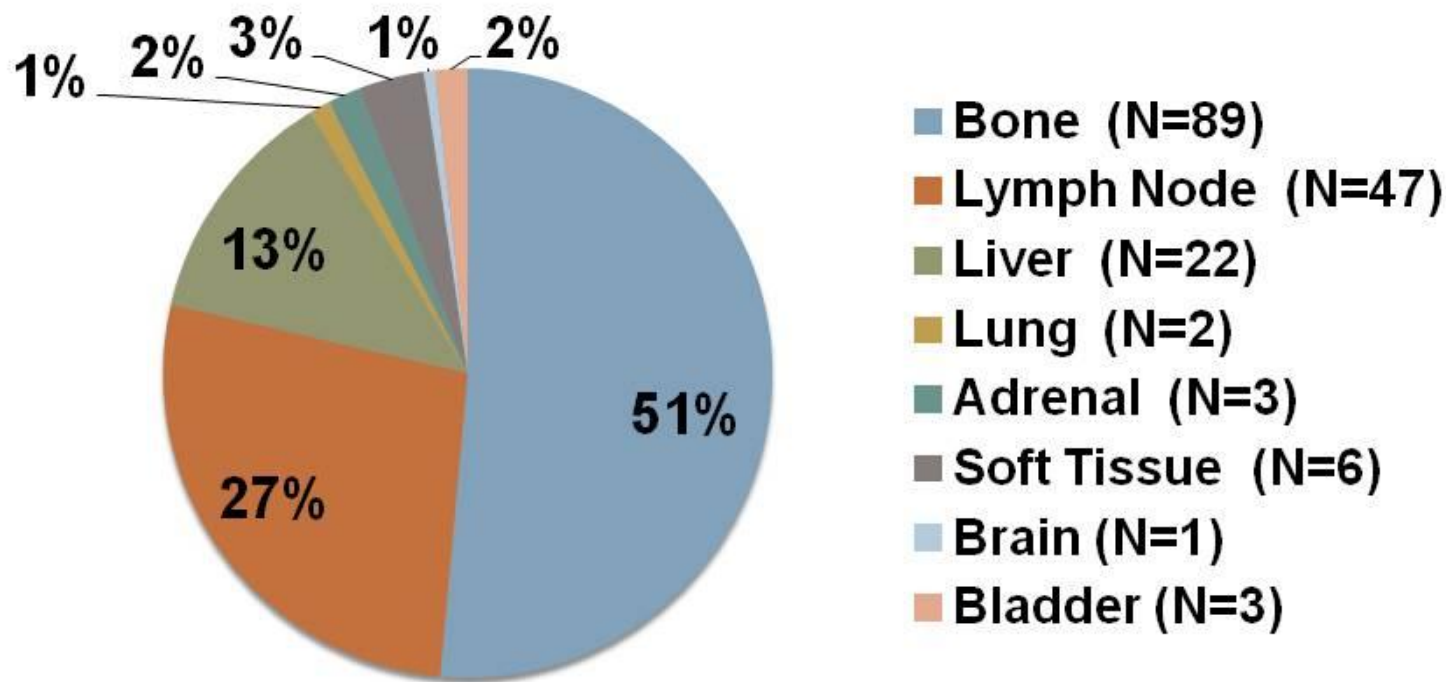
	N (%)
<b>Gleason score at diagnosis (%)</b>	
< 8	53 (42%)
≥ 8	72 (58%)
<b>Prior Treatment for mCRPC (%)</b>	
Abiraterone	54 (40%)
Enzalutamide	13 (10%)
Both	23 (17%)
Neither	45 (33%)
<b>Metastatic Sites</b>	
Liver	24 (20%)
Other Visceral	18 (15%)
Bone/node only	77 (64%)
<b>Median Lab Values (range):</b>	
PSA (ng/mL)	52 (0.4 – 2250)
Alkaline phosphatase (IU/L)	92 (20 – 1079)
LDH (IU/L)	204 (116 – 856)



PRESENTED AT: ASCO Annual '15 Meeting

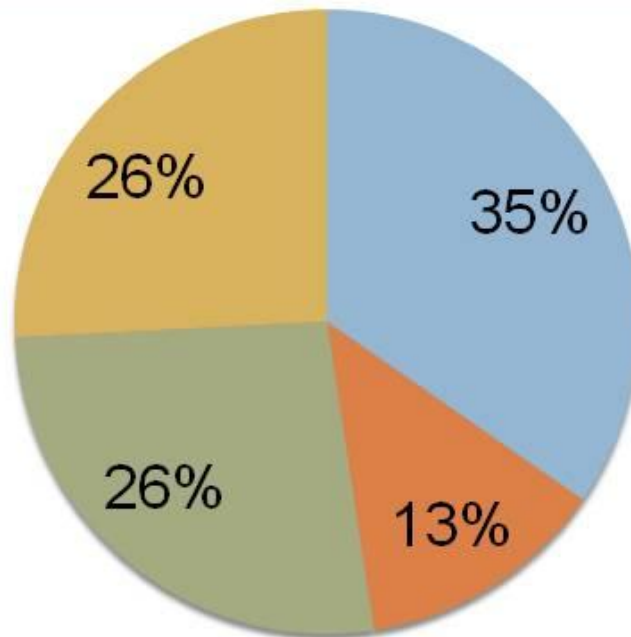
# Sites of Biopsy Acquisition

(as of 5/1/15, n = 173)

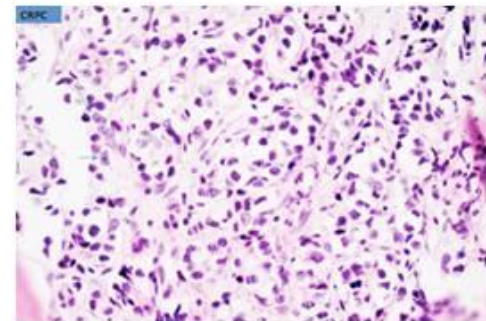


# Histology of 124 Evaluable Biopsies

35% of biopsies are pure adenocarcinoma



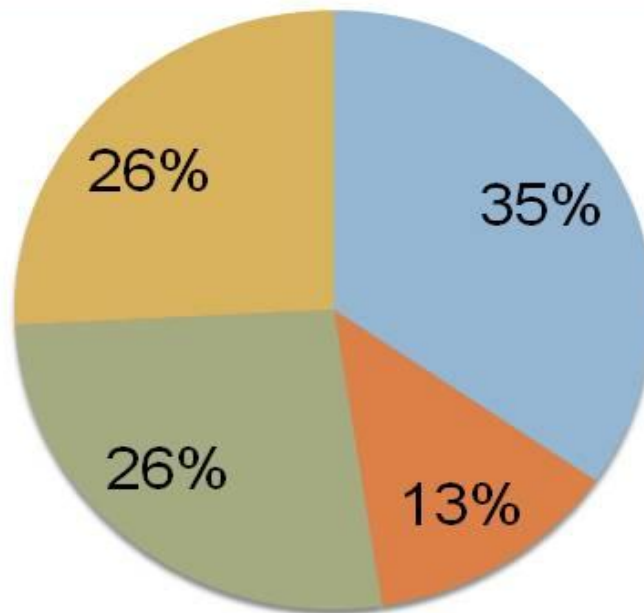
AdenoCA (N = 43)



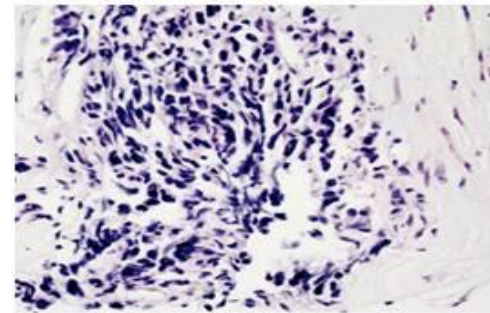


# Histology of 124 Evaluable Biopsies

13% of biopsies are pure classic small cell/neuroendocrine cancer (SCNC)

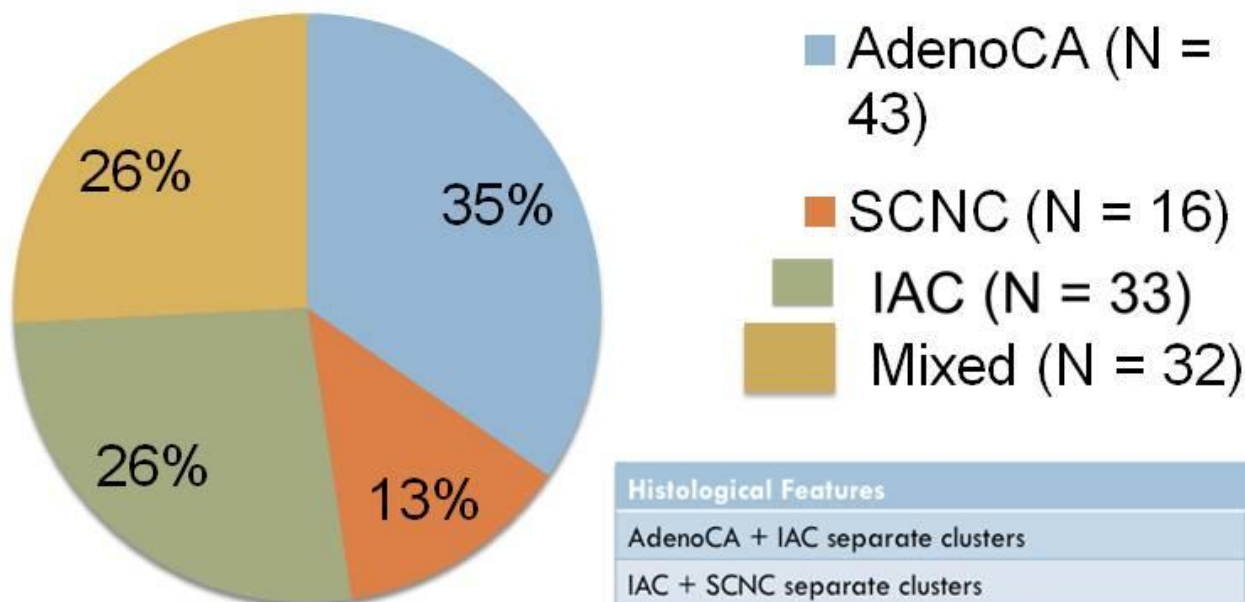


SCNC (N = 16)



## Histology of 124 Evaluable Biopsies

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



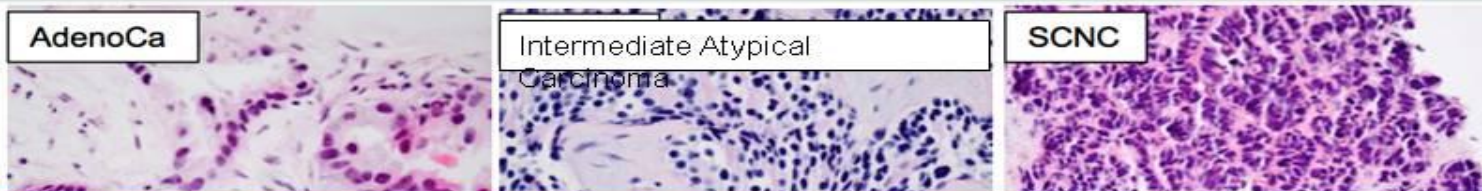
Histological Features	Count
AdenoCA + IAC separate clusters	11
IAC + SCNC separate clusters	4
AdenoCA + SCNC separate clusters	1
Non-adenoca cytology with adenoCA architecture	11

## Intermediate Atypical Carcinoma is a new, highly reproducible pathologic subclass

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

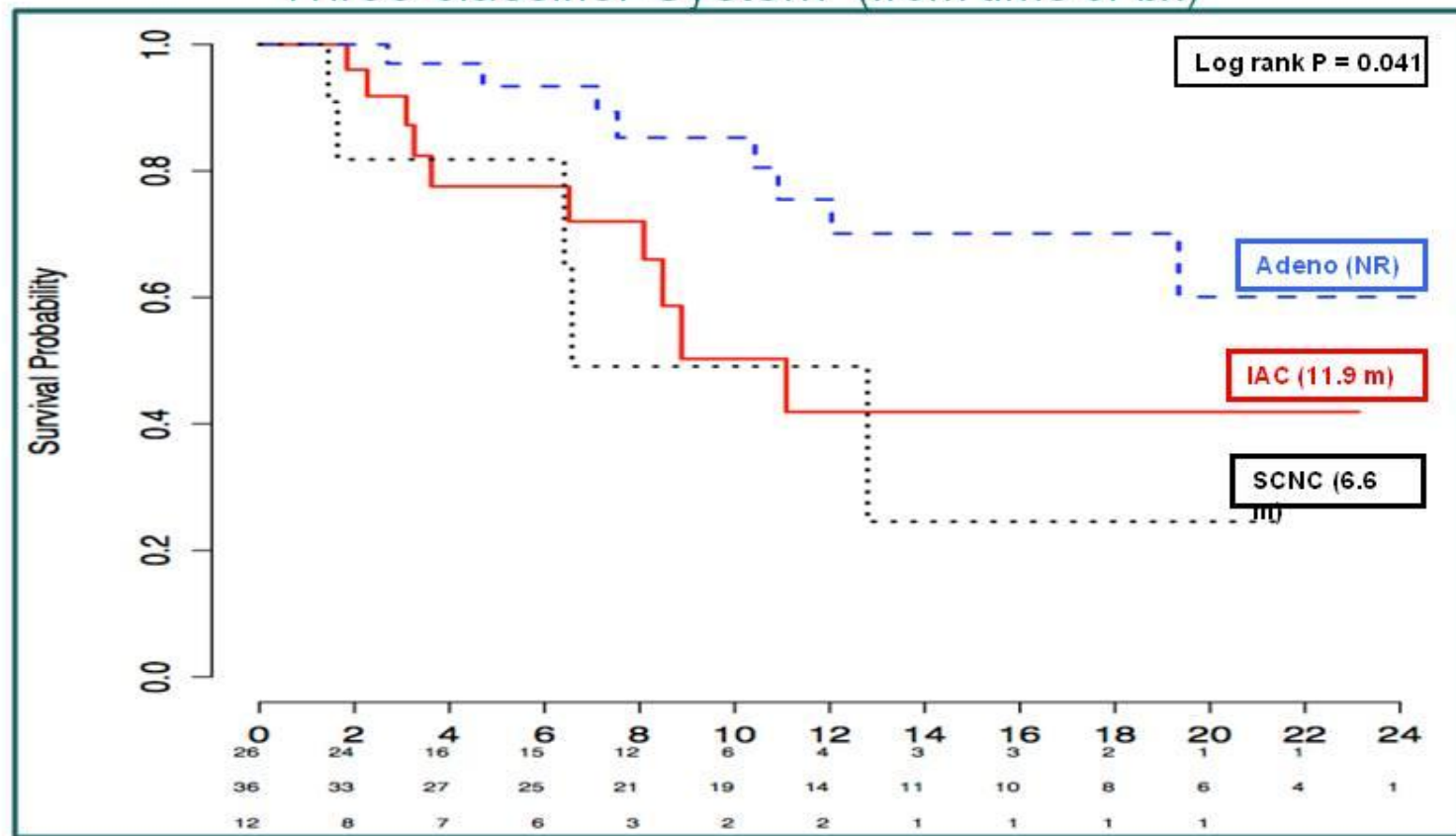
### Huang Criteria

“cytologically bland”

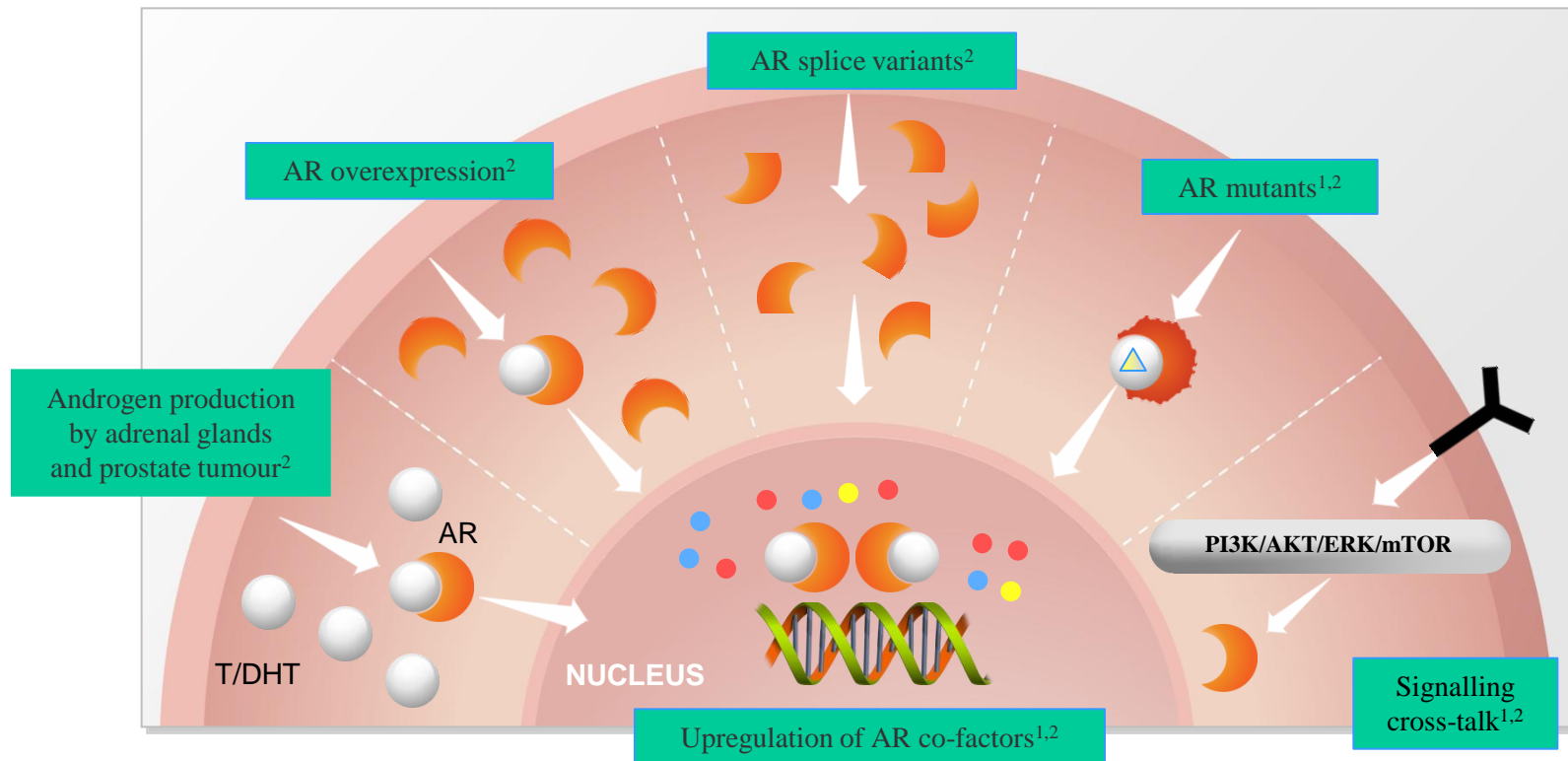


	AdenoCa	Intermediate Atypical Carcinoma	SCNC
<b>Cytoplasm</b>	Abundant	Moderate to abundant	Scant
<b>Nuclear chromatin</b>	Clumpy, vacuolated, open chromatin pattern	Fine homogeneous chromatin pattern	Fine homogeneous chromatin pattern
<b>Nuclear staining</b>	Light	Dark	Dark
<b>Nuclear shape</b>	Some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

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



# Der AR-signalweg ist der logische therapeutische Zielpunkt bei CRPC



AR=androgen receptor; CRPC=castration-resistant prostate cancer; DHT=dihydrotestosterone; ERK=extracellular signal-regulated kinase; mTOR=mammalian target of rapamycin; PI3K=phosphatidylinositol-3 kinase; T=testosterone.

1. Heinlein CA, Chang C. *Endocr Rev* 2004;25:276–308.
2. Hu R, et al. *Expert Rev Endocrinol Metab* 2010;5:753–64.

# CHAARTED: Sicherheit

- **Toxicity on testosterone suppression and docetaxel:**
  - **Fewer with lowered white blood cell count: 6%**
  - **Significant impact on nerves: 1% sensory, 1% motor**
  - **One of 397 patients who received early docetaxel died due to treatment**