SCUOLA di URONCOLOGIA

TUMORE della PROSTATA

21·22 NOVEMBRE 2014

ROMA

HOTEL SHERATON GOLF
PARCO DE' MEDICI

Viale Rebecchini, 145

PROGRAMMA 22 NOVEMBRE 2014

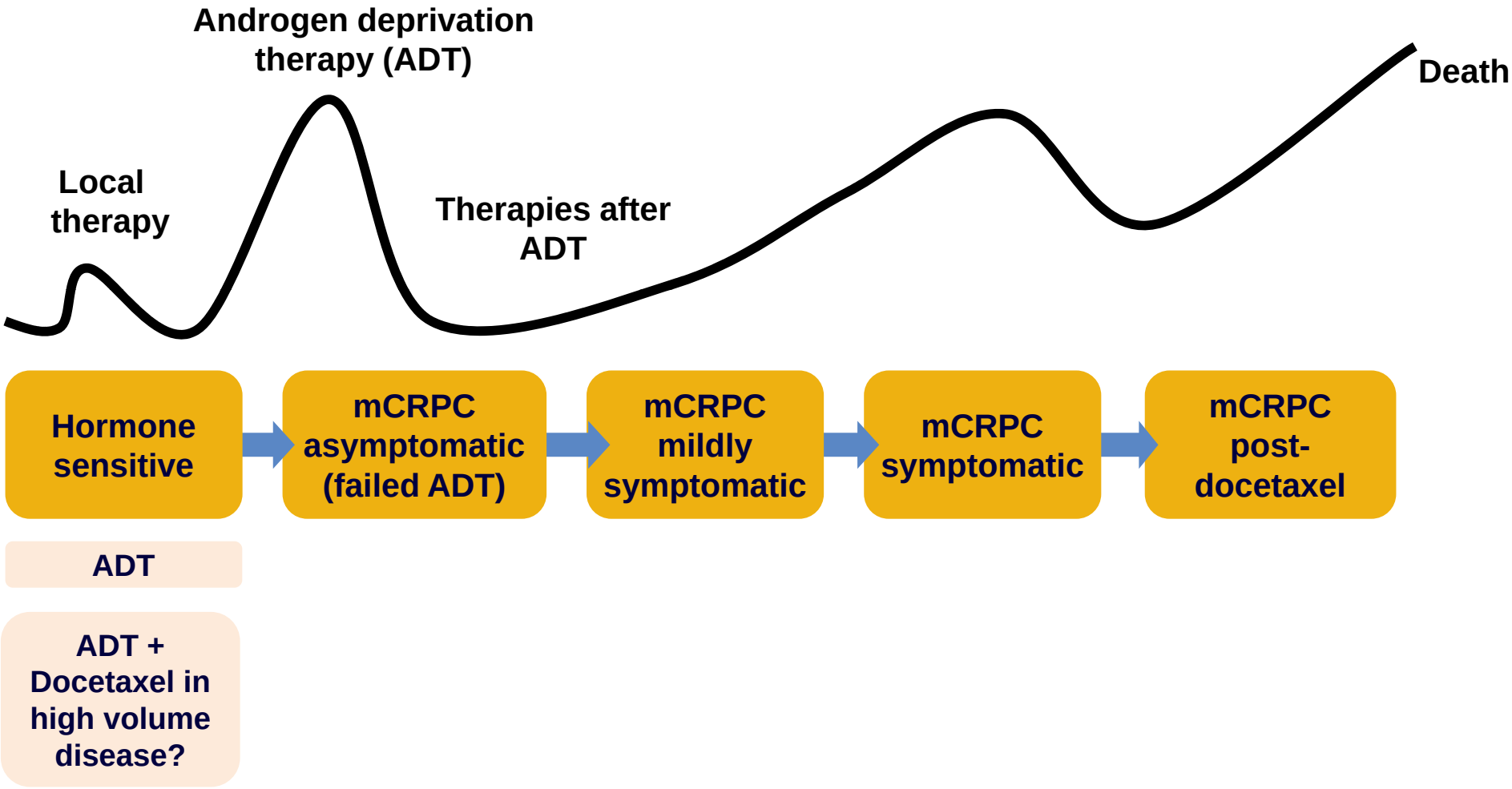
HOT TOPICS
CANCRO DELLA PROSTATA
Question Time
Le domande degli Urologi agli Oncologi

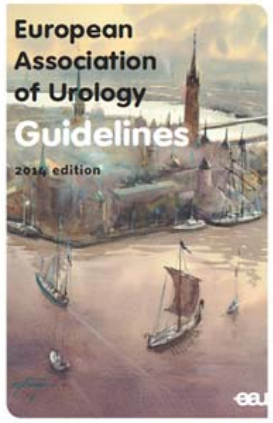
SESSIONE MALATTIA METASTATICA

08.30 Malattia ormonosensibile
D. VILLARI risponde **M. RIZZO**

Prima linea e seconda linea di trattamento
D. VILLARI risponde **E. VERZONI**

Natural History of Prostate Cancer





Definition of CRPC 2014

EAU Guidelines PCa_2014.pdf - Adobe Reader

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20.2 Definition of relapsing prostate cancer after castration

The precise definition of recurrent or relapsed PCa remains controversial and several groups have published practical recommendations for defining CRPC (20,21). Table 20.1 lists the key defining factors of CRPC.

Table 20.1: Definition of CRPC

Castrate serum testosterone < 50 ng/ml or 1.7 nmol/L plus either: Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL. or Radiological progression: The appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours) (22).

20.3 Assessing treatment outcome in CRPC

Precise quantification of the effect of treatments on metastatic disease is difficult to quantify and rarely used in clinical practice. Improvements in QoL, progression free survival and prostate cancer specific survival are all used but the gold standard remains overall survival (23).

20.3.1 PSA level as marker of response

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a surrogate marker. Trials of the vaccines sipuleucel-T (Provenge) (24) and TRICOM (PROSTVAC) (25) have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs (26).

In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA

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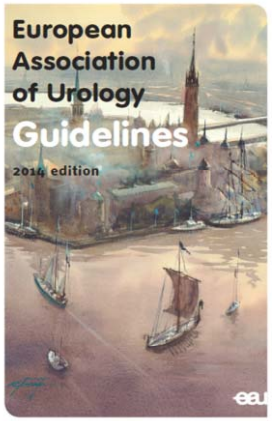
Definition of CRPC 2013

Table 21: Definition of CRPC

Castrate serum levels of testosterone < 50 ng/dL or < 1.7 nmol/L.
Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL.
Anti-androgen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide*
PSA progression, despite consecutive standard hormonal manipulations†

** Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done to fulfil the criteria for CRPC if patients have been treated with anti-androgens in the context of maximum androgen blockade or step-up therapy following PSA progression after failure of LHRH treatment.*

† Progression or appearance of two or more bone lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) with nodes ≥ 2 cm in diameter.



EAU Guidelines – 2014 edition

European association of urology - 2014.pdf (SECURED) - Adobe Acrobat Pro

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prostate

20.6 Classical hormonal treatment alternatives after CRPC occurrence

A number of second and third line hormonal manipulations remain in use despite the fact that no associated survival benefit has ever been reported.

20.6.1 ***Bicalutamide***

Bicalutamide has a dose response, with higher doses producing a greater reduction in PSA level (48). The largest cohort so far is based on 52 CRPC patients treated with 150 mg bicalutamide (49). A palliative effect was clear and a 20% PSA response (at least 50% decrease) was observed, without any link to the palliative effect. The addition of a non-steroidal anti-androgen to gonadal suppression at the time of PSA failure appears to result in declining PSA in only a few patients (50,51).

20.6.2 ***Anti-androgen withdrawal***

Approximately one-third of patients who had shown a PSA response to maximum androgen blockade will respond to anti-androgen withdrawal, as indicated by a > 50% PSA decrease, for a median duration of

approximately 4 months. Anti-androgen withdrawal responses have also been reported with bicalutamide and

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approximately 4 months. Anti-androgen withdrawal responses have also been reported with bicalutamide and megestrol acetate (52-57). In the SWOG 9426 trial, PSA progression despite CAB was reported in a subgroup of 210 patients with an M0 or M1 stage tumour (58). A response was observed in 21% of patients, even though there was no radiographic response. Median PFS was 3 months, with 19% (all M0) having PFS > 12 months. Increased PFS and OS were associated with longer use of non-steroidal drugs, lower PSA at baseline and M0-stage. These results were obtained with patients on CAB following androgen withdrawal. No data were available on the withdrawal effect following second-line anti-androgen treatment.

*20.6.3 **Oestrogens***

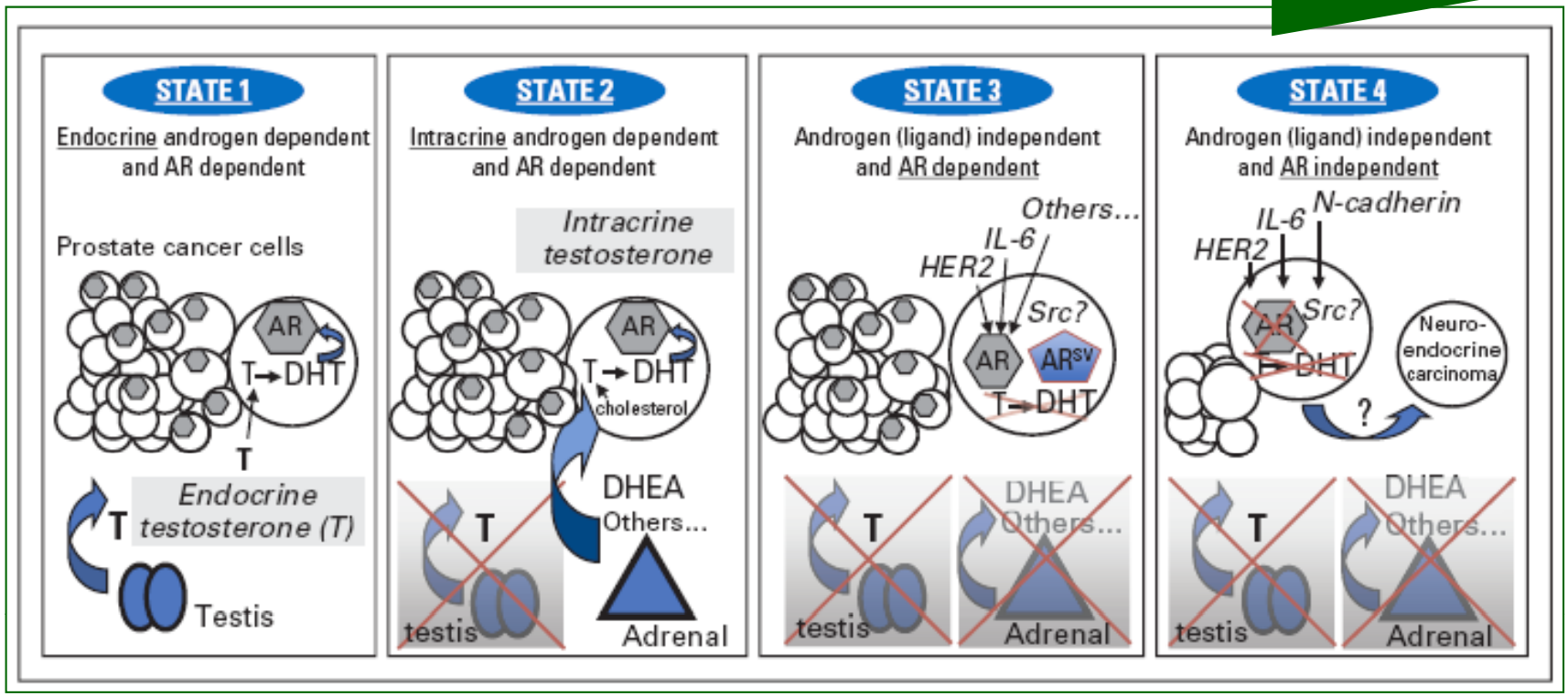
Prostate cancer usually expresses oestrogen receptors, which are upregulated after androgen ablation in animal models. Diethylstilboestrol (DES) (59-61) achieved a positive PSA response in 24% and 80% of patients, with an overall estimated survival of 63% at 2 years. However, even at low doses of DES, about one-third (31%) of patients developed deep venous thrombosis and 7% experienced myocardial infarction.

20.7 Novel hormonal drugs targeting the endocrine pathways

In the past 3 years, following early phase I/II trials in patients with CRPC, new compounds appeared for treating CRPC (Section 19.4). Most have been developed post docetaxel, but abiraterone acetate and Enzalutamide have been used before chemotherapy. The initial results of abiraterone use in the pre docetaxel setting have been recently published from the large phase III trial COU-AA-302, in which 1,088 chemonaïve CRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone (62). Patients were diagnosed with CRPC according to the PCWG2 criteria, and were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and asymptomatic or mildly symptomatic. The study had two joint primary

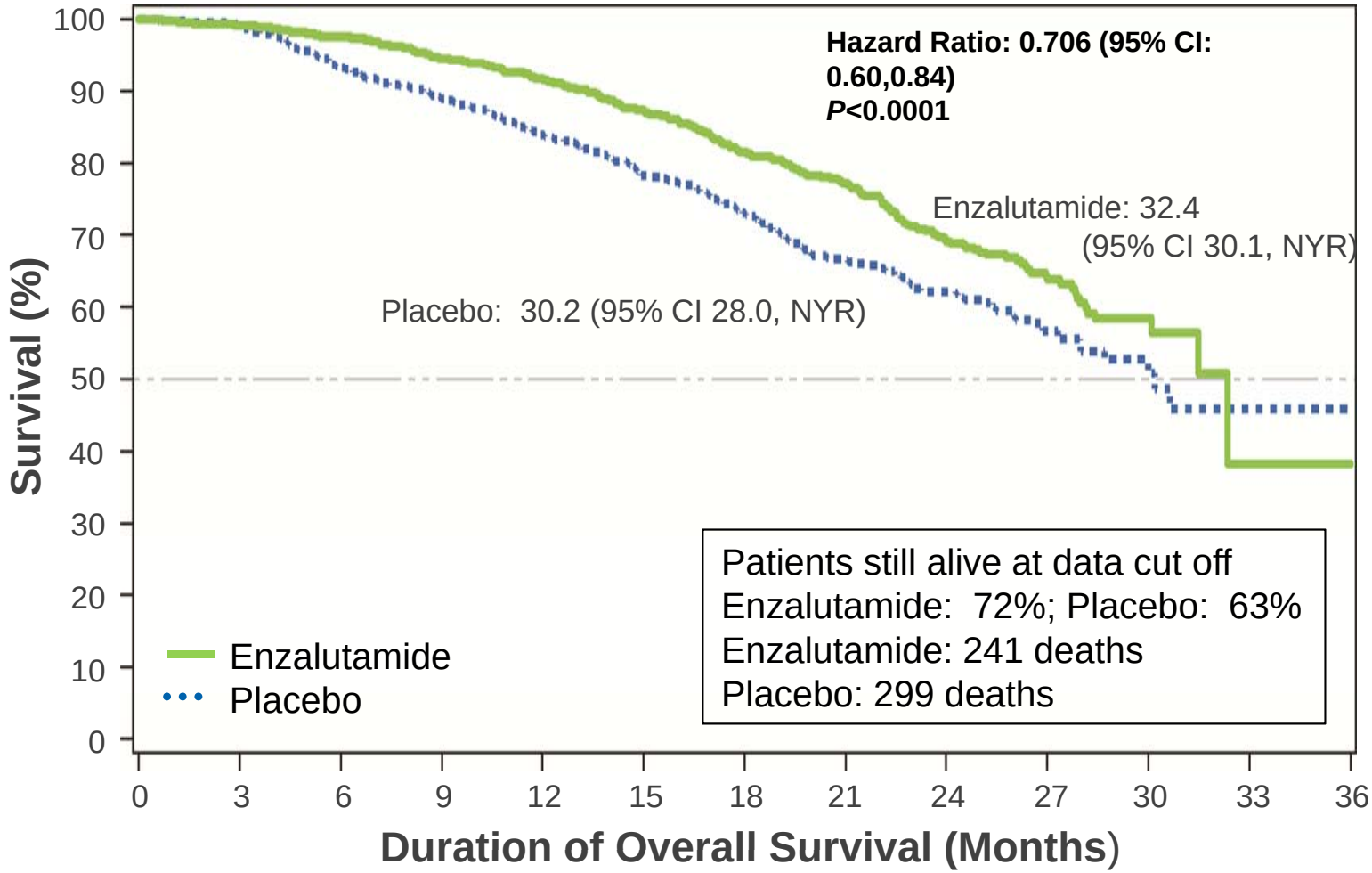
Il processo di progressione tumorale nel CaP

Totalmente dipendente da testosterone circolante ADT	**Autoproduzione di Testosterone** **TARGET: CYP17**	Attivazione di AR aspecifica	Androgeno indipendente AR indipendente



Mod. da Nelson et al, *J Clin Oncol* 2012

Enzalutamide Reduced Risk of Death by 29%



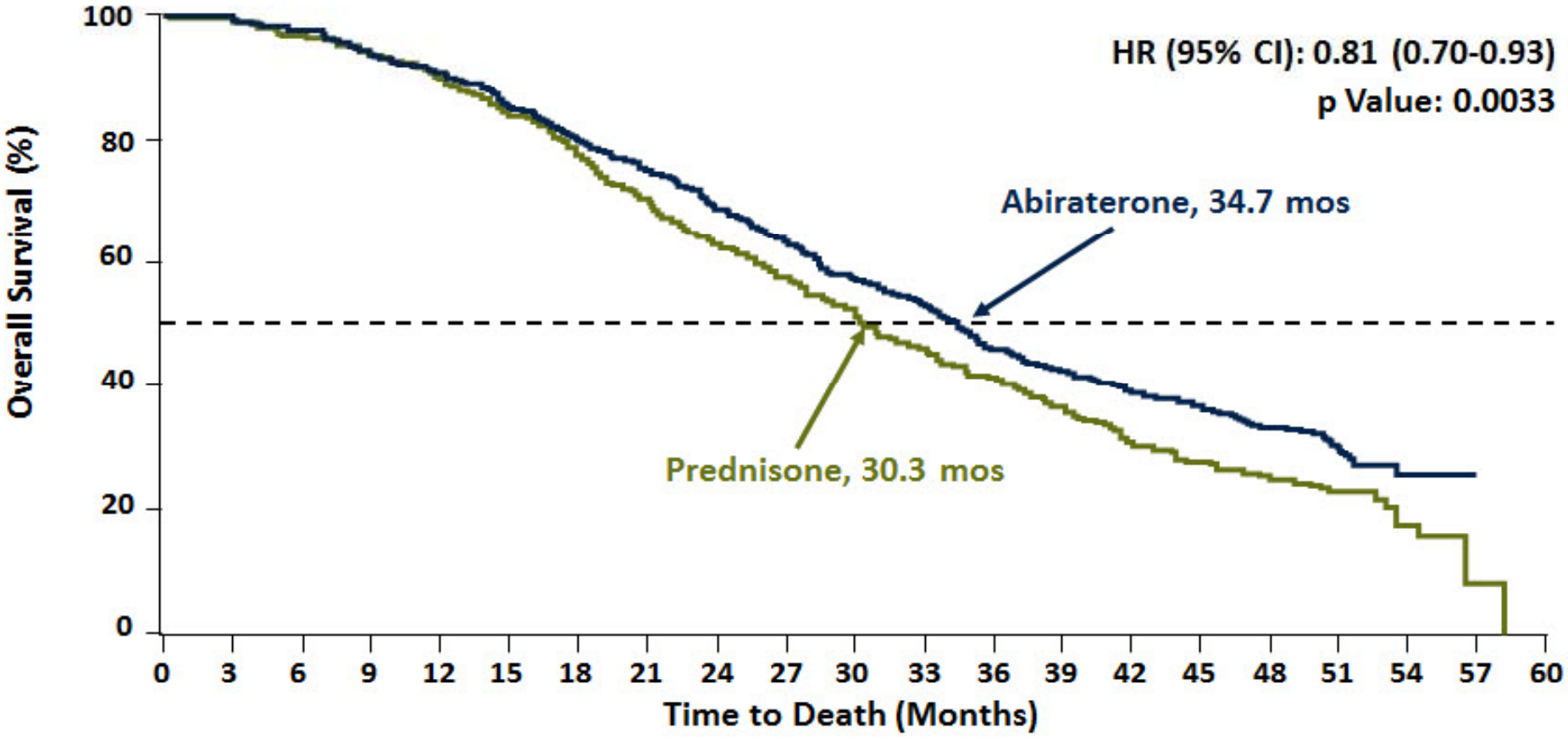
Patients at Risk

Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

Median Follow-up 22 Months

Beer et al, N Engl J Med. 2014; 371(5):424-33

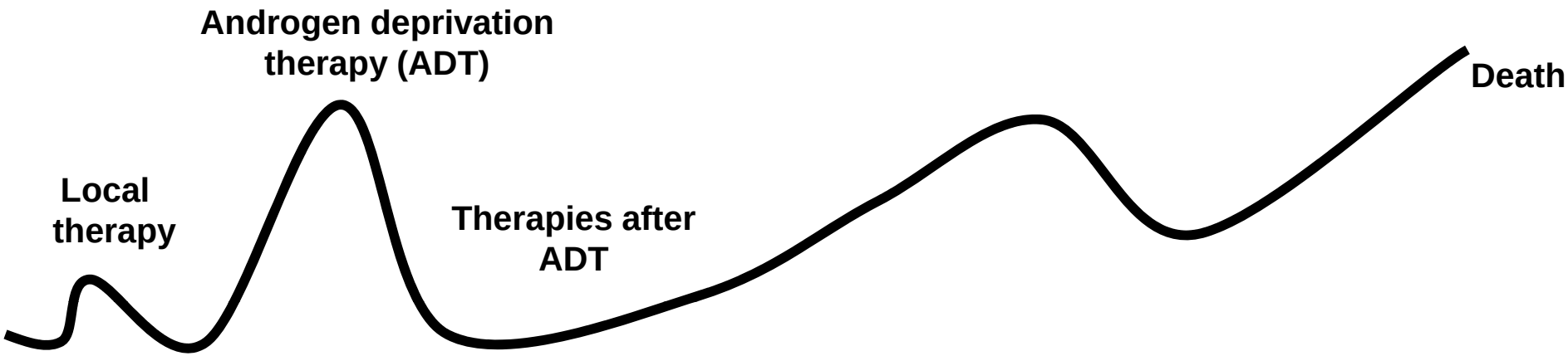
Final OS Analysis



Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- Median follow-up of 49.2 months
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

Current Treatment Paradigm is Evolving



Hormone sensitive → mCRPC asymptomatic (failed ADT) → mCRPC mildly symptomatic → mCRPC symptomatic → mCRPC post-docetaxel

ADT → Abiraterone → Abiraterone

Enzalutamide → Enzalutamide

ADT + Docetaxel in high volume disease?

Radium 223

Docetaxel → Cabazitaxel

Sipuleucel-T

supportive care (eg denosumab/bisphosphonates)