UPDATES ON NON SURGICAL MANAGEMENT OF PROSTATE CANCER

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To be discussed

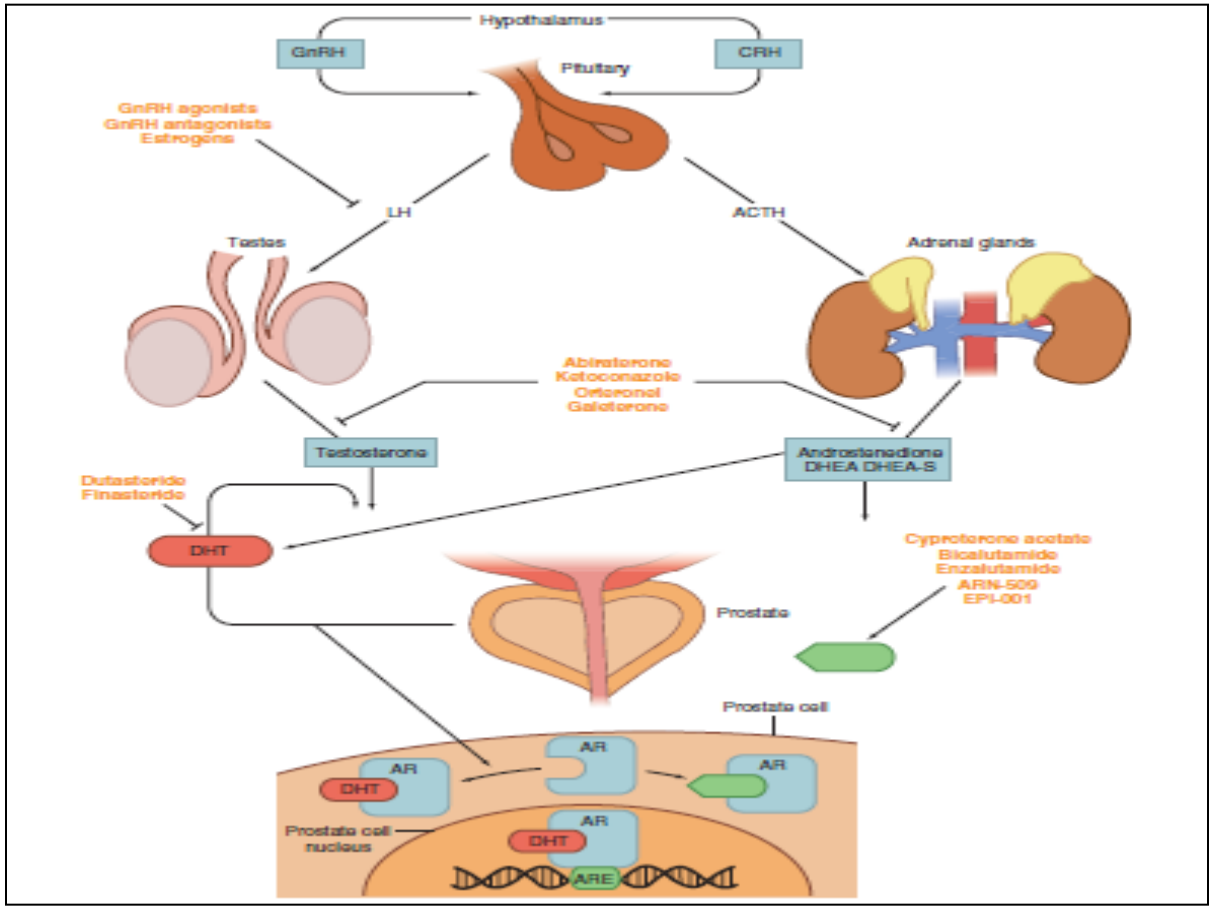
Management of Non Metastatic PrCa

- Radiotherapy
- Hormone therapy (NA ADT/ADj ADT)

Metastatic Pr Ca

- Molecular Biology
- Chemotherapy
- Hormone therapy
- CRPC
- Newer Molecules

Hormonal pathways



Devita 10th edition page 926

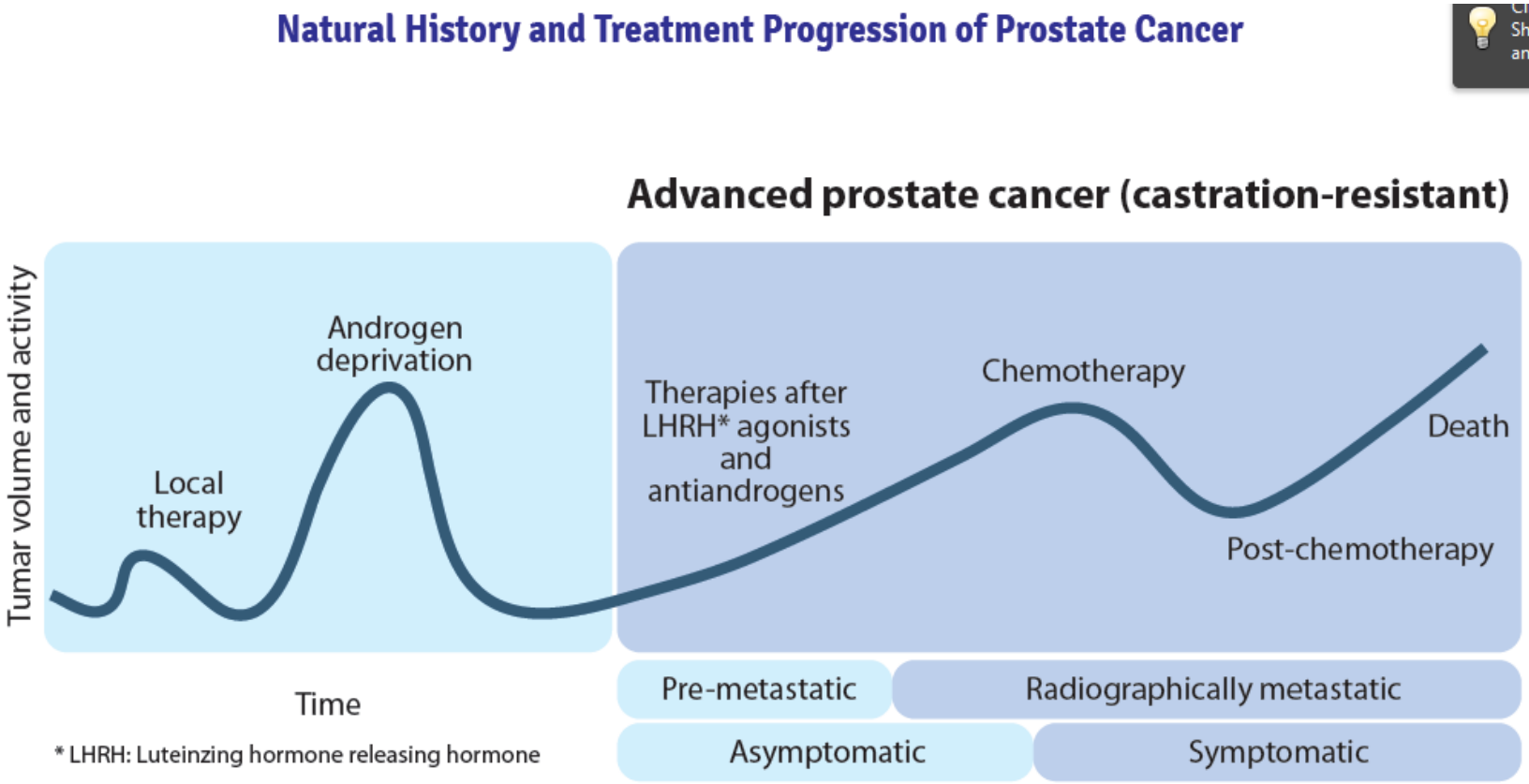
Types of prostate cancer

- Prostate cancer growth may be fueled even after androgen deprivation therapies
- 1. **Androgen/Castration Naïve/sensitive/dependent**

  Tumor cells grow in presence of DHT
- 2. **Androgen resistant/ insensitive/independent/castration Resistant (CRPC)**

  Tumor cells grow in androgen deprivation with a very low level of testosterone (<50ng/dl).

Progression of prostate cancer



Clinical states model of PrCa

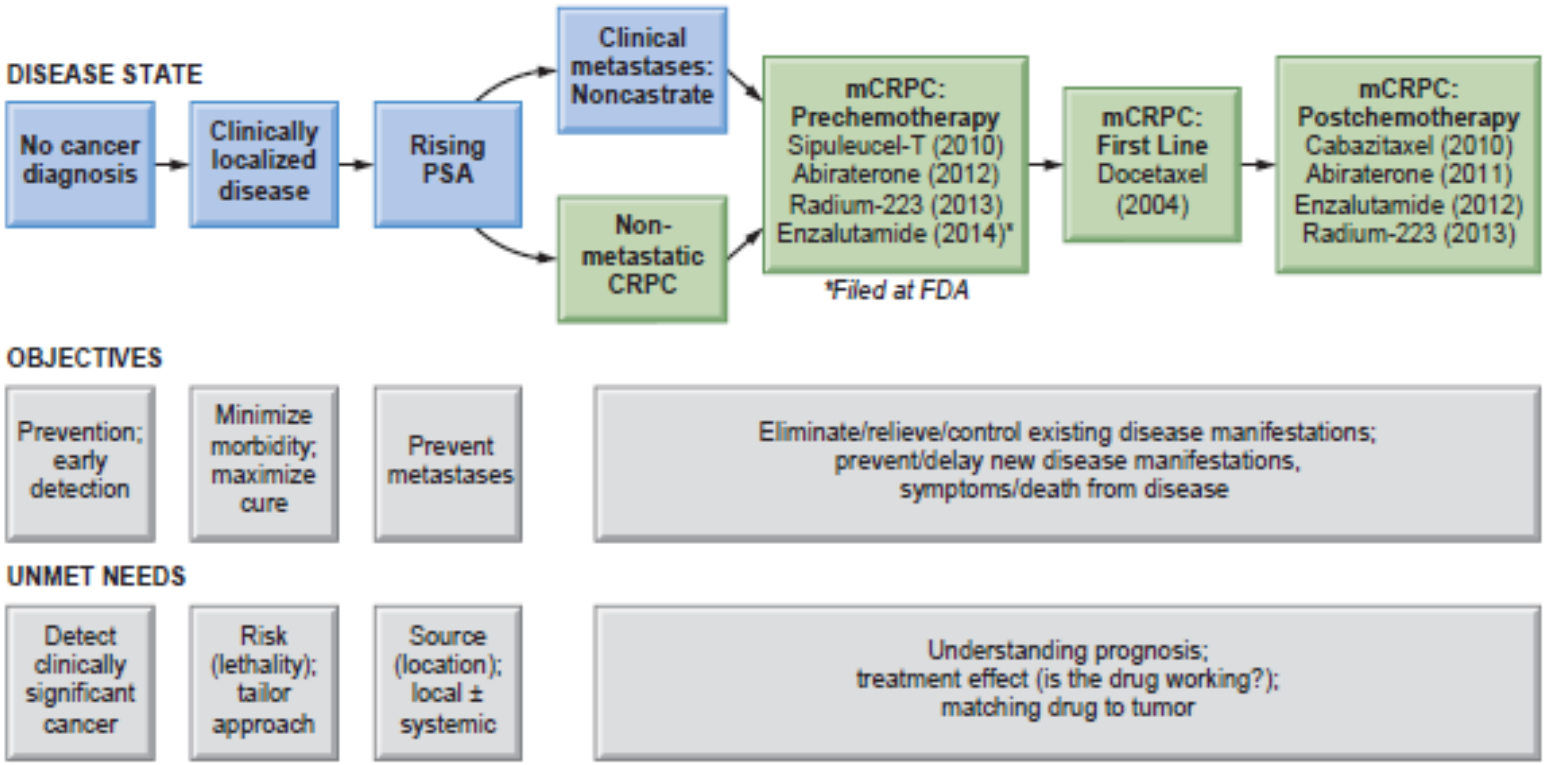


Figure 68.1 Clinical states model of prostate cancer progression. *Green boxes* indicate castration-resistant prostate cancer (CRPC) and *blue* indicate noncastrate disease. PSA, prostate-specific antigen; mCA RPC, metastatic castration-resistant prostate cancer. (Modified from Scher HI, Heller G. Clinical states in prostate cancer: towards a dynamic model of disease progression. *Urology* 2000;55:323–327.)

Devita 10th edition page 933

Overview

Table 1. Risk groups for localised prostate cancer [7]

Low risk	T1–T2a and GS ≤6 and PSA ≤10
Intermediate risk	T2b and/or GS7 and/or PSA10-20
High risk	≥T2c or GS8-10 or PSA >20

GS, Gleason score; PSA, prostate-specific antigen.

Table 3. Stage-matched therapeutic strategies

Localised disease	
Low risk	Active surveillance Brachytherapy Radical prostatectomy Radical radiotherapy
Intermediate risk	Active surveillance Brachytherapy Radical prostatectomy Radical radiotherapy ± neoadjuvant ADT
High risk	Neoadjuvant ADT + radical radiotherapy + adjuvant ADT Radical prostatectomy + pelvic lymphadenectomy
Locally advanced disease	
	Neoadjuvant ADT + radical radiotherapy + adjuvant ADT Radical prostatectomy + pelvic lymphadenectomy
Metastatic disease	
Hormone-naïve	ADT
Castration-resistant (first line)	Abiraterone Docetaxel Enzalutamide Radium-223 Sipuleucel-T
Second line (post-docetaxel)	Abiraterone Cabazitaxel Enzalutamide Radium-223

ESMO guideline 2015

FAQs on metastatic PrCa/CRPC

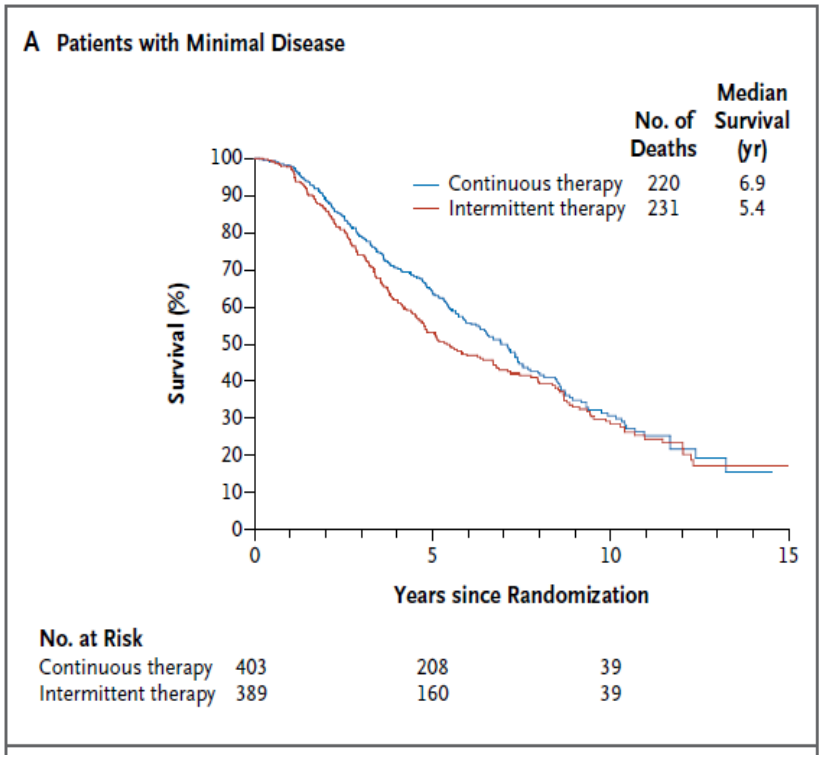
- Role of ADTs ?
- Intermittent vs Continuous ADT?
- Role of Chemotherapy in Hormone naïve Pr Ca?
- Issue of CRPC (Predictive model)?
- Role of Novel agents?
- Role of taxanes ?
- Sequencing of therapies CT>HT/HT>CT/HT>HT?
- Novel chemotherapy options?
- Newer molecules?

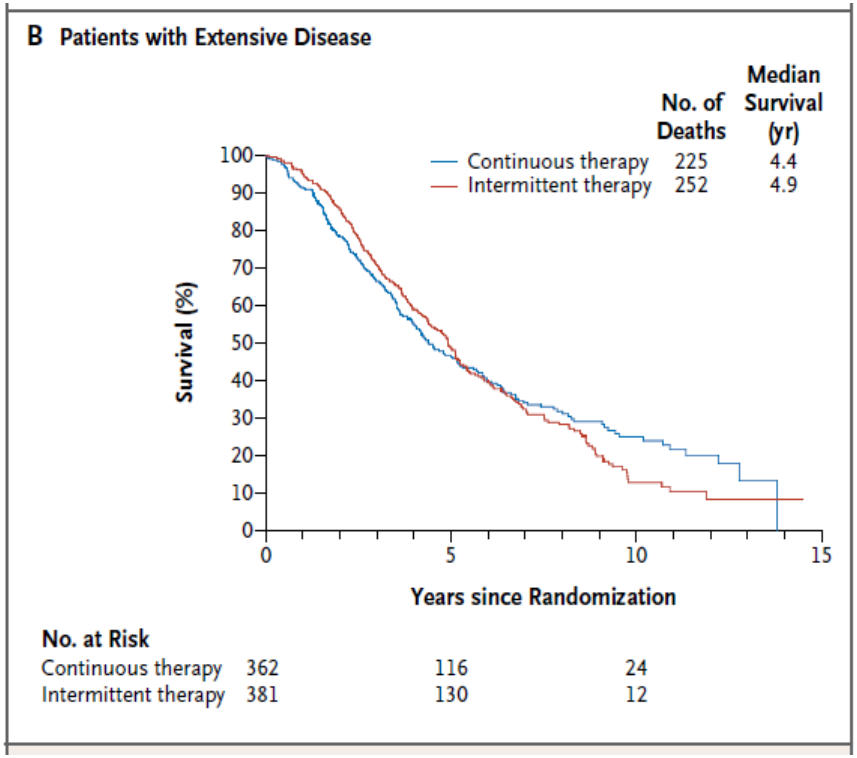
ADT in mPrCa

- Gold standard initial treatment
- **Intermittent Vs Continuous ADT (SWOG 9346)**
- Hormone naïve mPrCa treated with 7months of ADT with PSA <4ng/ml
- 1:1 RCT : Int. vs Cont. (n= 3040)
- Median F/U 9.8years
- MS Cont. Vs Int. (5.8yrs vs 5.2yrs){inconclusive}
- No toxicity difference in long F/U

Hussain M NEJM 2013

Subset analysis (SWOG 9346)





Better MS of Int. ADT in extensive disease indicates replacing androgen before progression may prolong androgen dependency in extensive mPrCa.

JAMA Oncology

Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer

A Systematic Review and Meta-analysis

Sindy Magnan, MD, MSc, FRCPC[1]; Ryan Zarychanski, MD, MSc, FRCPC[2,3]; Laurie Pilote, MD[1]; Laurence Bernier, MD[1]; Michèle Shemilt, MSc[4]; Eric Vigneault, MD, MSc, FRCPC[1,4]; Vincent Fradet, MD, PhD, FRCSC[4,5]; Alexis F. Turgeon, MD, MSc, FRCPC[4,6]

[+] Author Affiliations

JAMA Oncol. 2015;1(9):1261-1269. doi:10.1001/jamaoncol.2015.2895.

Results From 10510 references, we included 22 articles from 15 trials (6856 patients) published between 2000 and 2013. All but 1 study had an unclear or high risk of bias. We observed no significant difference between intermittent and continuous therapy for overall survival (HR, 1.02; 95% CI, 0.93-1.11; 8 trials, 5352 patients), cancer-specific survival (HR, 1.02; 95% CI, 0.87-1.19; 5 trials, 3613 patients), and progression-free survival (HR, 0.94; 95% CI, 0.84-1.05; 4 trials, 1774 patients). There was minimal difference in patients' self-reported quality of life between the 2 interventions. Most trials observed an improvement in physical and sexual functioning with intermittent therapy.

Conclusions and Relevance Intermittent androgen deprivation was not inferior to continuous therapy with respect to the overall survival. Some quality-of-life criteria seemed improved with intermittent therapy. Intermittent androgen deprivation can be considered as an alternative option in patients with recurrent or metastatic prostate cancer.

ADT : personalized approach

- Treat all mPrCa with 7months ADT
- Risk categorization after 7months: PSA

Low risk PSA <0.2ng/ml	Intermediate Risk PSA 0.2-4ng/ml	High Risk PSA >4ng/ml
MS 75months	MS 44months	MS 13months

- Monitor ADT related adverse events
- **Tailoring of Int vs Cont. on PSA and A/E**

Hussain M J Clin Oncol 2006

ADT adverse events

- **Osteoporosis (RR >21-50% than general pop)**
- Calcium and Vit D3 supplimentation
- Bisphosphonates/Denosumab
- DEXA scan

- **Diabetes (HR 1.44) and CVS disorder (HR 1.31)**
- Monitor regularly

Role of upfront chemotherapy in Hormone naïve metastatic Pr Ca

Role of Docetaxel

Docetaxel in Hormone Naïve mPrCa

- **CHAARTED trial (2006-2012)**
- Hormone Naïve mPrCa
- RCT (1:1) ADT alone vs ADT +Doce (6cycles)
- High Volume [HV] (visc met + ≥ bone mets) vs Low Volume [LV]
- Median Follow up 29months

Intent to treat analysis	ADT	ADT + D	P value	Hazard ratio (95%CI*)
PSA < 0.2 at 12 mos	9.4%	19.7%	<0.0001	
Median OS (mos)				
N=790	42.3	52.7	0.0006	0.63 (0.48, 0.82)
N=520-HV	32.2	49.2	0.0012	0.62 (0.46, 0.83)
N=270-LV	NR**	NR	0.0836	0.58 (0.31, 1.08)

* CI: confidence intervals; **NR: not reached.

- ADT + D improves OS over ADT alone in men with High Volume mPrCa

Sweeney C et al.Clin Oncol 32:5s, 2014(abs)

Docetaxel in Hormone Naïve mPrCa

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.

CHAARTED trial Sweeney CJ et al. NEJM 2015 (n= 790) Hormone Sensitive mPrCa	ADT + Docetaxel Vs ADT alone	OS 57.6m vs 44m Survival benefit pronounced in High Vol disease PSA<0.2ng/ml at 1yr 27.7 % vs 16.8% More neutropenia in doce arm

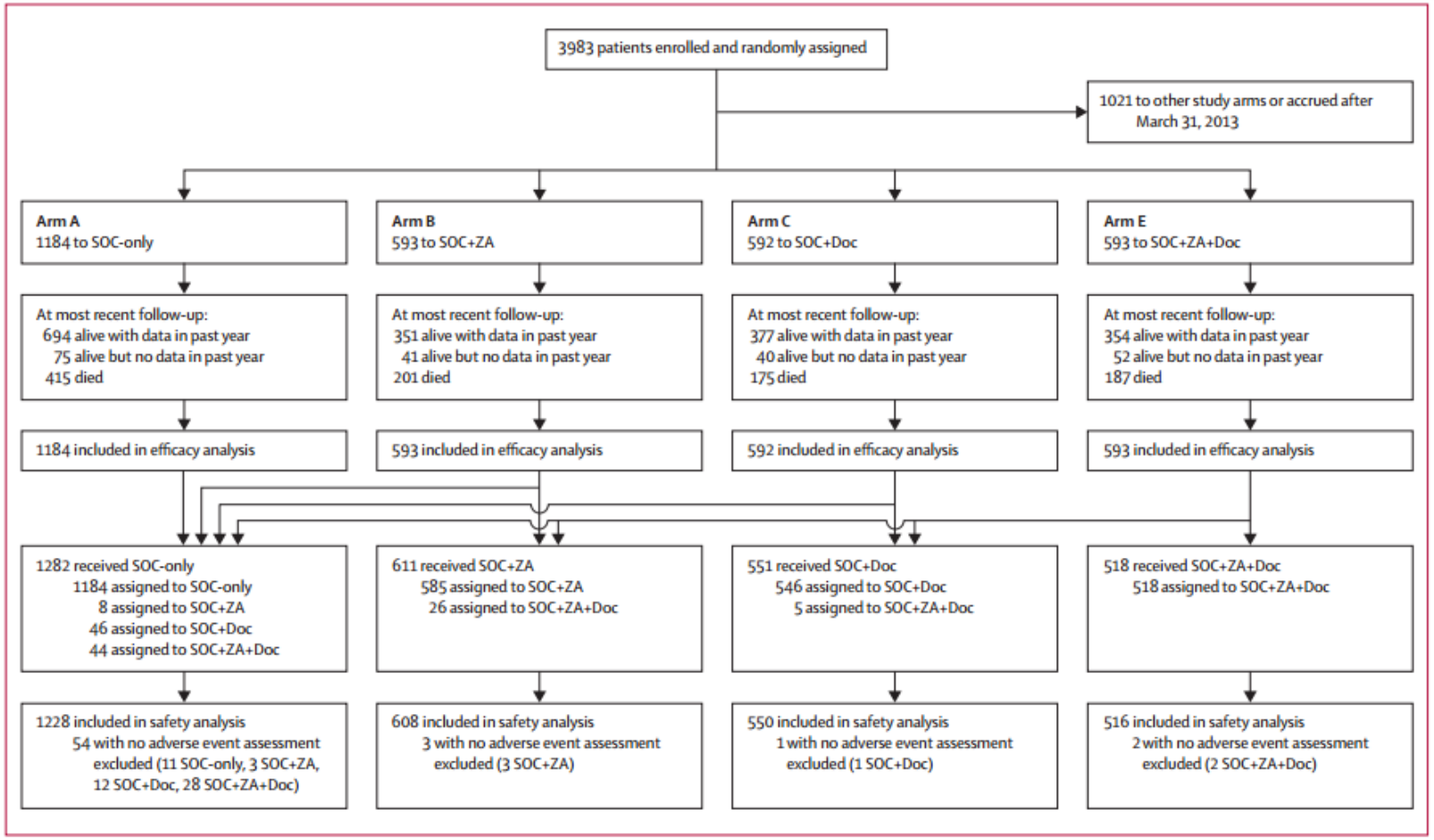
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

*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**

- Multi arm multi stage model (2006-2013)
- Hormone Naïve M0/M1 Pr ca
- N= 2962

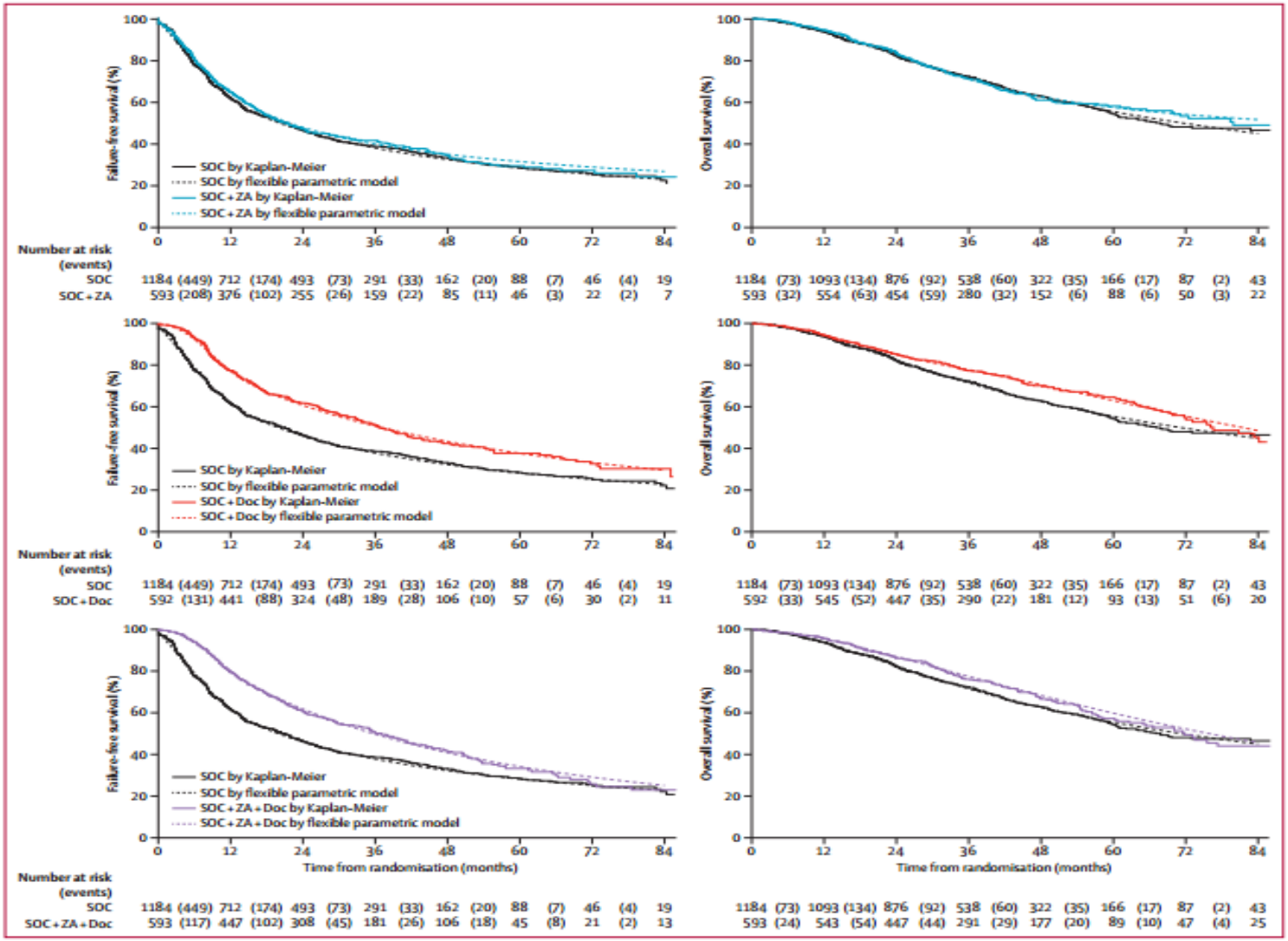
James ND et al. Lancet Oncol 2016

Multi arm multistage model



STAMPEDE Trial :

FFS and OS (KMS plot)



James ND et al. Lancet March 2016

STAMPEDE trial

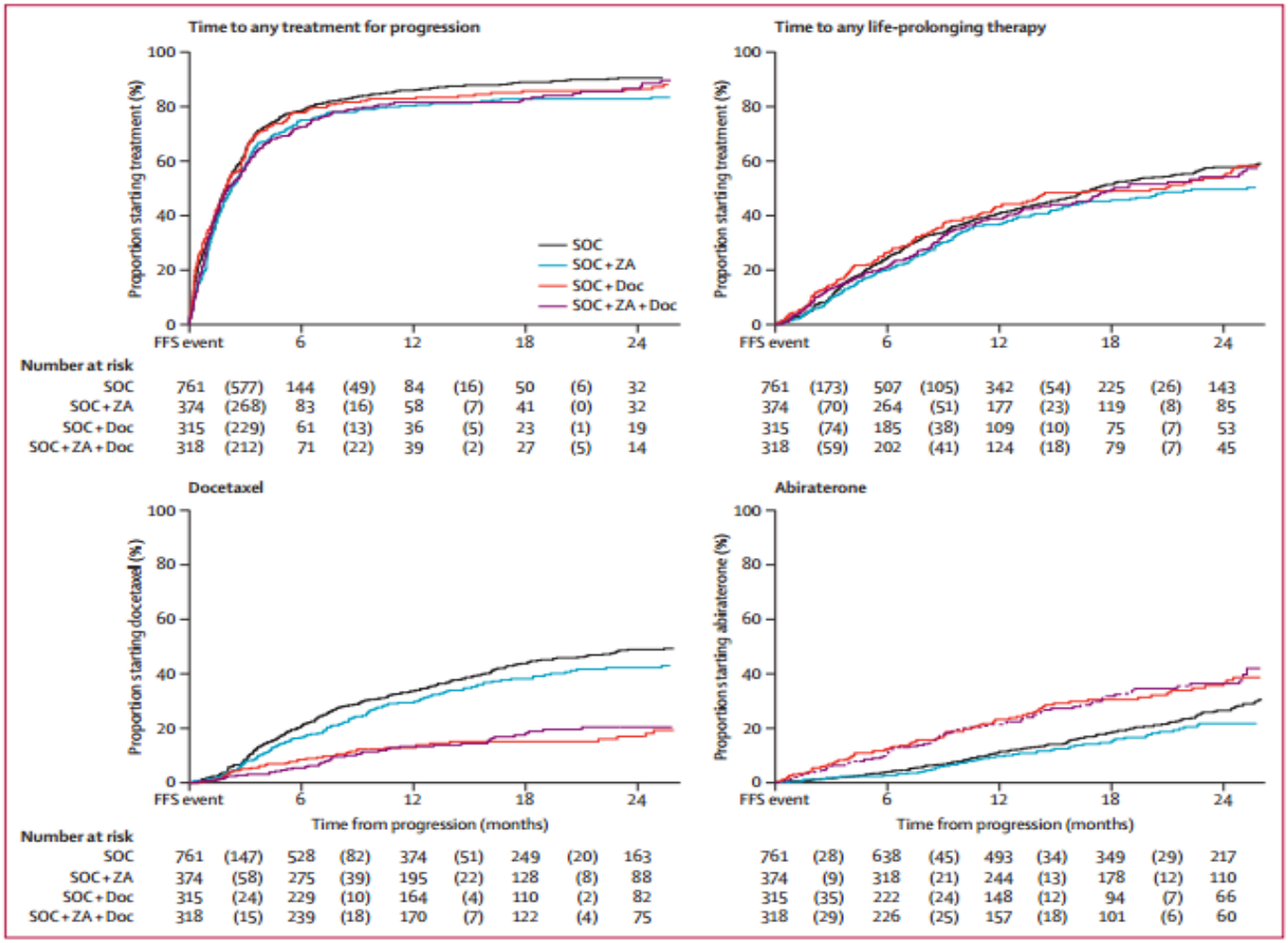


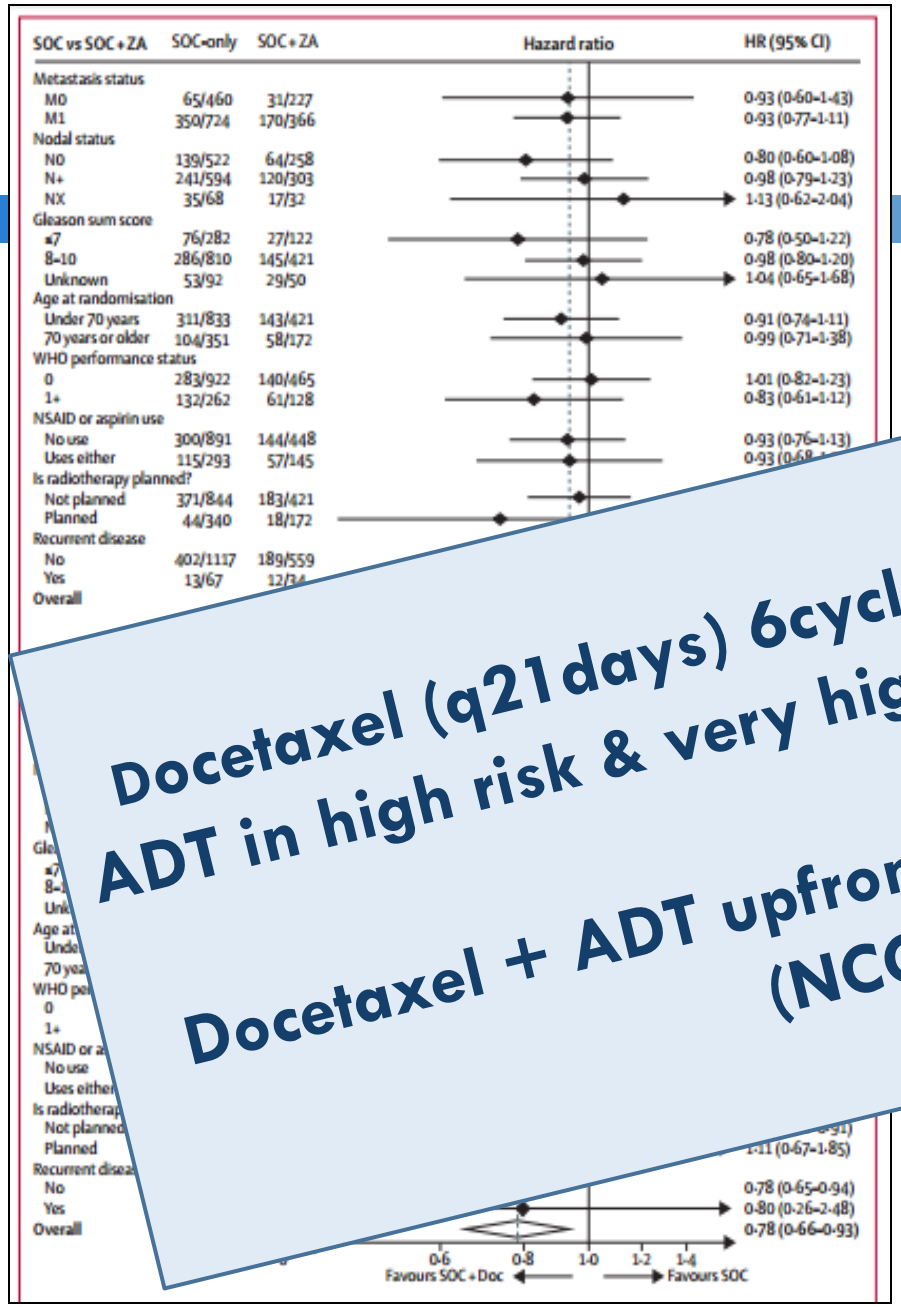
Figure 4: **Time to treatment after progression**

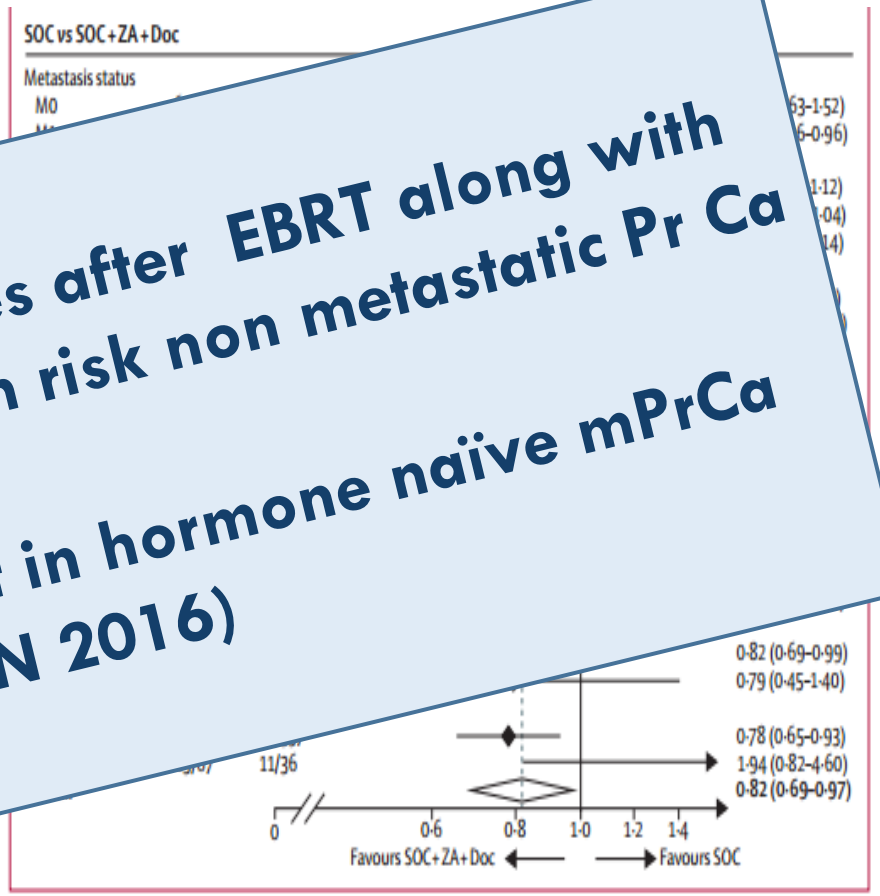
Time to first of any treatment after a FFS event and time to first life-extending therapy (defined as available agents with proven survival gain in castrate-refractory prostate cancer: docetaxel, abiraterone, cabazitaxel, enzalutamide, and radium-223).

James ND et al. Lancet March 2016

STAMPEDE trial

forest plots for treatment effects within subjects





Docetaxel (q21days) 6cycles after EBRT along with ADT in high risk & very high risk non metastatic Pr Ca

Docetaxel + ADT upfront in hormone naïve mPrCa (NCCN 2016)

James ND et al. Lancet March 2016

Castration Resistant Prostate Cancer

Hormone resistance

Primary Resistance (innate resistance)

- No PSA decline, no radiological or soft tissue response, no clinical benefit to first-line therapies (HT).

Acquired Resistance

- Initial response (6months -1yr) followed by progression after first-line therapies (HT)

Gillesen et al. Ann Oncol 2015

Molecular mechanism of CRPC

- Prostate cancer adopt castration by
- 1. Synthesis of intratumoral androgen/peripheral conversion of adrenal androgen to DHT for continued ligand mediated activation of AR
- 2. Aberrant AR signaling

Peripheral conversion mechanism

- **Enzyme up regulation of CYP 17 hydroxylase, CYP 17, 20 Lyase**

  Increased conversion of :

  Pregnenolone to DHAE

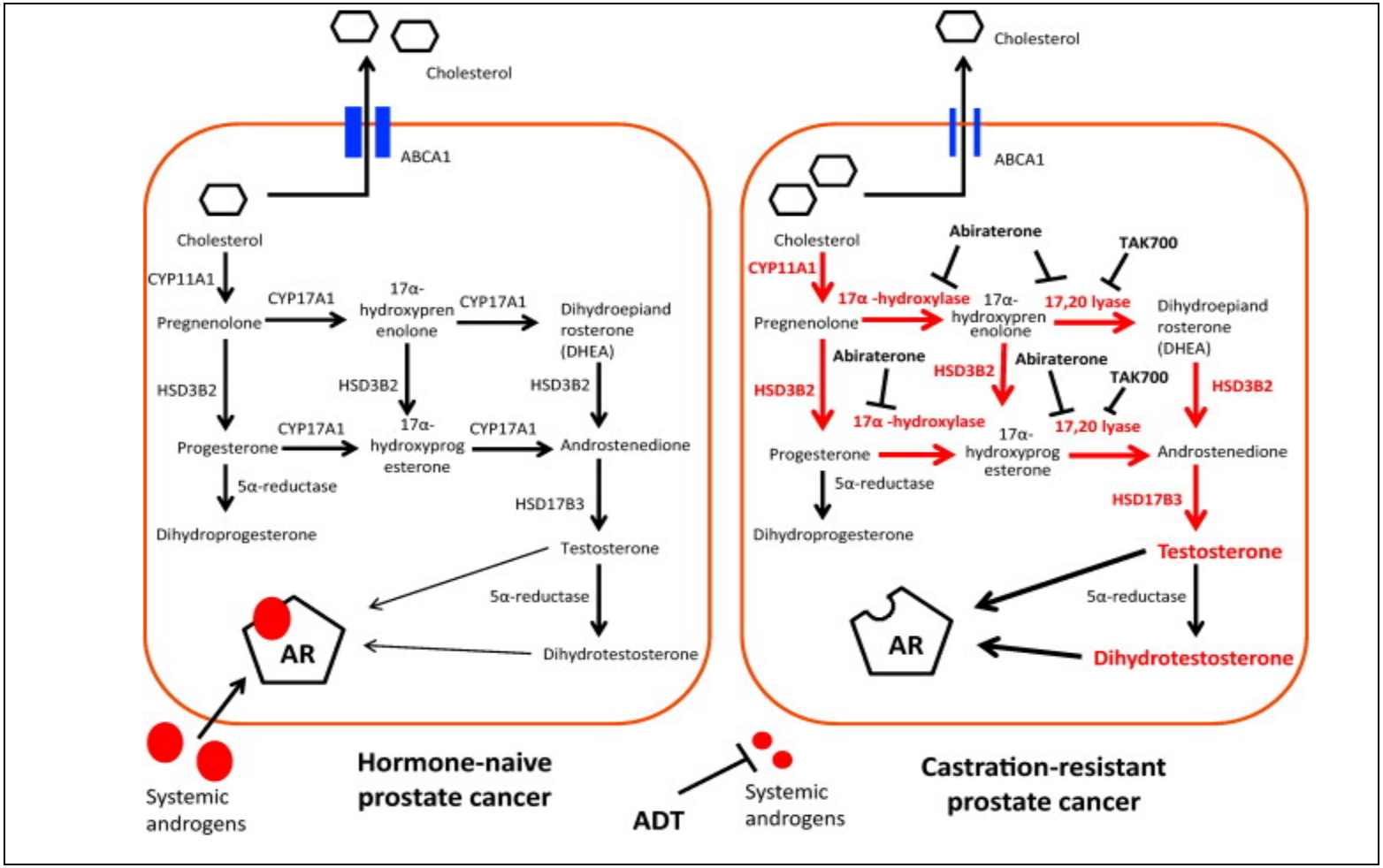
  progesterone to androstenedione

- **Gain of stability mutation of 3β Hydroxysteroid dehydrogenase (3βHSD1)**

  profound accumulation in cytoplasm

  increased conversion of DHEA to DHT

Molecular mechanism of CRPC



Karantanose T et al. European Urology March 2015

Aberrant AR signaling

- 1. **AR gene rearrangements**

- constitutively active AR gene truncated splice variants (AR-V)
- AR –Vs gene generate AR protein variants lacking lignand binding domain of AR
- ligand independent AR signaling
- ARV 7 responsible for resistance to enzalutamide and abiraterone which acts through Ligand binding site of AR.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

CONCLUSIONS

Detection of AR-V7 in circulating tumor cells from patients with castration-resistant prostate cancer may be associated with resistance to enzalutamide and abiraterone. These findings require large-scale prospective validation. (Funded by the Prostate Cancer Foundation and others.)

Androgen receptor splice variants (ARVs)

- Primary resistance to ENZ & AA in the AFFIRM III and COU-AA-301 trials, respectively[1]
- Significantly inferior outcomes compared to men without ARV7 like
  - Lower PSA response
  - Shorter PFS
  - Shorter OS [2]

1.Chandrasekar T, et al. BMC Medicine. 2015
2. Antonarakis ES, et al. JAMA Oncol. 2015

Androgen receptor splice variants (ARVs)

- When comparing the AA & Enza treated patients, the ARV7-positive subset treated with docetaxel/cabazitaxel had better PSA response and longer median PFS.

- **Taxanes may be less susceptible to primary resistance in ARV7-positive patients.[1,2]**

1. Antonarakis ES, et al. JAMA Oncol. 2015
2. Chandrasekar T, et al. BMC Medicine. 2015

Aberrant AR signaling

- 2. **Somatic Mutation of AR**

  (N terminal domain of AR coding region)

  Infrequently these mutated AR are activated by endogenous steroids (progesterone, corticosteroids)

  and by anti-androgens

- 3. **Novel AR mutation (ARF876L)**

  agonist like structural conformation of Enza and ARN 509 binding leading to tumor growth in presence of Enza/ARN509

  Bicalutamide escapes this pathway

Korpal M , Cancer Discov 2013

Other mechanisms

- **The TMPRSS2–ERG fusion gene**

  Most frequent genetic rearrangement in PrCa

  ERG non rearranged PrCa have a better survival (90% CSS over 8years)

  ERG rearranged (2+ Edel) PrCa have poor survival (28% CSS over 8years)[1]

  Validated also in COU –AA-301 trial[2]

- **ROR –Ÿ gene overexpression[3]**

1. Attard G Oncogene 2008
2. Attard G J Clin Oncol 2013
3. Nature 2016

Therapy options in CRPC

- Novel AR antagonists:
  - Abiraterone acetate
  - Enzalutamide
- Sipulicel T
- Ra223
- ADT withdrawal
- Sequencing of HT
- Chemotherapy (Taxanes)
- Older Hormonal agents
  - Antiandrogens
  - Ketoconazole
  - Steroids

Situations :

M0 CRPC

M1 CRPC

1. Asymptomatic or Mild symptomatic
2. Bone metastasis
3. Visceral metastasis

Abiraterone acetate (2011/2012)

- **CYP17A1 inhibitor**
- 1000mg Once daily orally
- Interaction with food: Given in empty stomach
- **A/E : (>10%)**
- Diarrhea
- Fatigue
- Hypertension
- Hypokalemia
- Peripheral Edema
- Monitor LFT
- Cardiac dysfuncion

Abiraterone in CRPC (Post CT)

- **COU- AA-301 trial (2012)**
- Docetaxel failed CRPC (n = 512)
- AA + Pred vs placebo + Pred (1:1)
- Median F/U 20.2months
- Significant benefits in AA arm :

  pain relief

  delayed pain progression

  prevention of SREs

Logothetis CJ et al. Lancet Oncol 2012

Abiraterone in CRPC (Pre CT)

- **COU –AA-302 trial (2012, Final report 2015)**
- Chemo naïve CRPC patients (n= 1195)
- AA + Pred vs placebo + Pred (1:1)
- Median F/U 49months
- Median OS was significantly longer in AA group than in the placebo group (34·7 months *vs* 30·3 months; hazard ratio 0·81; p=0·0033)[1,2.]
- Men in AA group who had ERG rearranged gene prostate tumors, had a significantly improved radiographic PFS and time to PSA progression, compared with those with ERG non-rearranged tumors.[3]

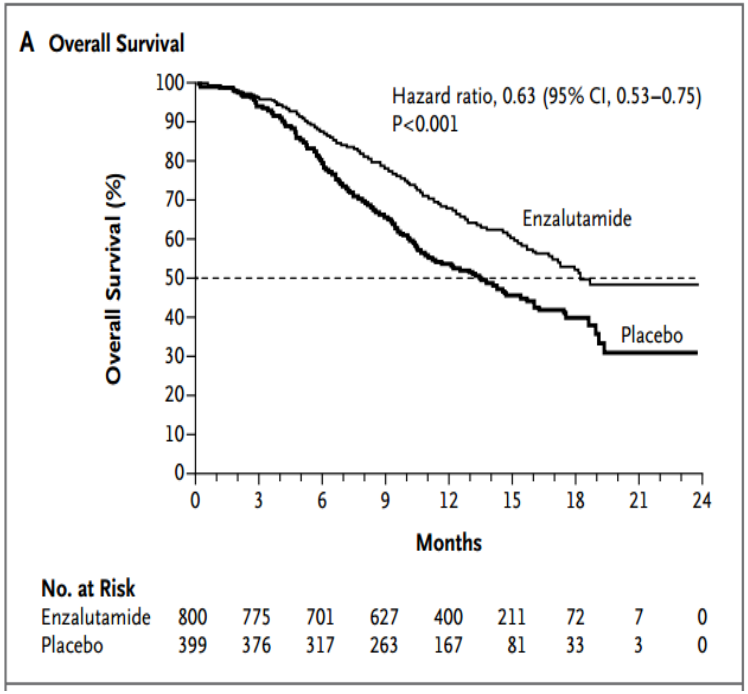
1. Fizazi K Lancet 2012
2. Ryne CJ Lancet 2015
3. Attar G J Clin Oncol 2013

Enzalutamide (MVD3100) (2012)

- **AR signal inhibitor and antagonist**
- Dose 160mg/day Oral
- **Adverse evens:**
- Fatigue/asthenia
- Diarrhea
- Hot flush/Gynaecomastia
- QTc Prolongation
- Hypertension
- Risk of seizure

Enzalutamide in CRPC (Post CT)

- **AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) (2012)**
- Post CT CRPC pts. Enzalutamide vs Placebo (2:1) (n= 1199)
- The median overall survival was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group
- Increased Radiographic response, soft tissue response, PSA reduction rate,time to first SRE,QoL in Enza arm.
- Enza arm had more fatigue, diarrhoea & hot flushes



Sher HI et al. NEJM 2012

Enzalutamide in CRPC (Pre CT)

- **PREVAIL study (n= 1717) (2014)**
- Chemo naive mPrCa : Enza vs Placebo (1:1)
- Study stopped after planned interim analysis
- The rate of radiographic PFS(1yr) was 65% vs 14% among enza arm vs placebo arm.
- 72% in Enza arm vs 63% in the placebo arm, were alive at the data-cutoff date (HR, 0.71 P<0.001).
- Decreased time to SRE and PSA Progression

Beer TM NEJM 2014

Sipuleucel T (2010)

- **Autologous vaccine :**
- Each pts. WBC (APC) exposed to PAP-GMCSF fusion protein
- Minimally symptomatic /Asymptomatic CRPC
- Sipuleucel T vs Placeo (2:1 RCT)) [n= 512]
- Median OS 25.8m vs 21.7m ($p<0.001$)
- 22% Mortality reduction in Vaccine arm (HR 0.78)
- No effect on time to progression
- Minor A/E like fever, headache in Vaccine arm

Kantoff PW et al. NEJM 2010

Chemotherapy in CRPC: Docetaxel

Name	Arms	Results
Tax 327 Tannock IF et al. 2004 NEJM (n= 1006)	Doce + Pred q3wk vs Doce + Pred q1wk vs Mitoxatrone +Pred	OS (18.9m vs 17.4m vs 16.5m) PSA decline >50% (45% vs 48% vs 32%) QoL improvement (23% vs 22% vs 12%) A/E more in Dpce arms
SWOG 9916 Petrylak DP et al. 2004 NEJM (n=770)	Doce + Estramustine Vs Mitoxantrone + Pred	OS 17.5m vs 15.6m) Median Time to progression (6.3m vs 3.2m) PSA decline rate > 50% (50% vs 21%) Febrile Neutropenia more in Estramustine + Doce arm

Cabazitaxel (2010)

- It binds to the ß-subunit of the tubulin within the microtubule
- Stabilization of microtubules
- Dose : 25mg/m2 IV q3wks with 10mg Prednisone
- **A/E**
- Febrile neutropenia
- Peripheral neuropathy

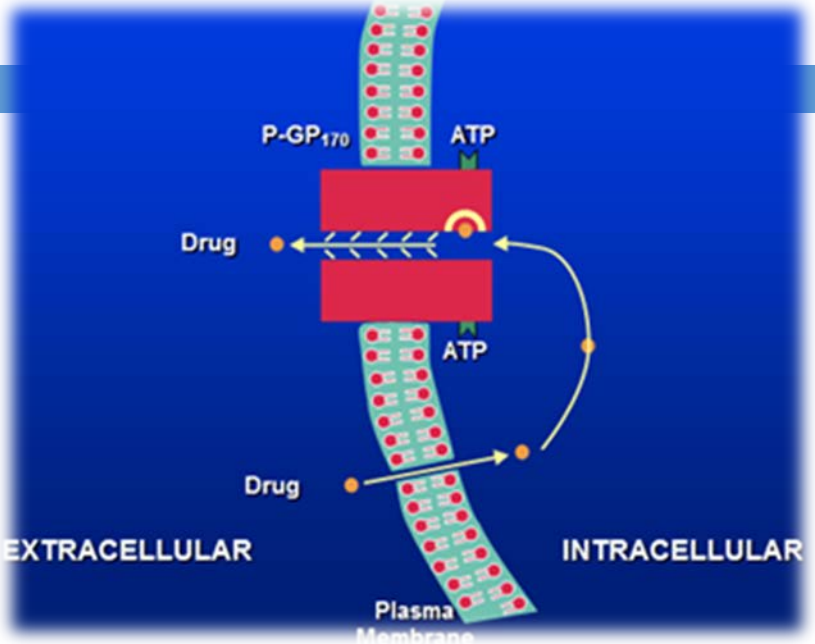
Rationale

- Some tumors do not respond to Docetaxel (acquired or constitutional resistance)

  This may be due to:

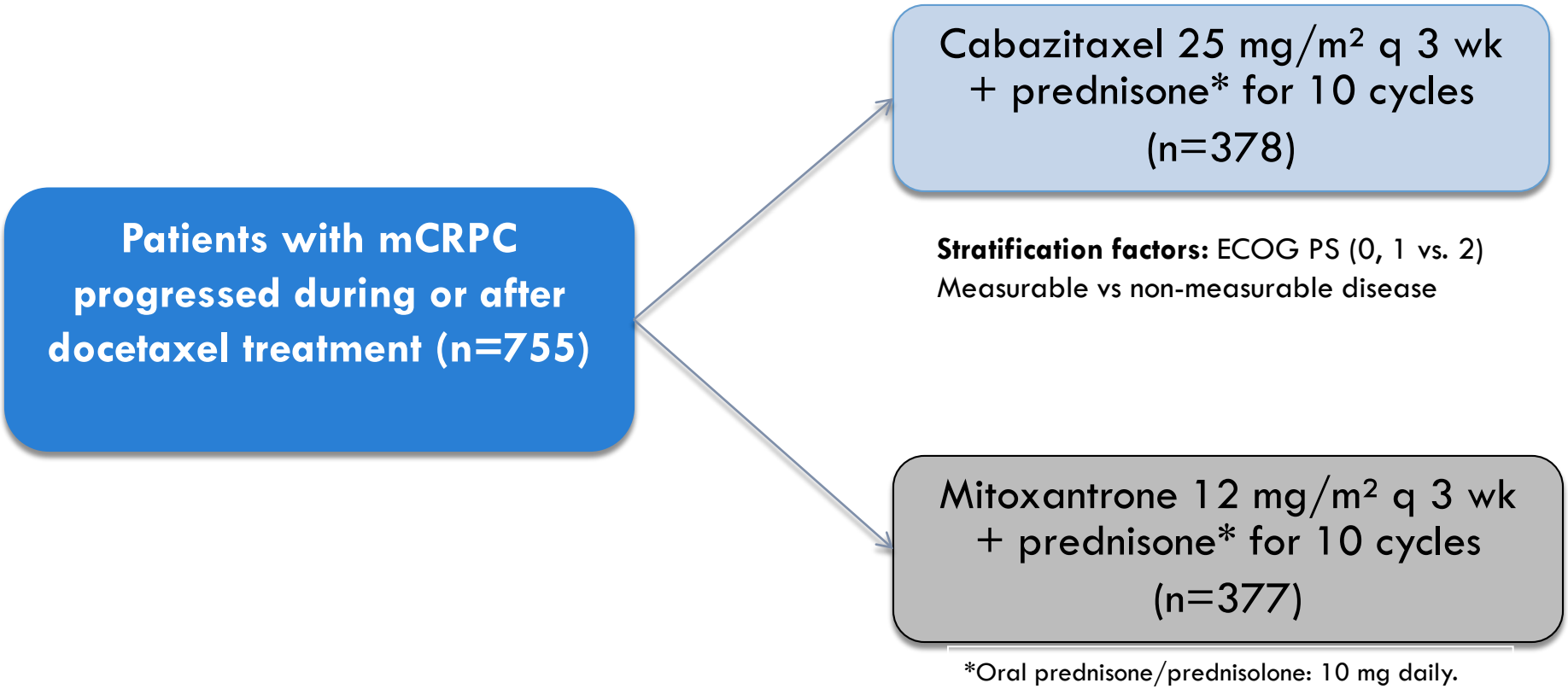
  - Affinity for multidrug resistant (MDR) membrane-associated P-glycoprotein (PgP) efflux pump,

- Cabazitaxel:
  - Poor affinity for the PgP efflux pump
  - Active in vitro and in vivo tumors resistant to Docetaxel



- Docetaxel and paclitaxel have a strong affinity for the PgP pump
- If the PgP pump is expressed, it drives drug out of tumour cell

TROPIC trial

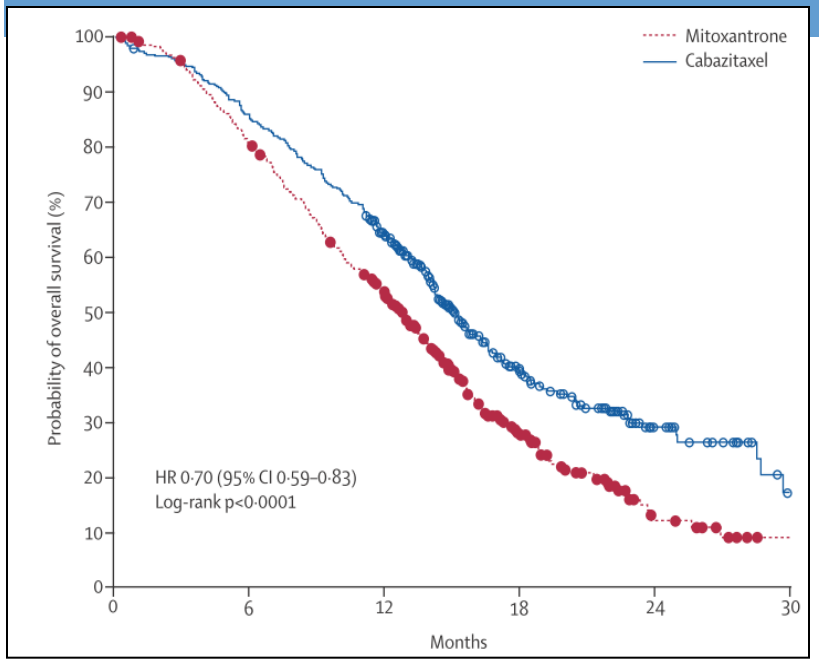


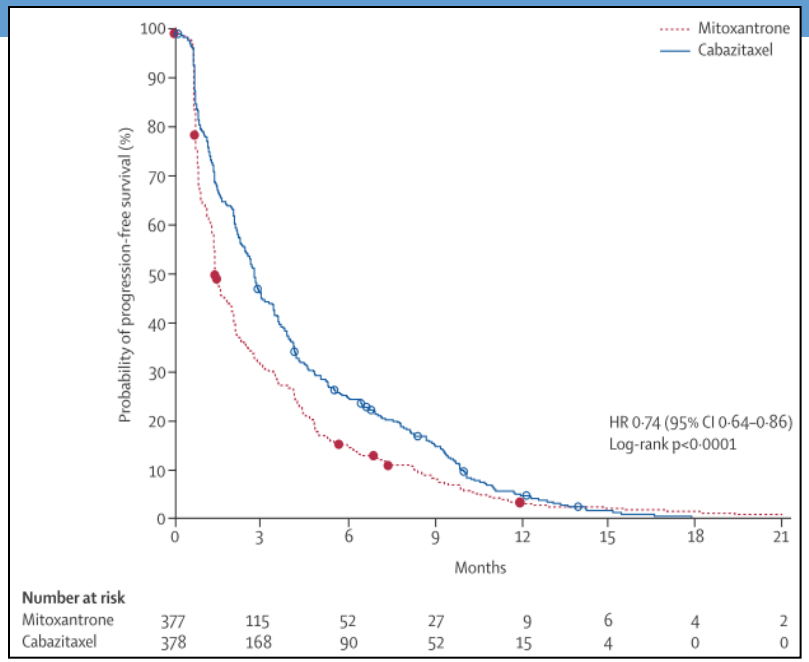
Stratification factors: ECOG PS (0, 1 vs. 2)
Measurable vs non-measurable disease

*Oral prednisone/prednisolone: 10 mg daily.

de Bono JS, Oudard S, Ozguroglu M, *et al.Lancet* 2010;376:1147-1154

TROPIC trial : Results





	MP	CBZP
Median OS (months)	12.8	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
***P* Value**	<.0001	

	MP	CBZP
Median PFS (months)	**1.4**	**2.8**
Hazard ratio	**0.74**	
95% CI	**0.64–0.86**	
P-value	**<0·0001**	

de Bono JS, Oudard S, Ozguroglu M, *et al.Lancet* 2010;376:1147-1154

TROPIC trial

Cabazitaxel vs mitoxantrone for mCRPC post-doctaxel

Endpoints (months)	Cabazitaxel + prednisone	Mitoxantrone + prednisone	Hazard ratio (p value)
Median Time to tumor progression	**8.8**	5.4	0.61 (p<0.0001)
Median Time to PSA progression	**6.4**	3.1	0.75 (p=0.001)
PSA response rate	**39.2%**	17.8%	p=0.0002
Tumor response rate	**14.4%**	4.4%	P=0.0005

The most common ≥ grade 3 adverse events :
Febrile Neutropenia

de Bono JS, Oudard S, Ozguroglu M, *et al.Lancet* 2010;376:1147-1154

TROPIC trial : Final analysis (2013)

Annals of Oncology 24: 2402–2408, 2013
doi:10.1093/annonc/mdt194
May 2013

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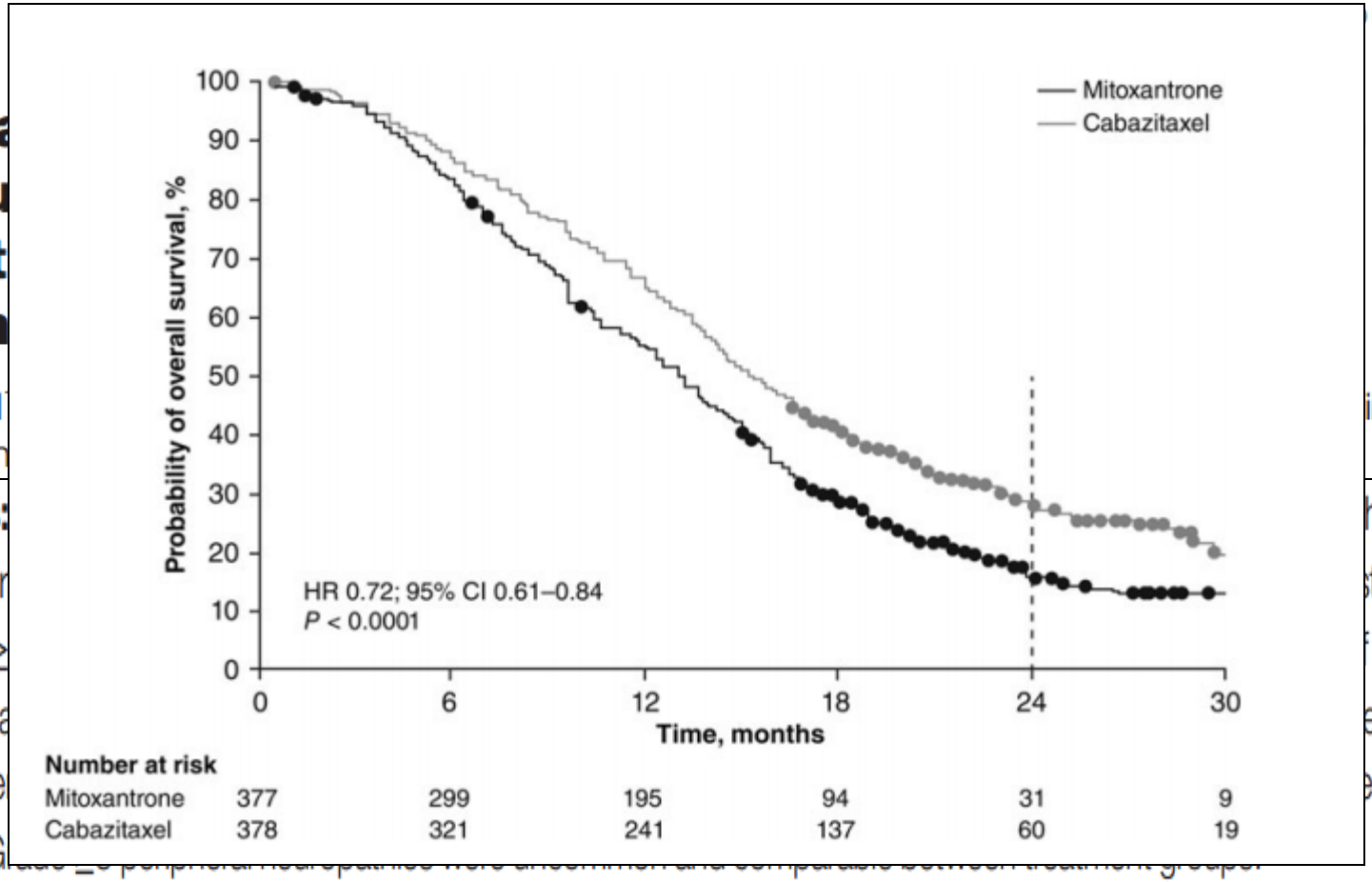

Results:
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Conclusions: Cabazitaxel prolongs OS at 2 years versus mitoxantrone and has low rates of peripheral neuropathy. Palliation benefits of cabazitaxel were comparable to those of mitoxantrone.The study was registered with www.ClinicalTrials.gov (NCT00417079).

Sequencing strategy

Logic :

- Differential effectiveness of CT/HT due to different mechanism of Resistance.
- Impaired activity of AR pathway inhibitors when used sequentially helped to test sequencing of chemotherapy with hormonal agents.

Original Study

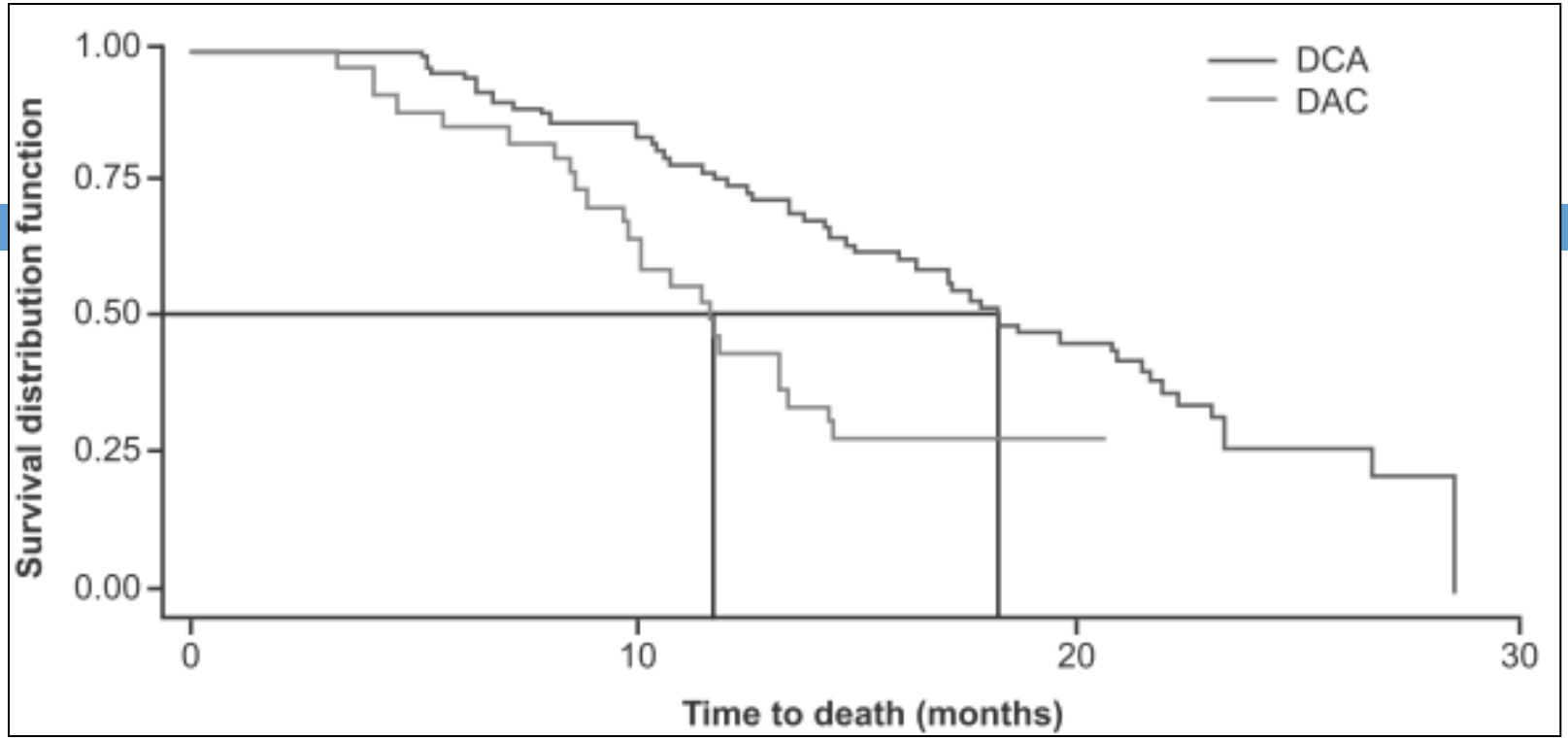
CrossMark

Sequencing of Cabazitaxel and Abiraterone Acetate After Docetaxel in Metastatic Castration-Resistant Prostate Cancer: Treatment Patterns and Clinical Outcomes in Multicenter Community-Based US Oncology Practices

Guru Sonpavde,[1] Menaka Bhor,[2] Daniel Hennessy,[3] Debajyoti Bhowmik,[2] Liji Shen,[3] Leonardo Nicacio,[3] Debra Rembert,[2] Mark Yap,[2] Ian Schnadig[4]

- Rerospective analysis to assess patients with mCRPC who received treatment with Doce and were subsequently treated with Cabazi or AA, or both
- Patients (n=350) received 2 or 3 drugs: DA, DC, DAC, or DCA
- Subsequent therapy distribution
  - DA in183 (52.3%)
  - DC in 54 (15.4%)
  - DCA in 77 (22.0%)
  - DAC in 36 (10.3%)

Sonpavde G et al. Clinical Genitourinary Cancer, 2015



- 3-drug sequences were associated with improved OS versus 2-drug sequences (hazard ratio [HR], 0.21; P =0.0002).
- OS was significantly greater for DCA versus DAC (18.2 vs.11.8m;P=0.023)
- In a multivariable analysis, adjusted comparisons suggested that significant lower risk of mortality in the DCA versus DAC cohorts (HR, 0.13;P=0.0210)

Sonpavde G et al. Clinical Genitourinary Cancer, 2015

IJC
International Journal of Cancer

CAST: A retrospective analysis of cabazitaxel and abiraterone acetate sequential treatment in patients with metastatic castrate-resistant prostate cancer previously treated with docetaxel

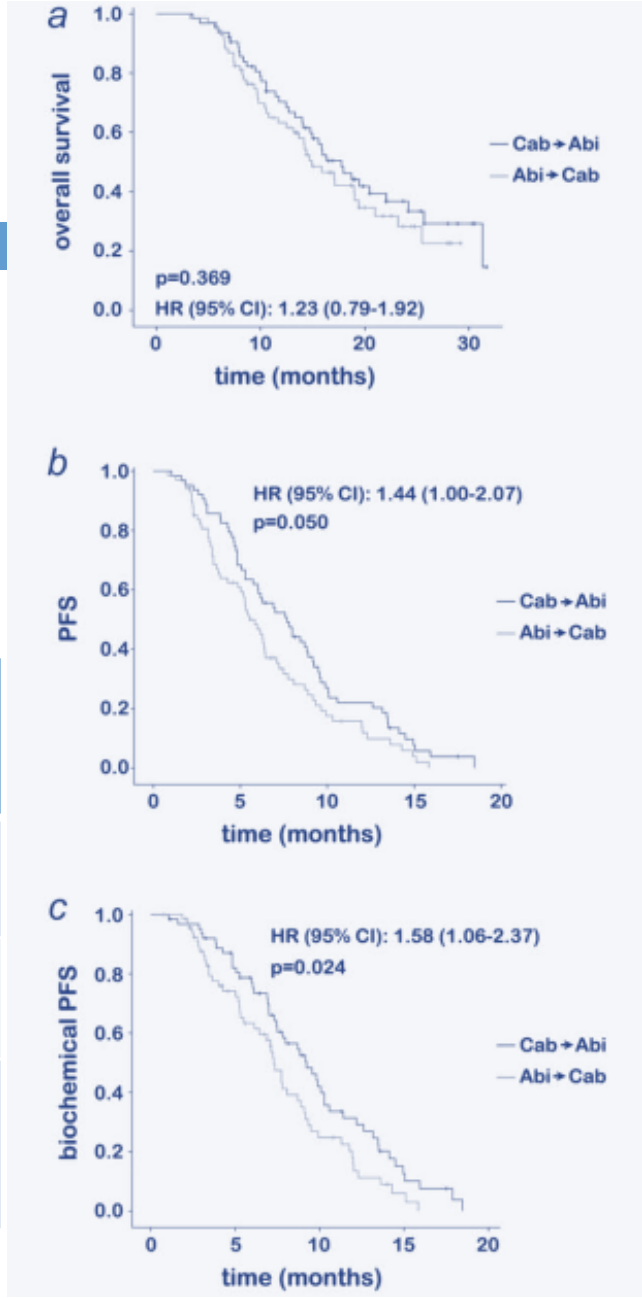
- Retrospective, multicenter, observational study
- From collected data 63 patients had received cabazitaxel followed by abiraterone (DCA), and 69 patients had received abiraterone followed by cabazitaxel (DAC)

Wissing MD et al. Int. J. Cancer 2015

Results

- **CAST study**
  - Compared outcomes of DCA vs. DAC in CRPC previously treated with docetaxel

End point	DCA (n=63)	DAC (n=69)	p value
Median OS	**19.1**	17.0	0.369
Median PFS	**8.1**	6.5	0.050
Biochemical PFS	**9.5**	7.7	0.024



Wissing MD et al. Int. J. Cancer 2015

Other Chemotherapy

- **Eribulin Mesylate Phase II study: (2006-2007)**
- mPrCa (CRPC) [+/- Prior Taxane]
- Single arm (Eribulin iv) [end point : PSA response rate]
- Median cycle number of 4
- PSA decrease of >50% in 22.8% taxane naïve pts. and 8.5% taxane pretreated pts.
- Relatively favorable toxicity profile

de Bono JS et al. Ann Oncol 2012

New drugs for CRPC

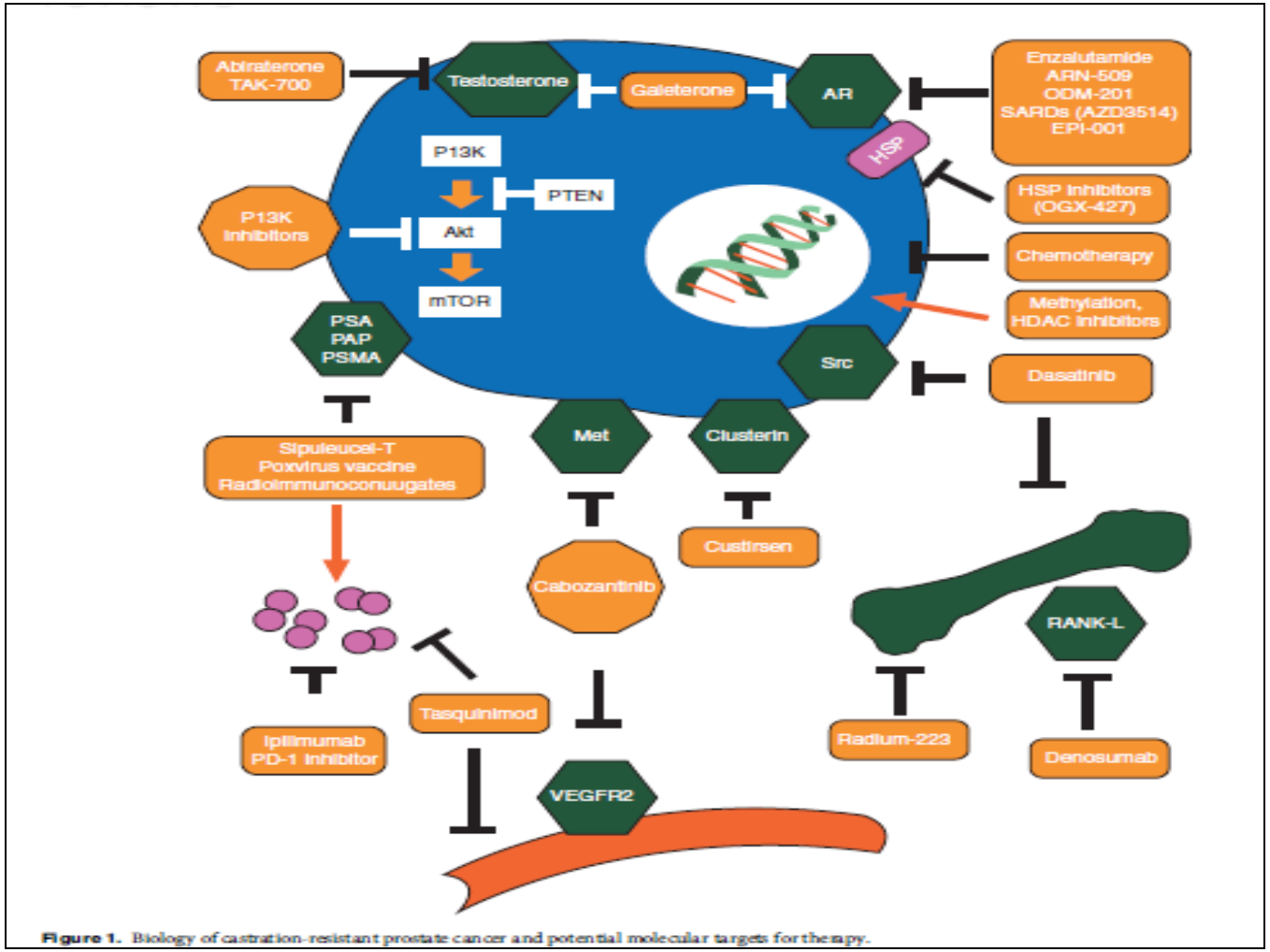


Figure 1. Biology of castration-resistant prostate cancer and potential molecular targets for therapy.

Agarwal N et al.
Ann Oncol 2014

Newer targeted therapy options

CYP 17 inhibitors

- Orteronel (TAK 700)

Androgen Receptor Inhibitor

- ARN 509
- ODM 201
- AZD 3514
- EPI- 001

Antibody Conjugate

- Anti PSMA antibody + Y99 Radioimmunotherpay

C MET/VEGF TKI

- Cabozatinib

PARP inhibitors

(BRCA1/2,CHECK2 mutation)

- Olaparib

Dual androgen synthesis & signal Inhibiotrs

- Galoterone (TAK 700)

POX virus based vaccine

- PROSTVAC –VF

CTLA 4 Inhibitors

- Ipilimumb

Anti sense oligonucleotide

- Clustirsen (OGX 11)

HSP 27 Inhibitors (Antisense agents)

- OGX427

Anti androgenic Immunomodulators

- Tasquimod

Newer targeted therapy options

Molecular target	Arms	Population	Primary end point	Comments	Clinical trial ID
CYP17	TAK-700 + P Placebo + P	Docetaxel pretreated	OS	Preliminary results showed no improvement in the primary end point of OS, but significant improvement in rPFS (a secondary end point). Post-trial treatment with abiraterone may have confounded OS data.	NCT01193257
CYP17,17.20 lyase activity	TAK-700 + P versus Placebo + P	Chemonaïve	OS, rPFS	Accrual: completed; results: pending.	NCT01193244
AR	MDV3100 Placebo	Chemonaïve	OS, PFS	Results showed significant improvement in the primary endpoints of OS, and rPFS.	PREVAIL NCT01212991
AR	ARN-509 Placebo	Nonmetastatic chemonaive[a]	Metastasis-free survival	Accrual: ongoing	SPARTAN NCT01946204
Clusterin mRNA	Custirsen + CBZ-P Placebo + CBZ-P	Docetaxel pretreated	Pain palliation	Accrual: completed; results: pending.	SATURN NCT01083615
Clusterin mRNA	Custirsen + DP Placebo + DP	Chemonaïve	OS	Accrual: completed; results: pending.	SYNERGY NCT01188187
Immune response	PROSTVAC ± GM-CSF versus placebo	Asymptomatic or minimally symptomatic chemonaïve disease	OS	Accrual: ongoing.	PROSPECT NCT01322490
c-MET and VEGFR2	Cabozantinib Prednisone	Docetaxel and abiraterone pretreated relatively asymptomatic disease	OS	Accrual: completed; results: pending.	NCT01605227
c-MET and VEGFR2	Cabozantinib MP	Docetaxel and abiraterone pretreated	Pain response	Accrual: completed; results: pending.	NCT01522443

Agarwal N et al. , Ann Oncol 2014

Newer targeted therapy options

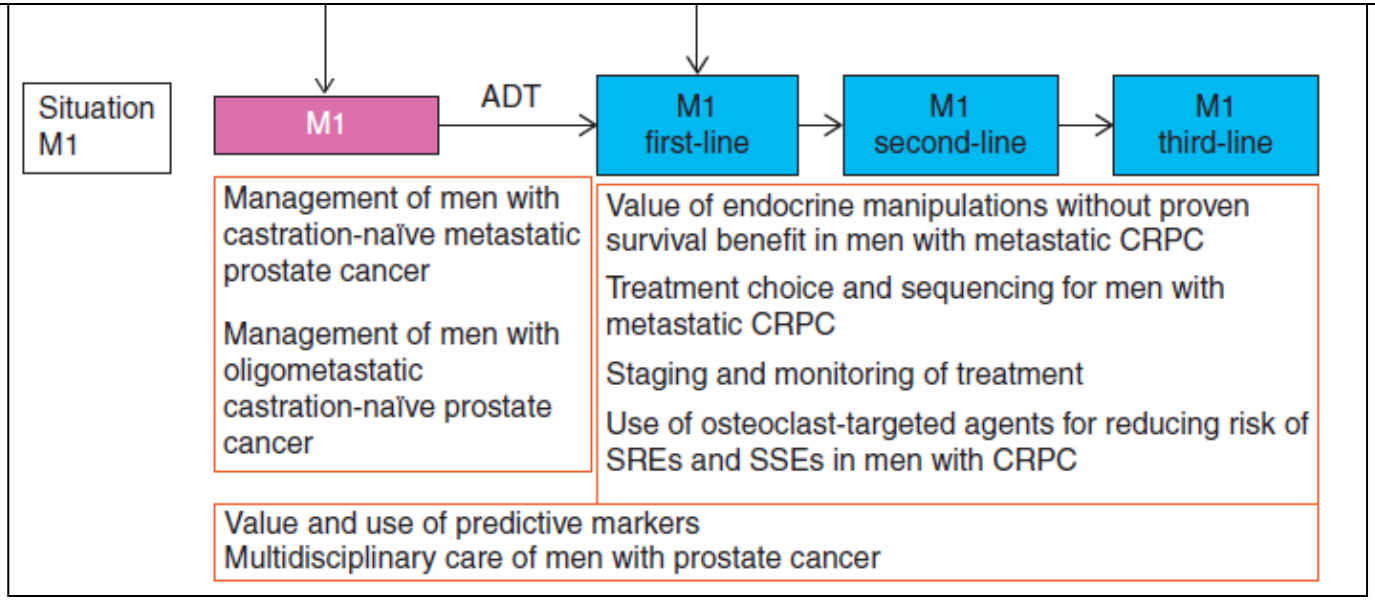
Molecular target	Arms	Population	Primary end point	Comments	Clinical trial ID
Src-family kinases	Dasatinib + DP Placebo + DP	Chemonaïve disease	OS	Results showed no improvement in OS, the primary end point.	READY NCT00744497
Immune-modulatory protein S100A9	Tasquinimod Placebo	Asymptomatic or minimally symptomatic chemonaive disease	PFS	Accrual: completed; results: pending.	NCT01234311
Immune-modulatory protein S100A9	Tasquinimod Placebo	Docetaxel pretreated stable disease	PFS	Currently accruing.	NCT01732549
CTLA-4	Ipilimumab Placebo, (following a single dose of radiotherapy)	Docetaxel pretreated	OS	Preliminary results showed no improvement in OS, the primary end point. Prespecified subset analyses suggested improved efficacy of ipilimumab in men with lower disease burden.	NCT00861614
CTLA-4	Ipilimumab Placebo (following a single dose of radiotherapy)	Asymptomatic or minimally symptomatic chemonaïve disease	OS	Accrual: completed; results: pending. Ipilimumab may be more effective in this setting, given results from its post-docetaxel trial	CA-184-095 NCT01057810
Microtubules	CBZ-P DP	Chemonaïve disease	OS	Accrual: completed; results: pending. Primary end point is improved OS with CBZ-P over DP.	FIRSTANA NCT01308567

Agarwal N et al. , Ann Oncol 2014

Annals of Oncology 26: 1589–1604, 2015
doi:10.1093/annonc/mdv257
Published online 3 June 2015

Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015

S. Gillessen[1,†*], A. Omlin[1,†], G. Attard[2], J. S. de Bono[2], E. Efstathiou[3,4,5], K. Fizazi[6], S. Halabi[7], P. S. Nelson[8], O. Sartor[9], M. R. Smith[10], H. R. Soule[11], H. Akaza[12], T. M. Beer[13], H. Beltran[14], A. M. Chinnaiyan[15,16,17], G. Daugaard[18], I. D. Davis[19], M. De Santis[20,21], C. G. Drake[22], R. A. Eeles[23], S. Fanti[24], M. E. Gleave[25], A. Heidenreich[26], M. Hussain[27], N. D. James[20,28], F. E. Lecouvet[29], C. J. Logothetis[3,4], K. Mastris[30], S. Nilsson[31], W. K. Oh[32], D. Olmos[33,34,35], A. R. Padhani[36], C. Parker[37], M. A. Rubin[38], J. A. Schalken[39], H. I. Scher[14,40], A. Sella[41], N. D. Shore[42], E. J. Small[43], C. N. Sternberg[44], H. Suzuki[45], C. J. Sweeney[46], I. F. Tannock[47,‡] & B. Tombal[48,‡]



iADT vs Cont. ADT

- In patients with metastatic prostate cancer achieving an adequate PSA decline (confirmed PSA fall below 4 ng/ml after 6 months of ADT),
- 71% of the panelists recommended *intermittent ADT* ***only*** *for a* ***minority of selected patients.***

CAB vs ADT alone

- Half of the panel did not recommend CAB whereas 35% recommended it in a **minority of selected patients** and 15% recommended it in the majority of patients.

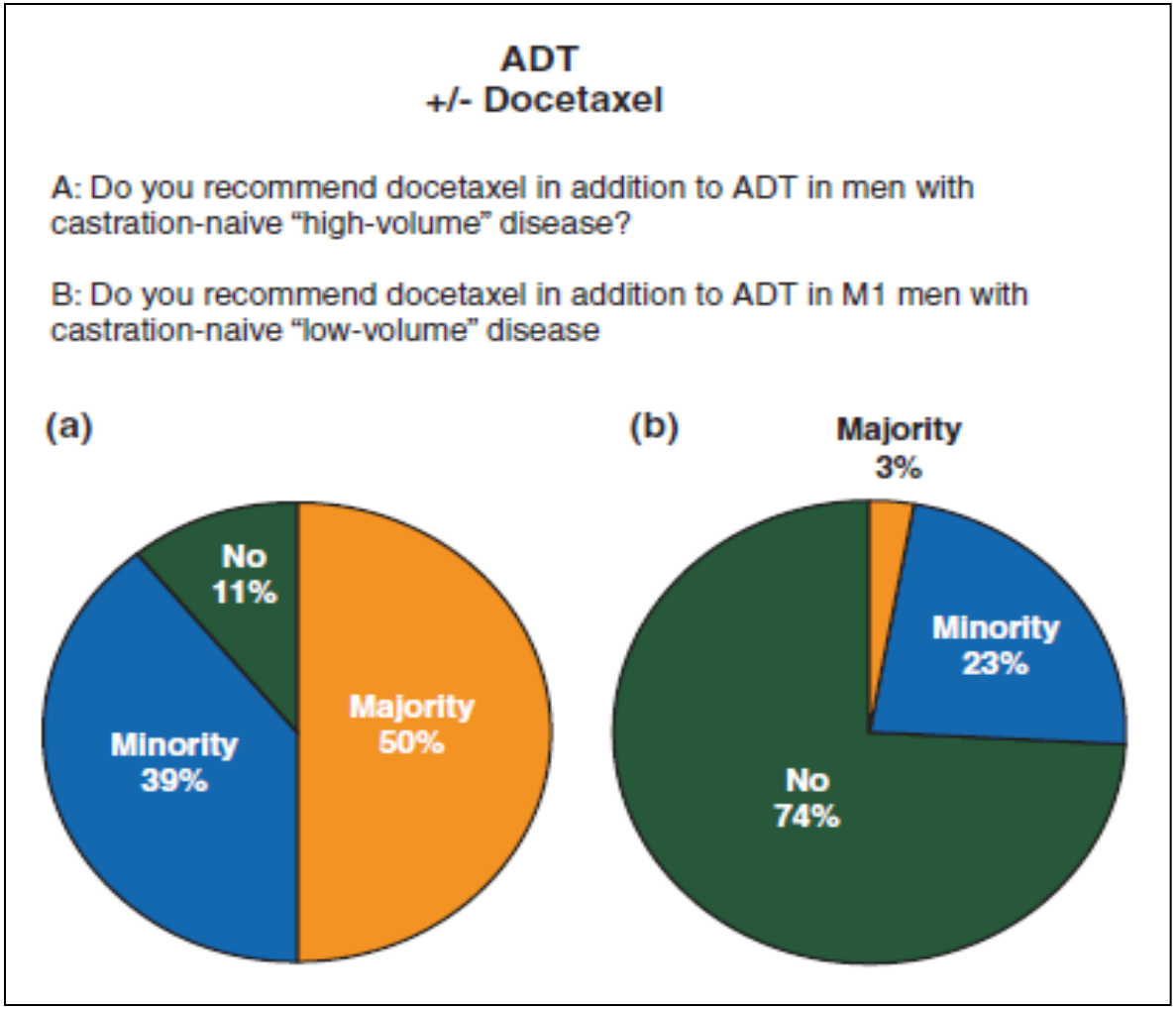
Docetaxel in castration Naïve PrCa

- **Based on CHAARTED trial:**
- **Definition of High volume disease:**

  visceral (lung or liver) and/or 4 bone metastases,

  ≥ beyond pelvis and vertebral column]
- High volume definition should be used in daily clinical practice.
- Half of the panel recommended **docetaxel with ADT in castration-naïve M1 patients with high-volume disease.**

ADT in M1 Castration Naïve PrCa



Based on CHAARTED and STAMPEDE data NCCN 2016 recommended docetaxel upfront with ADT in high risk M0/M1 PrCa

Oligo-metastatic castration naïve PrCa

- **Definition of Oligometastases:**
- According to 85% of the panel: ≤ 3 synchronous metastases (bone and/or lymph nodes)
- **62% of the panel recommended ADT.**
- In minority of cases local treatment for primary and met focus will suffice.

Castration Resistance

- As a consensus, 82% of the panel recommended a **testosterone level <50 ng/dl** (<1.7 nmol/l) as an appropriate cut-off value in daily clinical practice.
- According to 94% of the panel a confirmed (by a 2nd value ≥ 3wks later) rising PSA on ADT in the presence of suppressed testosterone is sufficient.
- If testosterone is not sufficiently suppressed in the presence of suppressed LH, the panel

next management options

B/L orchiectomy (22%),

Alternative GnRH agonist (22%),

GnRH antagonist (44%),

Addition of an AR antagonist (9%).

Non Metastatic CRPC (M0)

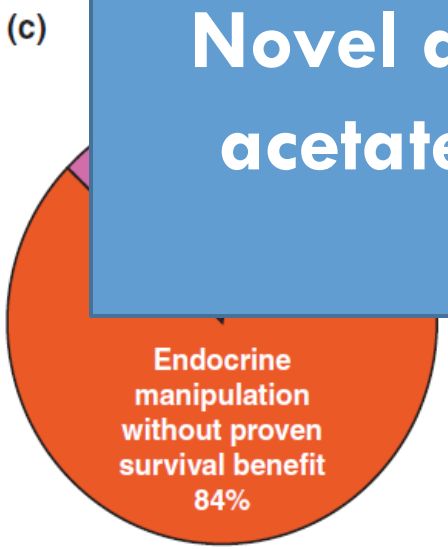
- A clear consensus (91% of the panel) that a PSA-based trigger (level and/or kinetics) should be used for restaging asymptomatic patients with rising PSA on ADT and no known metastases.
- To initiate imaging 2-10ng/ml(total PSA) should be the cutoff (56%).
- For PSA-DT as a trigger for imaging, 74% of the panel recommended a PSA-DT of 6 months.
- According to 77% of the panel daily clinical practice a negative CT (thorax and abdomen/pelvis) and a negative bone scan are sufficient for diagnosis of M0 disease.

M0 CRPC treatment

"withholding additional treatment in a patient who knows that his PSA is rising on ADT can be challenging"

No treatment option with proven survival benefit

C: If you recommend treatment for M0 CRPC outside of clinical trials: what is your preferred treatment option for men with M0 CRPC (negative imaging, rising PSA) apart from maintaining ADT?



Novel agents like abiraterone acetate or Enzalutamide are preferred

Endocrine manipulation without survival benefit:

- AR antagonist

Bicalutamide/Flutamide/Nilutamide

Low A/E profile

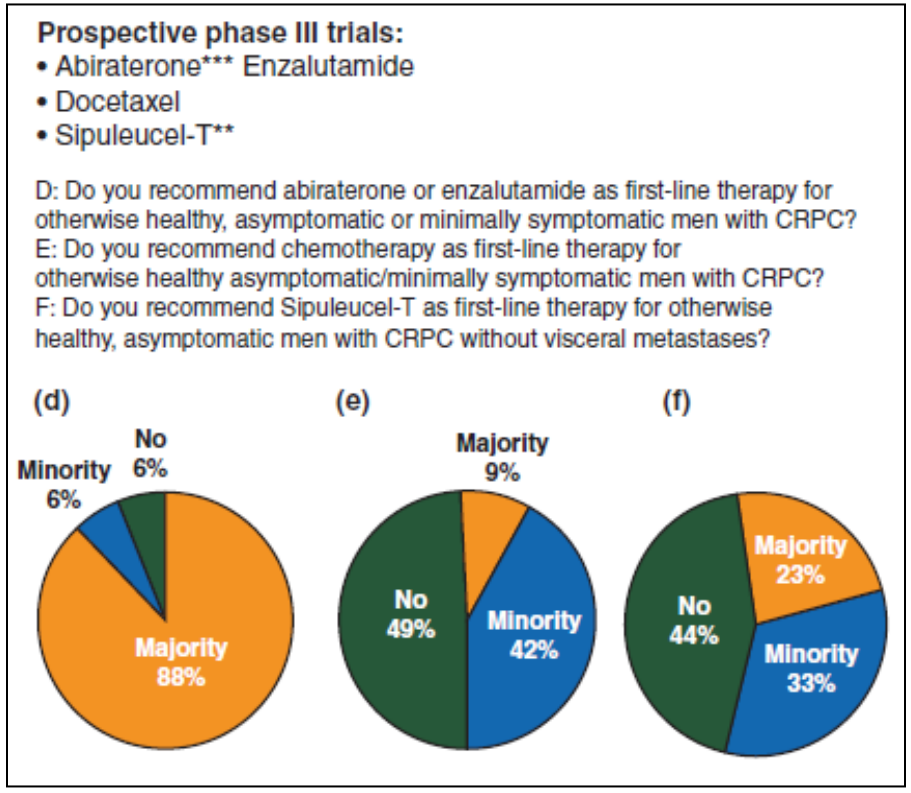
Disadv:

No OS benefit

Metastatic CRPC: First Line

- **Asymptomatic/mild symptomatic M1CRPC**

No pain medication/pain medication if needed.



Abiraterone (39%),
Enzalutamide (27%)
or
either one of the two
(33%)

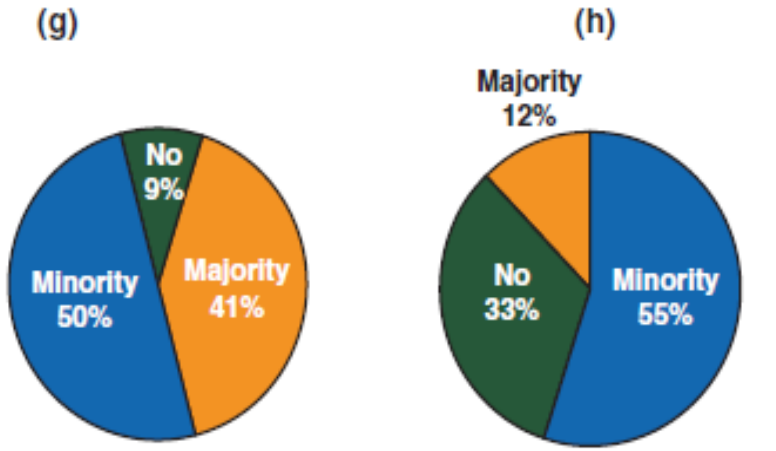
Clinicians decision based on comorbidity

Metastatic CRPC: First Line

- Symptomatic M1 CRPC

Prospective phase III trials
- Docetaxel
- Radium-223*

G: Do you recommend chemotherapy (usually taxane based) as first-line therapy for otherwise healthy symptomatic men with CRPC in addition to ADT?
H: Do you recommend radium-223 as a first-line treatment for symptomatic men with CRPC with bone but no visceral metastases?



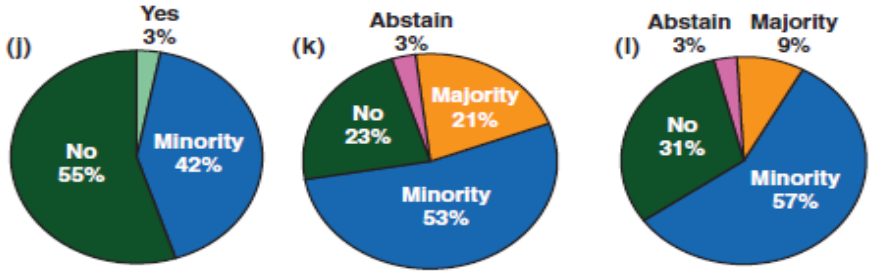
M1 CRPC 2nd line/3rd line

Metastatic CRPC Second-Line

Prospective phase III trials (post-docetaxel) 2nd line:
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Radium-223*

No prospective phase III trials for 2nd line after abiraterone, enzalutamide, radium-223 or sipuleucel-T. Options for patients with good PS:
- Abiraterone
- Cabazitaxel
- Docetaxel
- Enzalutamide
- Radium-223 *

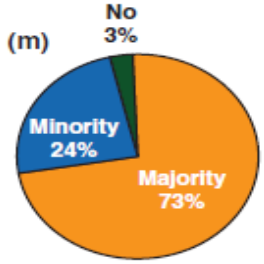
I: Do you recommend second-line treatment with abiraterone or enzalutamide in otherwise healthy patients judged to have primary (innate) resistant disease (no PSA decline, no radiological improvement, no clinical benefit) to first-line abiraterone or enzalutamide?
K: Do you recommend second-line treatment with abiraterone or enzalutamide in otherwise healthy patients with secondary (acquired) resistance (initial response followed by progression) to first-line abiraterone or enzalutamide
L: Do you recommend second-line treatment with cabazitaxel in otherwise healthy patients after first-line docetaxel (prior to abiraterone/enzalutamide/radium-223)?



Metastatic CRPC Third-Line

No prospective phase III trials
Options for patients with good PS:
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Radium-223 *

M: Do you recommend third-line treatment with cabazitaxel in otherwise healthy patients after second-line docetaxel(post first-line abiraterone or enzalutamide)?



Consider clinical trial participation

*Bone metastases and symptomatic, no visceral or bulky lymph node metastases, not fit, unwilling to have no access to chemotherapy or post-chemotherapy
** Low tumour volume, no visceral metastases
*** no visceral metastases

Staging & Monitoring treatment

Before newline of treatment:

- Blood ALP/LDH/PSA
- CECT Thx/Abdomen-pelvis
- Bone Scan+/- MRI spine (selective)
- ? PET (?? PSMA PET)

Monitoring :

- Blood ALP/LDH/PSA (2-4monthly)
- +/- CECT scan

When to stop/change to next line

- Consensus of 82% of panel to fulfill ≥ criteria

1. PSA progression
2. Radiographic progression
3. Clinical deterioration

- Unequivocal Visceral progression only:

Stop treatment

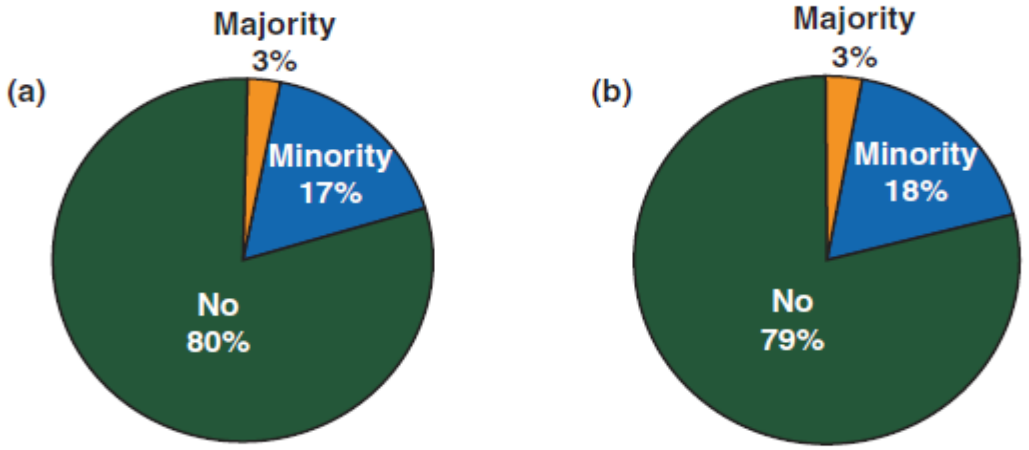
Re biopsy (search for 2nd cancer/NE histology)

Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

- (Based on CALGB90202 trial)
- Castration Naïve M1 PrCa (bone mets)

Ca and Vitamin D supplementation
For osteoporosis and increased risk of fractures:
- **Bisphosphonate at osteoporosis dose**
- **Denosumab (60mg, 6-monthly)**

A: Do you recommend zoledronic acid (4mg every 3-4 weeks) in castration-naïve M1 patients with bone metastases?
B: Do you recommend denosumab (120mg every 4 weeks) in castration-naïve M1 patients with bone metastases?

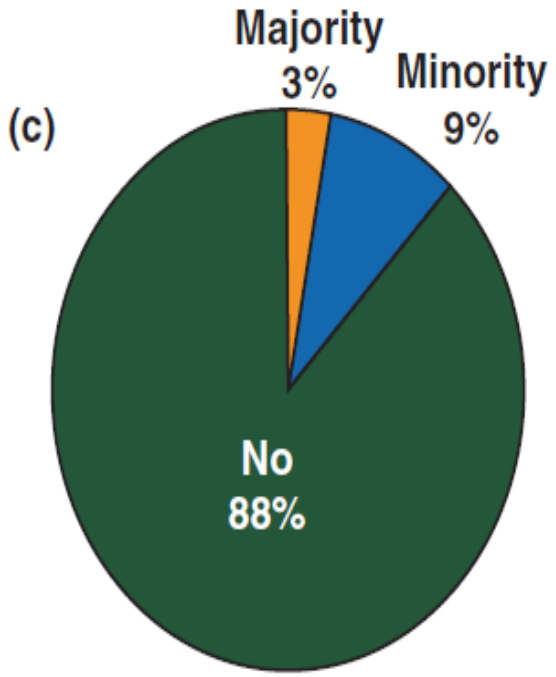


Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

- M0 CRPC

Ca and Vitamin D supplementation
For osteoporosis and increased risk of fractures:
- **Bisphosphonate at osteoporosis dose**
- **Denosumab (60mg, 6-monthly)**

C: Do you recommend an osteoclast-targeted therapy for CRPC patients without bone metastases for delaying onset of metastases?



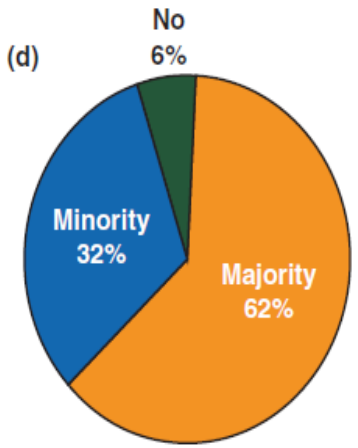
Osteoclast targeted agents
Reducing risk of SRE/ for SRE in M0/M1 stage

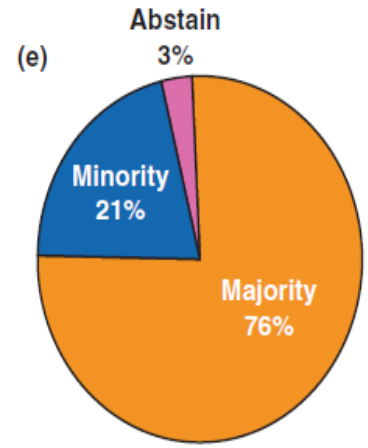
- M1CRPC (Bone mets)

Calcium and Vitamin D supplementation
Dental check before initiation of osteoclast-targeted therapies

• Denosumab (120mg, 4 w)
or
• Zoledronic acid (4mg, 3-4 w)

D: Do you recommend an osteoclast-targeted therapy for reduction in risk of SRE in CRPC patients with bone metastases?
E: Do you recommend a dental check for CRPC patients with bone metastases prior to starting an osteoclast-targeted therapy?





zoledronic acid (30%), denosumab (42%) and either of the two options (27%).

47% of the panel recommended a total duration of 2 years for reducing risk of SREs/SSEs

Predictive markers

- **92% consensus: No valid predictive tool**

- **Factors favoring CT > (ENZA/ AA):**

1. Expression of AR-V7 splice variants (47% vs 44%)
2. Presence of visceral metastases (50% vs 50%)
3. Short response (1yr) to 1st line ADT (53% vs 47%)
4. Low PSA (<20 ng/ml) in the setting of high tumor volume (65% vs 35%)

The unmet needs

- Role of ADT withdrawal in M0 CRPC (on ADT).
- Sequencing of AR antagonists in 1^0 /acquired resistance in CRPC.
- Some CRPCs have differential response to HT/CT/Biologics.
- No predictive tool for selection of CT vs HT
- Optimal use (sequencing/choice/duration/frequency of Osteoclast targeted therapies.
- Overlapping SRE related effects of novel agents narrowing use of osteoclast targeted agents.