Sequencing Strategies in Metastatic Castration Resistant Prostate Cancer (MCRPC)

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Disclosures

- Advisory Boards and Honoraria:
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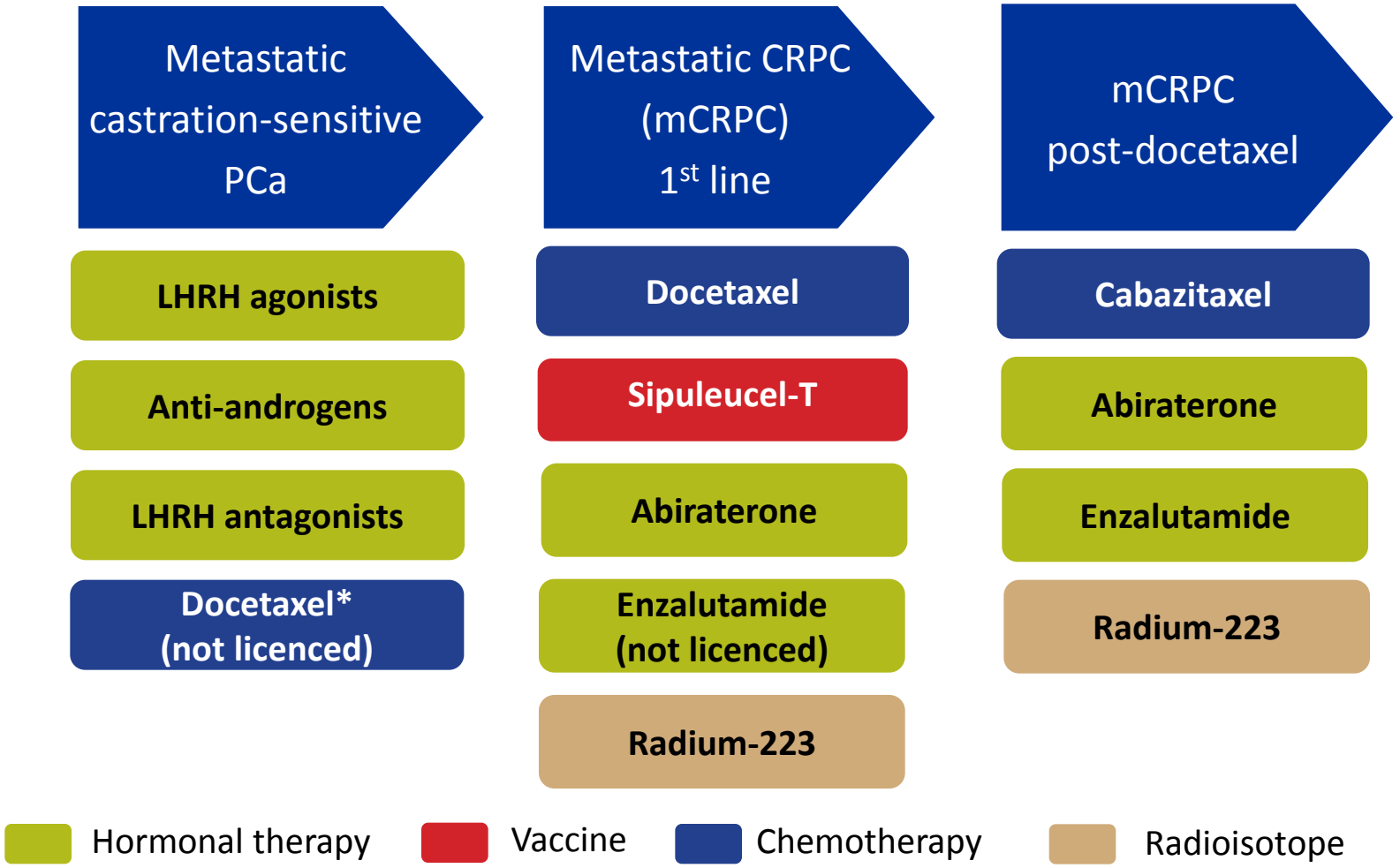
Management of advanced prostate cancer (PCa): Current options available



CRPC: castration-resistant prostate cancer; LHRH: luteinising hormone-releasing hormone

*Sweeney C *et al*. J Clin Oncol 2014;32 (June 20 suppl):abstract LBA2– Docetaxel is not licenced in this population

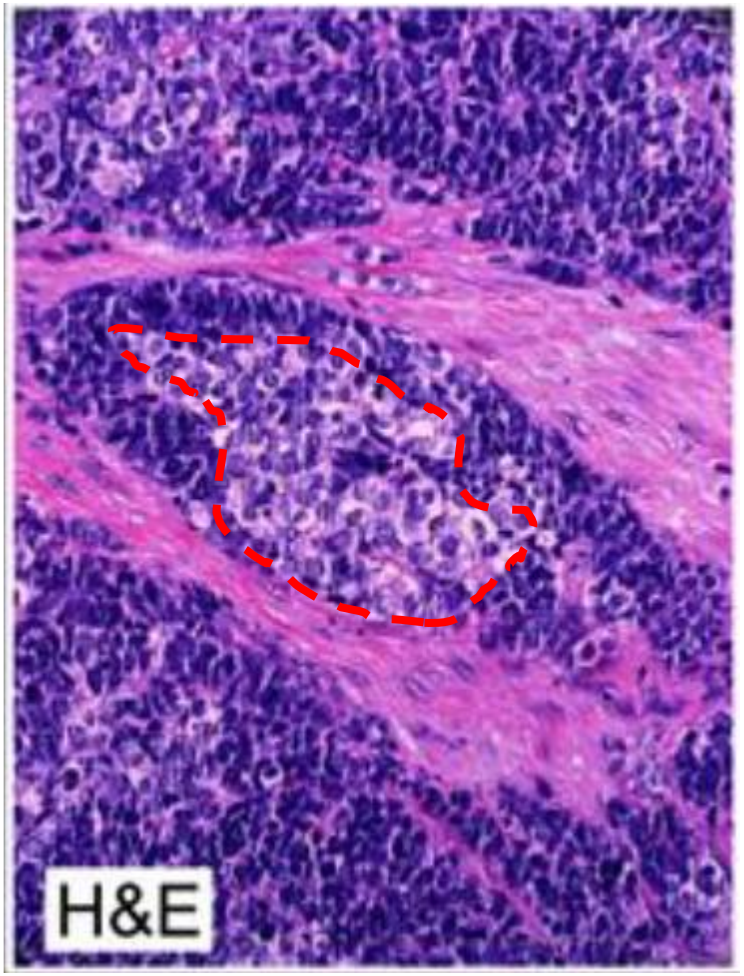
Phase III clinical trials in mCRPC

Study	Agents	N	Indication	HR	Δ OS
TAX-327[1]	DOC/P vs mito/P	1,006	mCRPC	0.76	+2.9
IMPACT[2]	Sipuleucel-T vs pbo	512	mCRPC (pre-DOC)	0.78	+4.1
COU-AA-302[3] COU-AA-301[4]	ABI/P vs P ABI/P vs P	1,088 1,195	mCRPC (pre-DOC) mCRPC (post-DOC)	0.81 0.74	+4.4 +4.6
PREVAIL[5] AFFIRM[6]	ENZ vs pbo ENZ vs pbo (or P)	1,717 1,199	mCRPC (pre-DOC) mCRPC (post-DOC)	0.71 0.63	+2.2 (est) +4.8
TROPIC[7]	CAB/P vs mito/P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[8]	Radium-223 vs pbo	921	mCRPC	0.70	+2.8

ABI: abiraterone; CAB: cabazitaxel; DOC: docetaxel; HR: hazard ratio; OS: overall survival; P: prednisone; pbo: placebo; mito: mitoxantrone

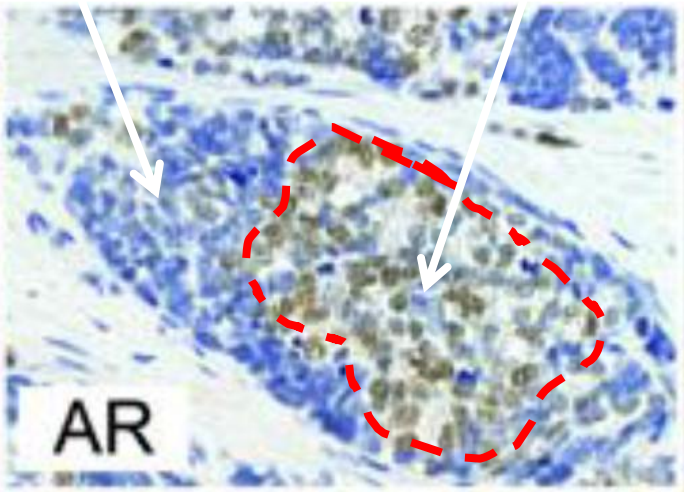
1. Tannock IA *et al*. N Engl J Med 2004;351:1502-12; 2. Kantoff PW *et al*. N Engl J Med 2010;363:411-22; 3. Ryan CJ *et al*. Lancet Oncol 2015; doi:10.1016/S1470-2045(14)71205-7; 4. Fizazi K *et al*. Lancet Oncol 2012;13:983-92; 5. Beer TM *et al*. N Engl J Med 2014;371:424-33; 6. Scher HI *et al*. N Engl J Med 2012;367:1187-97; 7. De Bono J *et al*. Lancet 2010;376:1147-54; 8. Parker C *et al*. N Engl J Med 2013; 369:213-23

Coexistence of AR+ and AR- tumour cells in a same patient at biopsy



AR negative tumour cells

AR positive tumour cells



Beltran H. Cancer discovery 2011; 1: 487-495

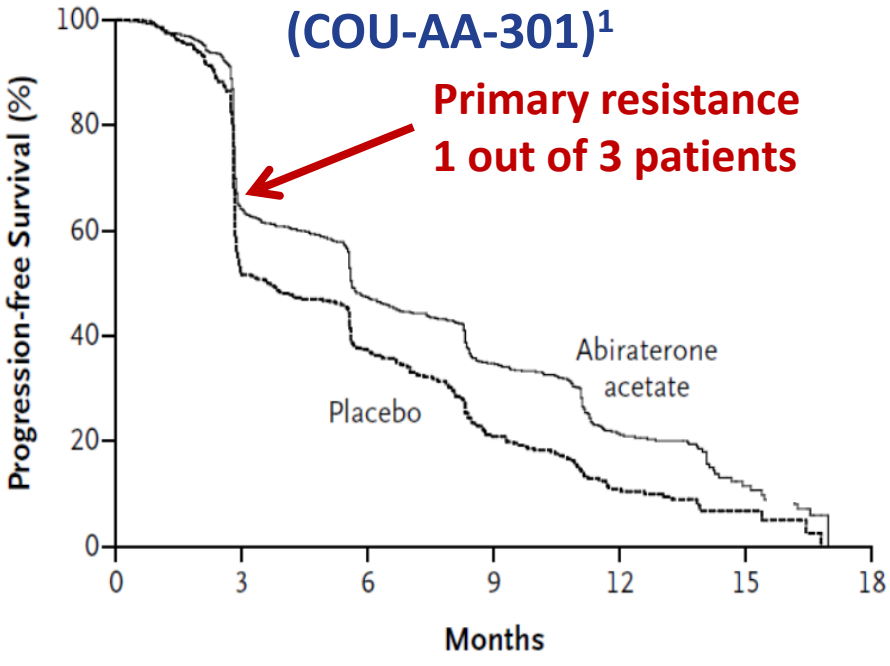
Primary resistance and predictive factors in mCRPC

- Existence of primary resistance
- Are there predictive factors for resistance to treatments?

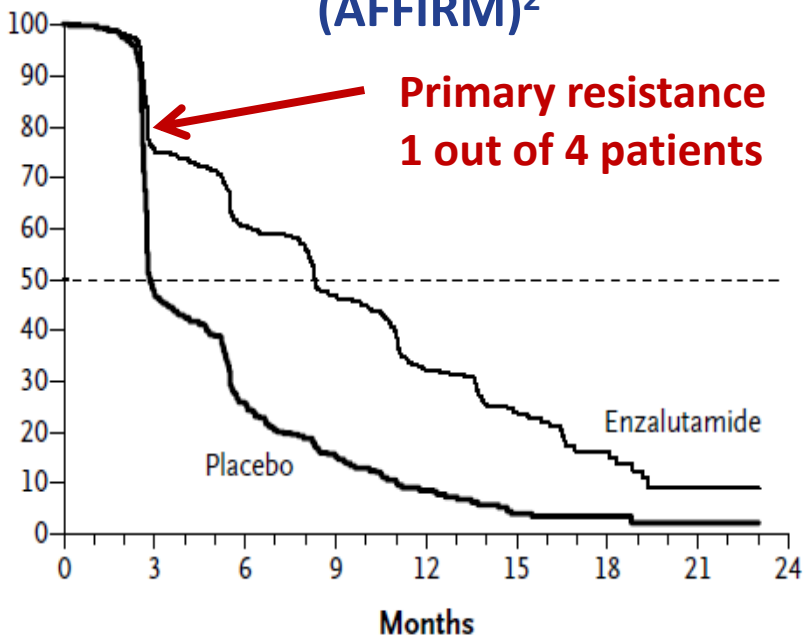
Primary resistance to AR-targeted agents

Radiological progression-free survival (rPFS)

ABI+P (COU-AA-301)[1]



ENZ±P (AFFIRM)[2]



- COU-AA-301 and AFFIRM primary endpoint was OS

1. De Bono JS *et al*. N Engl J Med 2011;364:1995-2005; 2. Scher H *et al*. N Engl J Med 2012;367:1187-97

Short response to first ADT (1 year) may predict poor response to AR-targeted therapies

AR targeted agents[1]

- Retrospective analysis in 108 patients with metastatic PCa
- Poor response to subsequent hormone therapies (including abiraterone, enzalutamide) if time to CRPC with first ADT < 16 months

Duration of response	< 16 mths	≥ 16 mths
↓ PSA ≥50%	18%	58%
Median TTP	3 mths	5 mths

Docetaxel[2]

- 188 patients with mCRPC in 2 prospective databases
- High Gleason score and visceral mets more common if early CRPC (≤1 year)
- Good response to docetaxel irrespective of time to CRPC:

Duration of response	≤ 1yr	> 1yr
↓ PSA ≥50%	67%	81%
Median TTP	6.1 mths	7.1 mths

1 Loriot Y *et al*. ASCO GU 2012 (abstract 213) ; 2 Huillard ASCO 2013 (abstract 5075)
TTP: time to progression; mths: months

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

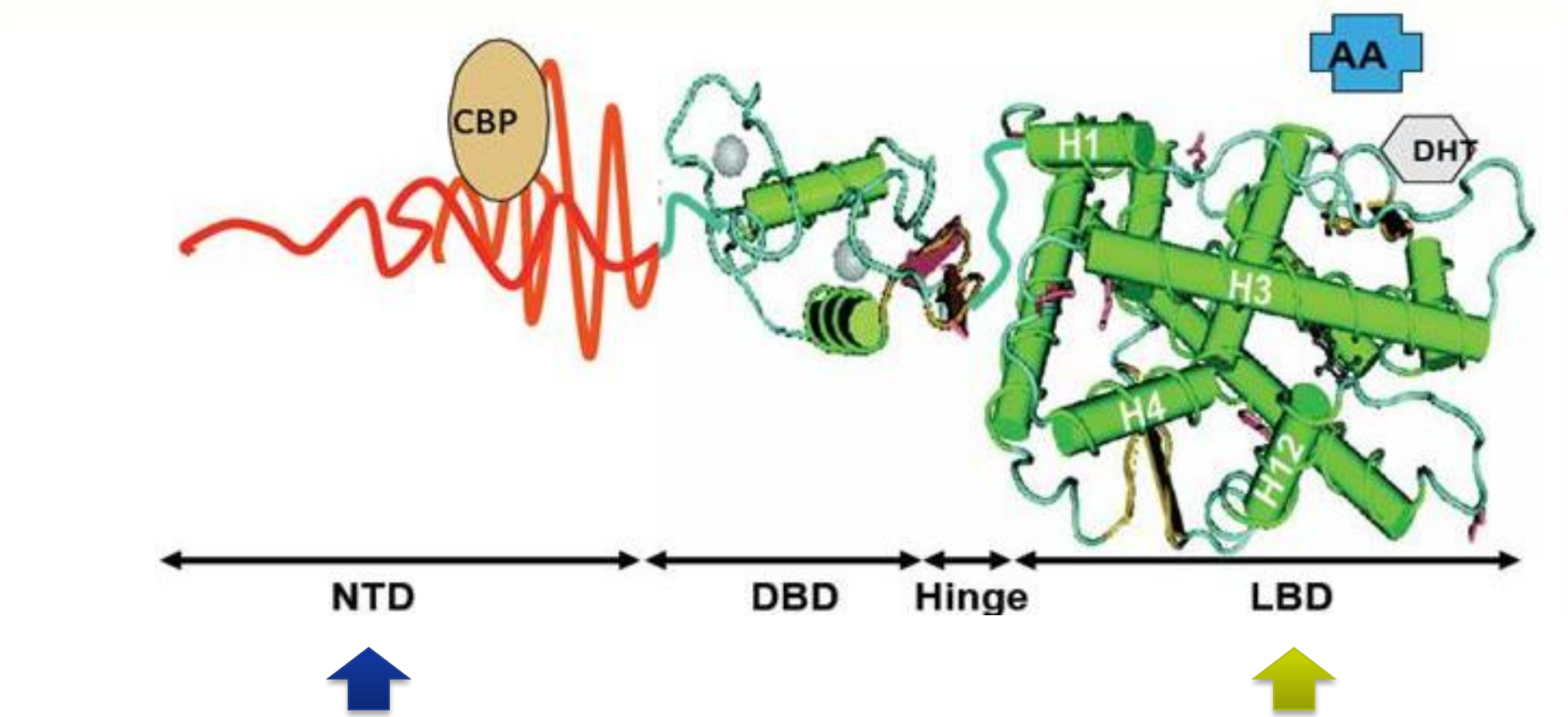
Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John 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.

Constitutively active splice variant

AR-FL: Full-Length Androgen Receptor; NTD: N-Terminal Domain; DBD: DNA-Binding Domain; LBD: Ligand-Binding Domain; U: Unique N- or C-terminal sequence

Antonarakis *et al*. N Engl J Med. 2014;371:1028-1038.
Guo Z *et al*. Int J Biol Sci. 2011;7:815-822.

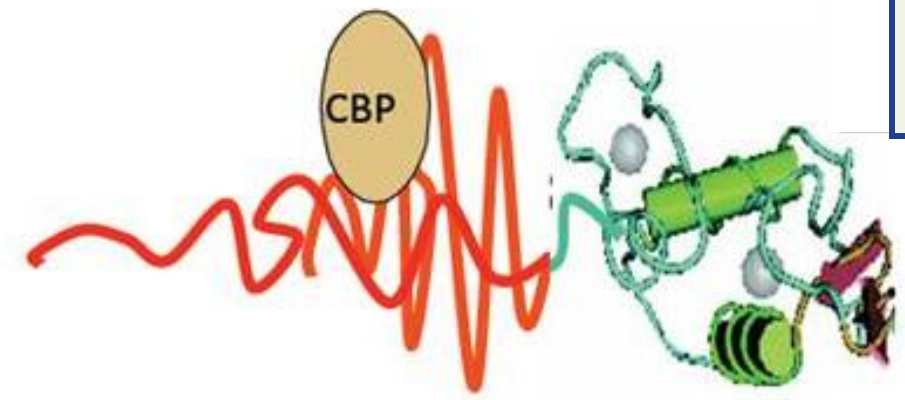
Full-Length AR (AR-FL)



Activation Function-1:
Required for transcriptional activity

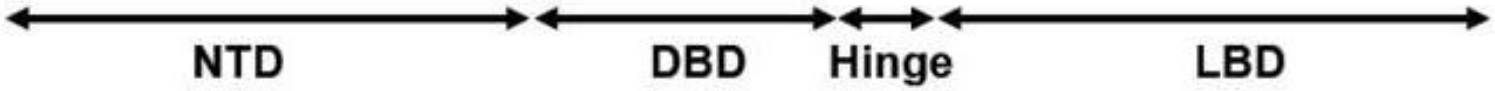
Androgen (DHT)
Antiandrogens (AA)

AR-V7: Truncated, Lacks LBD

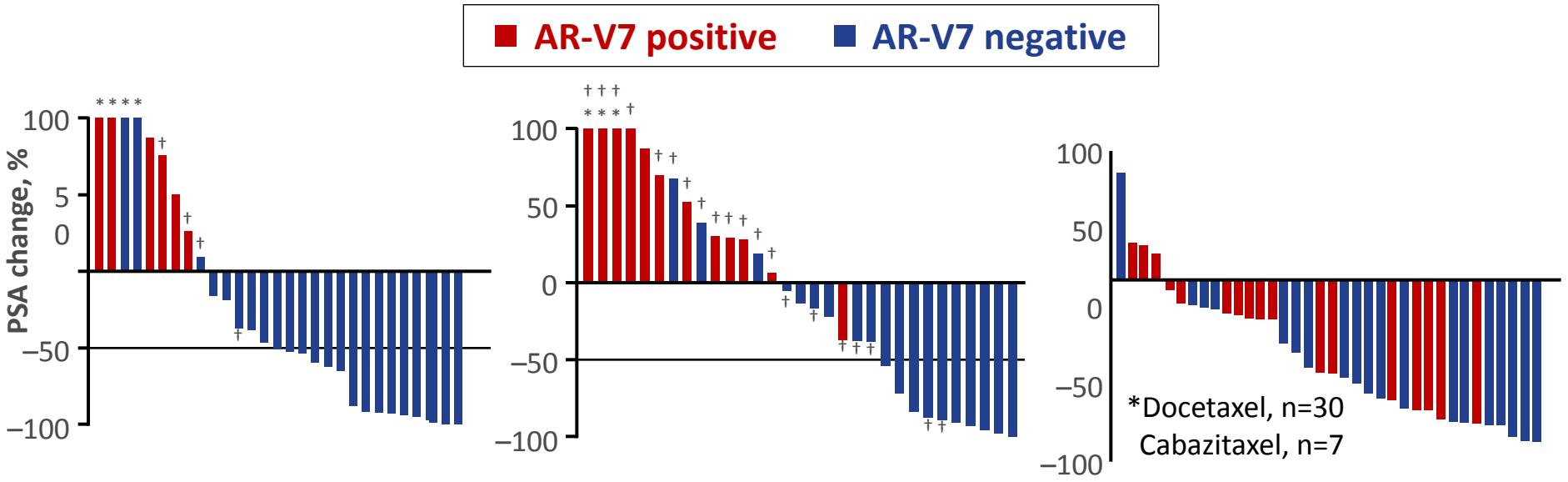


CRPC contain variants which lack the LBD

No current therapies can inhibit because they work through the LBD



Taxanes are also efficent in AR-V7+ patients



PSA response rate
AR-V7 positive: 0% (95% CI: 0-46%)
AR-V7 negative: 68.0% (95% CI: 46-85%)
P=0.004

PSA response rate:
AR-V7 positive: 0% (95% CI: 0-26%)
AR-V7 negative: 52.6% (95%CI: 29-76%)
P=0.004

PSA response rate:
AR-V7 positive: 41% (95% CI: 18-67%)
AR-V7 negative: 65% (95%CI: 41-85%)
P=0.19

Antonarakis ES *et al*. N Engl J Med 2014;371:1028-38; Antonarakis ES *et al*. ASCO GU 2015 (abstract 138)

Is there cross-resistance between therapies?

- Abiraterone after enzalutamide?
- Enzalutamide after abiraterone?
- Primary refractoriness to docetaxel?
- Docetaxel after abiraterone or enzalutamide?
- What about cabazitaxel?
- Where does Ra223 best fit in?

Poor response to abiraterone in patients progressing on enzalutamide and vice versa?

Author	Year published	N pts	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
ENZ → ABI					
Loriot et al.[1]	2013	38	3 mo	8%	2.7 mo
Noonan et al.[2]	2013	30	13 wks	3%	3.6 mo
ABI → ENZ					
Schrader et al.[3]	2013	35	4.9 mo	29%	-
Badrising et al.[4]	2014	61	3 mo	21%	-
Bianchini et al.[5]	2014	39	2.9 mo	13%	-
Schmid et al.[6]	2014	35	2.8 mo	10%	-
Brasso et al.[7]	2014	137	3.2 mo	18%	-

[1-7] trials are retrospective studies in mCRPC pts in post-DOC setting

1. Loriot Y et al. Ann Oncol 2013;24:1807-12; 2. Noonan KL et al. Ann Oncol 2013;24:1802-7; 3. Schrader AJ et al. Eur Urol 2014;65:30-6; 4. Badrising S et al. Cancer 2014;120:968-75; 5. Bianchini D et al. Eur J Cancer 2014;50:78-84; 6. Schmid SC et al. Adv Ther 2014;31:234-41; 7. Brasso K et al. Eur Urol 2014; doi: 10.1016/j.eururo.2014.07.028; 1-7. Zhang T et al. Expert Opin Pharmacotherap 2014;16:1-9

Response in primary docetaxel-refractory patients

Cabazitaxel/predisone

- Retrospective review of 186 mCRPC patients
- 33 (17.7%) DOC-refractory*
- Subsequent therapies:
  - Cabazitaxel
  - AR-targeted agents (ABI or ENZ)
- Multivariate analysis: significant OS benefit with cabazitaxel vs new AR-targeted agents

Abiraterone/prednisone

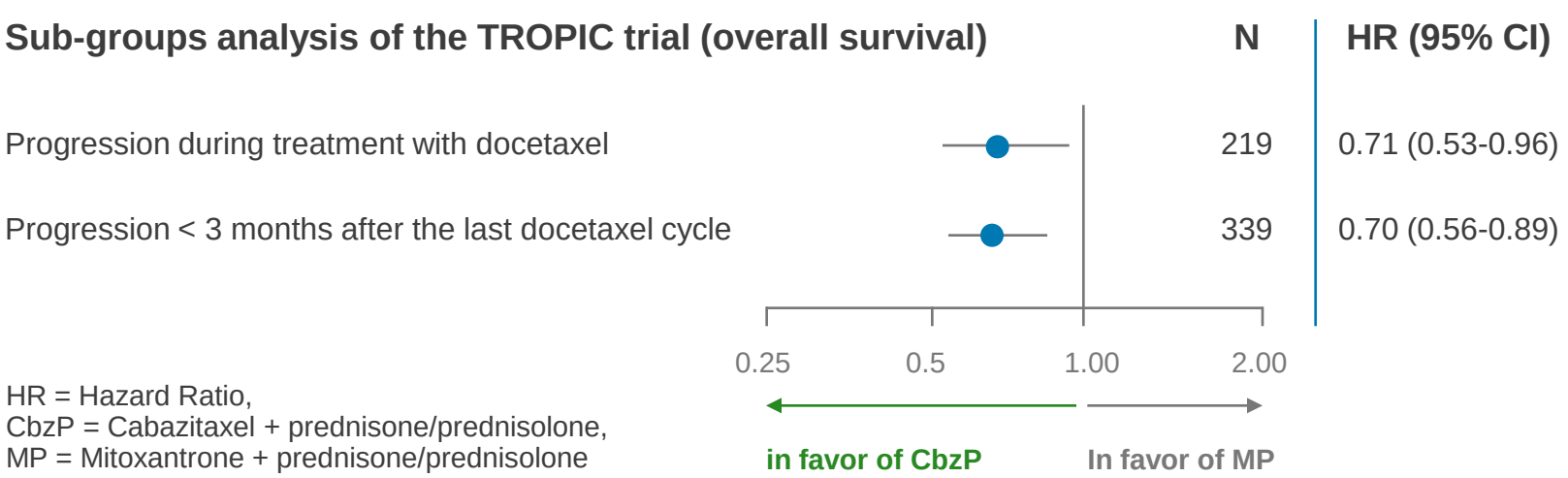
- Retrospective study of 44 patients with mCRPC
- Treated with DOC → ABI
- 7/44 patients DOC-refractory
- No PSA, radiological or clinical response to ABI

**DOC refractoriness defined as disease progression occurring within 3 months of initiation of docetaxel (DOC) and after adequate exposure to DOC (ie cumulative dose of ≥225 mg/m²)*

Di Lorenzo G *et al*. Eur Urol 2014,65:502-7

Cabazitaxel is effective in patients with rapid progression during or just after treatment with docetaxel

Cabazitaxel also acts in cases of resistance to docetaxel

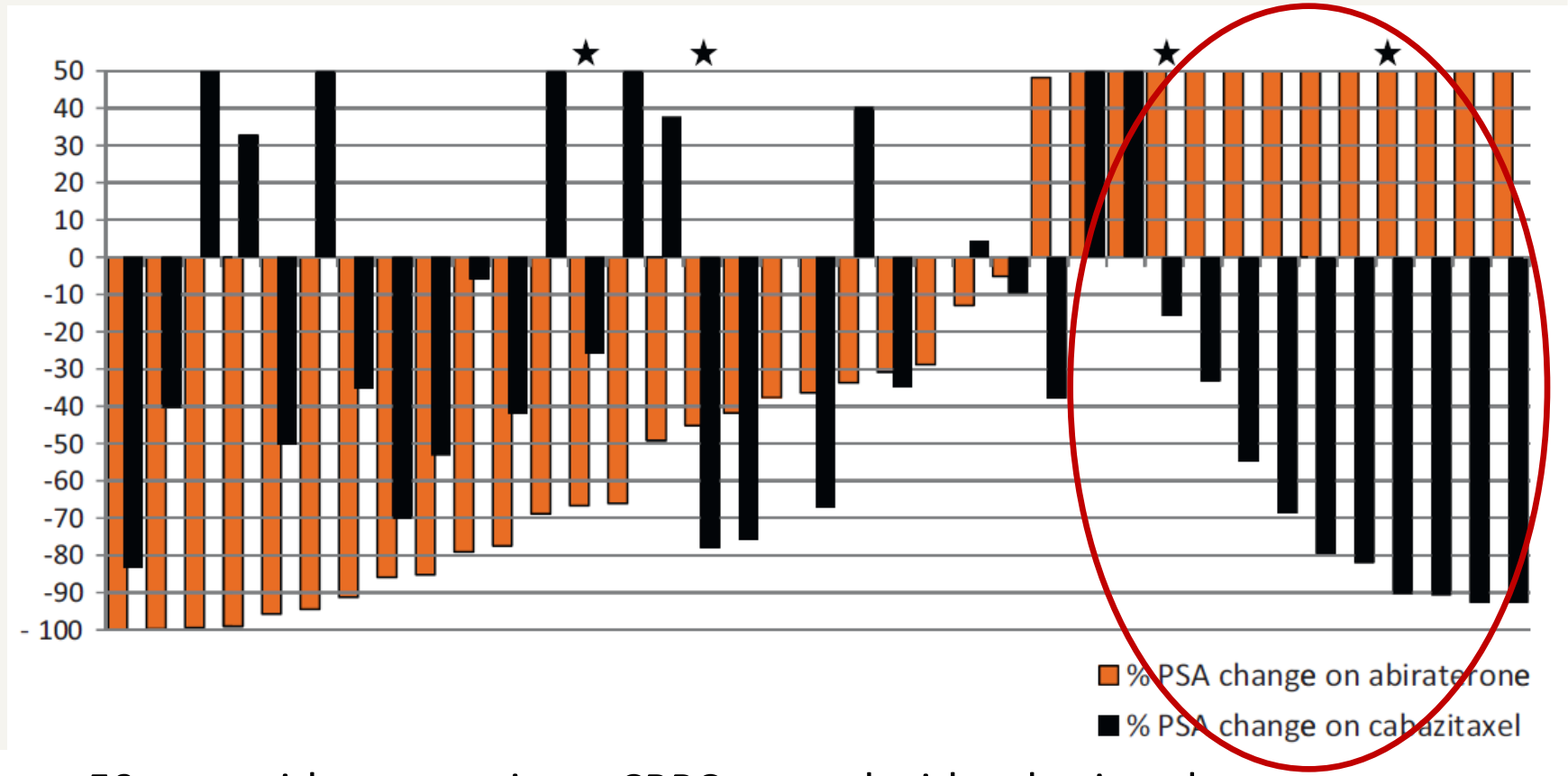


HR = Hazard Ratio,
CbzP = Cabazitaxel + prednisone/prednisolone,
MP = Mitoxantrone + prednisone/prednisolone

Cabazitaxel overcomes resistance to chemotherapy in patients with mCRPC that have progressed during or < 3 months following treatment with docetaxel.

Oudard, S., *et al.* TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncol 7, 497-506 (2011).

PSA response with cabazitaxel does not seem influenced by prior AR-targeted agents



- 59 men with progressing mCRPC treated with cabazitaxel,
  - 37 of whom had received prior abiraterone
  - 9 of whom had received prior enzalutamide

Pezaro CJ *et al*. Eur Urol 2014;66:459-65

The 'Laws' of Sequencing: My adaptation of Newton's laws

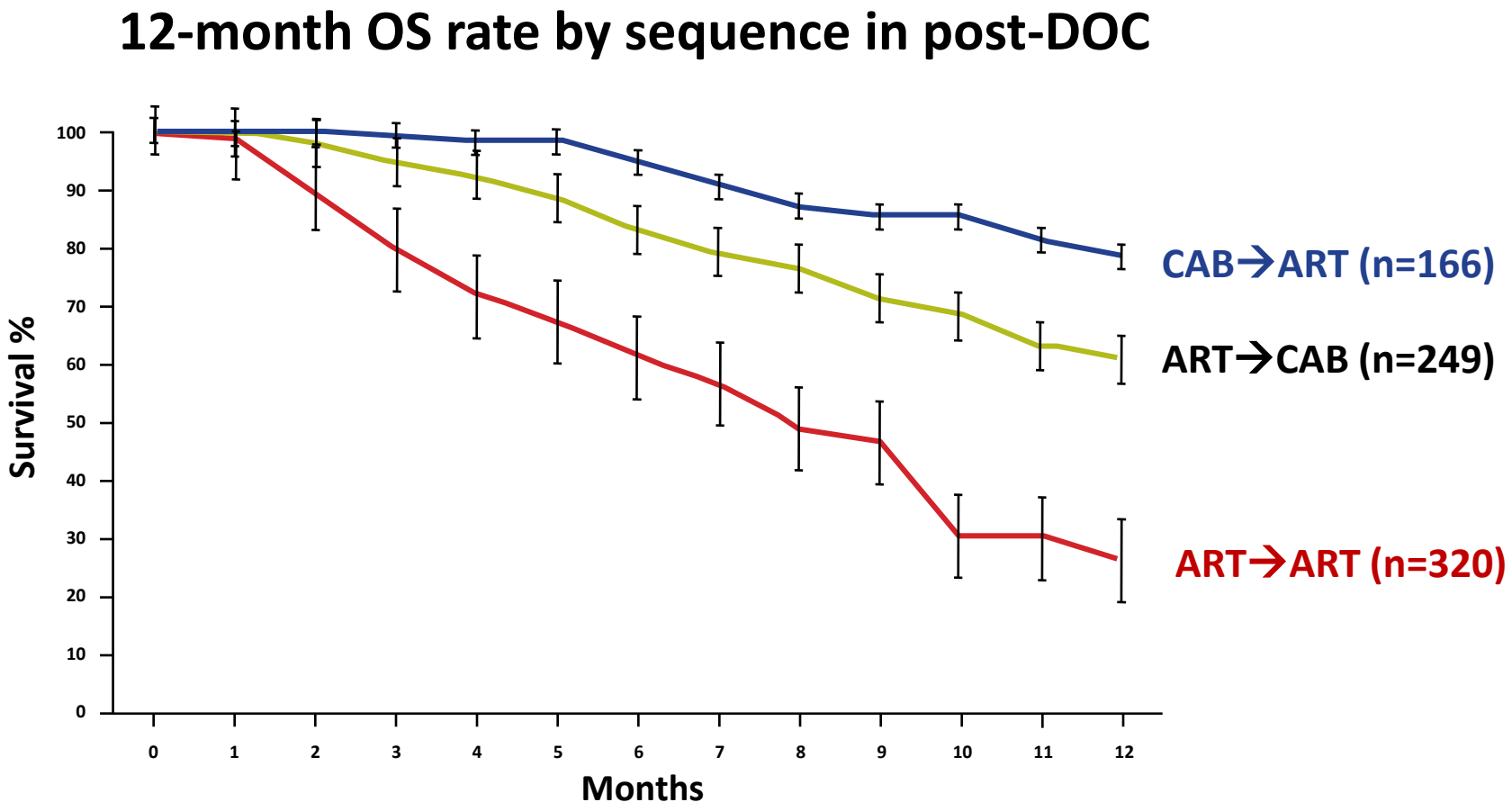
- Every selection has a reason
- Every selection has a reaction
- Every selection impacts on further selection
- Based on the concept that more treatments = increased survival
  - It is likely that 2nd treatment will be less effective than 1st treatment and 3rd treatment will be less effective than 2nd treatment

  (Irrespective of the type of treatment unless we have specific biomarker related therapy)
- 2 philosophical approaches
  - Give the potentially less toxic agent first
  - Give the potentially more toxic agent first

Caution: To stimulate discussion only!

Is there an optimal treatment sequence in mCRPC?

Similar results in a meta-analysis of 10 published retrospective studies (n = 735)



Possible better OS with the sequence DOC→CAB→ART?

ART: Androgen receptor targeted agents

Maines F *et al*. ASCO GU 2015 (abstract 258)

Treatment of MCRPC in my practice

- Important to establish the goals for long term
- Remember it is NOT ***'one OR the other'*** it is ***'one AFTER the other'***

Toxicity/Side-Effects

- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium 223

Important to factor both efficacy and toxicity in the decision making process

My Decision Tree

Metastatic CRPC

- Short response (<1 year) to 1st-line ADT
- Or high Gleason score
- Or rapid PSA doubling time
- Or visceral metastases
- Or progression on docetaxel

Poor predicted response to hormonal therapy
(including abiraterone/enzalutamide)

Indication for chemotherapy
(Docetaxel → Cabazitaxel)

Overall conclusions

- Management of CRPC is rapidly evolving
- New drugs in development: need to move to a tailored therapy
- The most appropriate sequencing of these new agents remains to be determined and chemotherapy remains a valid treatment option in mCRPC

'The right drug, at the right time, for the right patient at the right place and by the right team'
……with access to trials