Where are we with chemotherapy?

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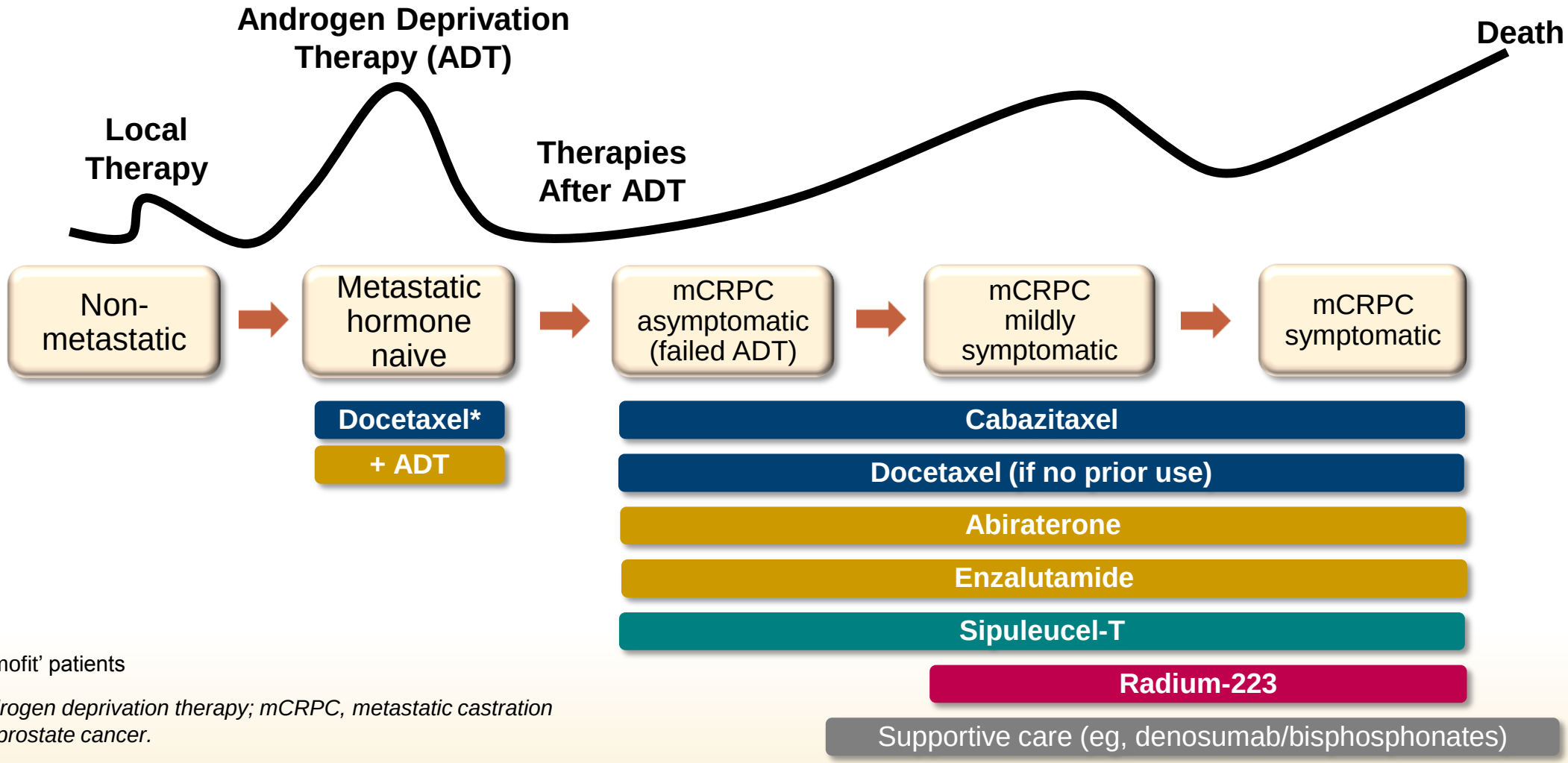
Disclosure

- Advisory Boards and Honoraria:
  - Amgen, Astellas, Bayer, Janssen, Novartis, Sanofi, MSD, Ipsen
- Research Grants:
  - Ipsen, Sanofi
- Meeting Sponsorship
  - Astellas, Bayer, Janssen, Roche, Sanofi, MSD, Ipsen

Advanced Prostate Cancer: Treatment Paradigm in 2017 Mainly Sequential Therapy



*for 'chemofit' patients

ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer.

Docetaxel + prednisone is only registered for the treatment of patients with hormone-refractory metastatic prostate cancer

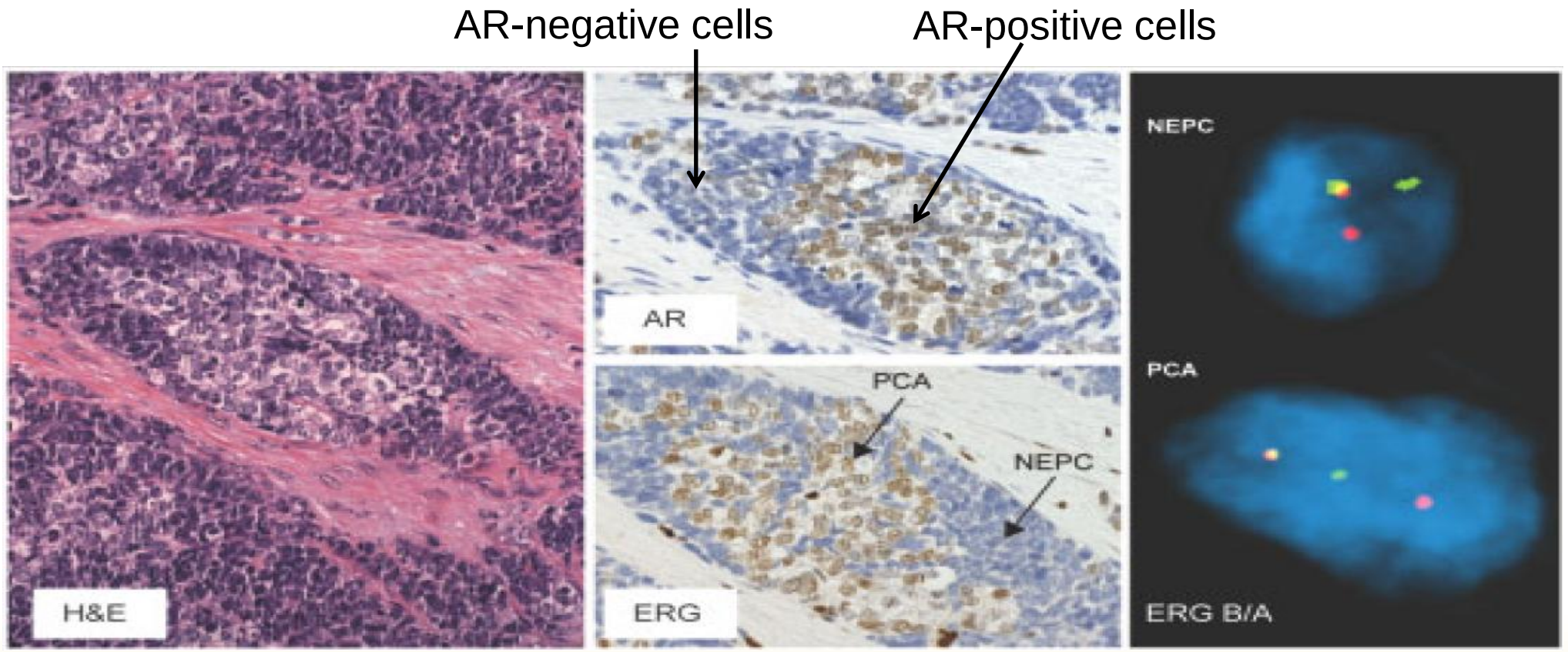
Phase III Trials With Life-Prolonging Therapies in Advanced Prostate Cancer

	Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
2017	STAMPEDE[1]	ABI/P/SOC vs SOC	1,917	Metastatic hormone-naïve	0.63 (0.52-0.76)	NR
2017	LATITUDE[2]	ABI/P/ADT vs ADT	1,199	Metastatic hormone-naïve	0.62 (0.51-0.76)	NR
2016	STAMPEDE[3]	DOC/SOC vs SOC	1,086	Metastatic hormone-naïve	0.73 (0.59-0.89)	+22.0
2015	CHAARTED[4]	DOC/ADT vs ADT	790	Metastatic hormone-naïve	0.61 (0.47-0.80)	+13.6
2017	PREVAIL[5]	ENZA vs pbo	1,717	mCRPC (pre-DOC) mild/no symptoms , 11% visceral mets	0.71 (0.60-0.84)	+4.0
2012	AFFIRM[6]	ENZA vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63 (0.53-0.75)	+4.8
2015	COU-AA-302[7]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms - No visceral mets	0.81 (0.70-0.93)	+4.4
2012	COU-AA-301[8]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74 (0.64-0.86)	+4.6
2013	ALSYMPCA[9]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70 (0.55-0.88)	+2.8
2010	TROPIC[10]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70 (0.59-0.83)	+2.4
2010	IMPACT[11]	Sipuleucel-T vs pbo	512	mCRPC (pre-DOC) mild/no symptoms - No visceral mets	0.78 (0.61-0.98)	+4.1
2004	TAX-327[12]	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76 (0.62-0.94)	+2.9

ABI, abiraterone; ADT, androgen deprivation therapy; CABA, cabazitaxel; DOC, docetaxel; ENZA, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; mito, mitoxantrone; P, prednisone; Pbo, placebo; SOC, standard of care.

1. James ND et al. N Engl J Med. 2017 Jun 3. doi: 10.1056/NEJMoa1702900 2. Fizazi K, et al. *N Engl J Med.* 2017;377:352-360; 3. James ND. *Lancet*. 2016;387:1163–77; 4. Sweeney CJ. *N Engl J Med*. 2015;373:737–46;
5. Beer TM. *Eur Urol.* 2017 Feb;71(2):151–54; 6. Scher HI. *NEJM*. 2012;367:1187–97; 7. Ryan C. *Lancet Oncol*. 2015;16:152–60; 8. Fizazi K. *Lancet Oncol.* 2012;13:983–92;
9. Parker C et al. *NEJM.* 2013;369:213–23; 10. de Bono JS. *Lancet*. 2010;376:1147–54; 11. Kantoff PW. *NEJM*. 2010;363:411–22; 12. Tannock IF. *NEJM*. 2004;351:1502–12.

Prostate Cancer Is Heterogeneous With Co-Existence of AR-Dependent & AR-Independent Tumors Cells in the Same Patient



Tumor with mixed features of neuroendocrine PCa and prostate adenocarcinoma

Beltran H et al. *Cancer Discov*. 2011;1:487–95.

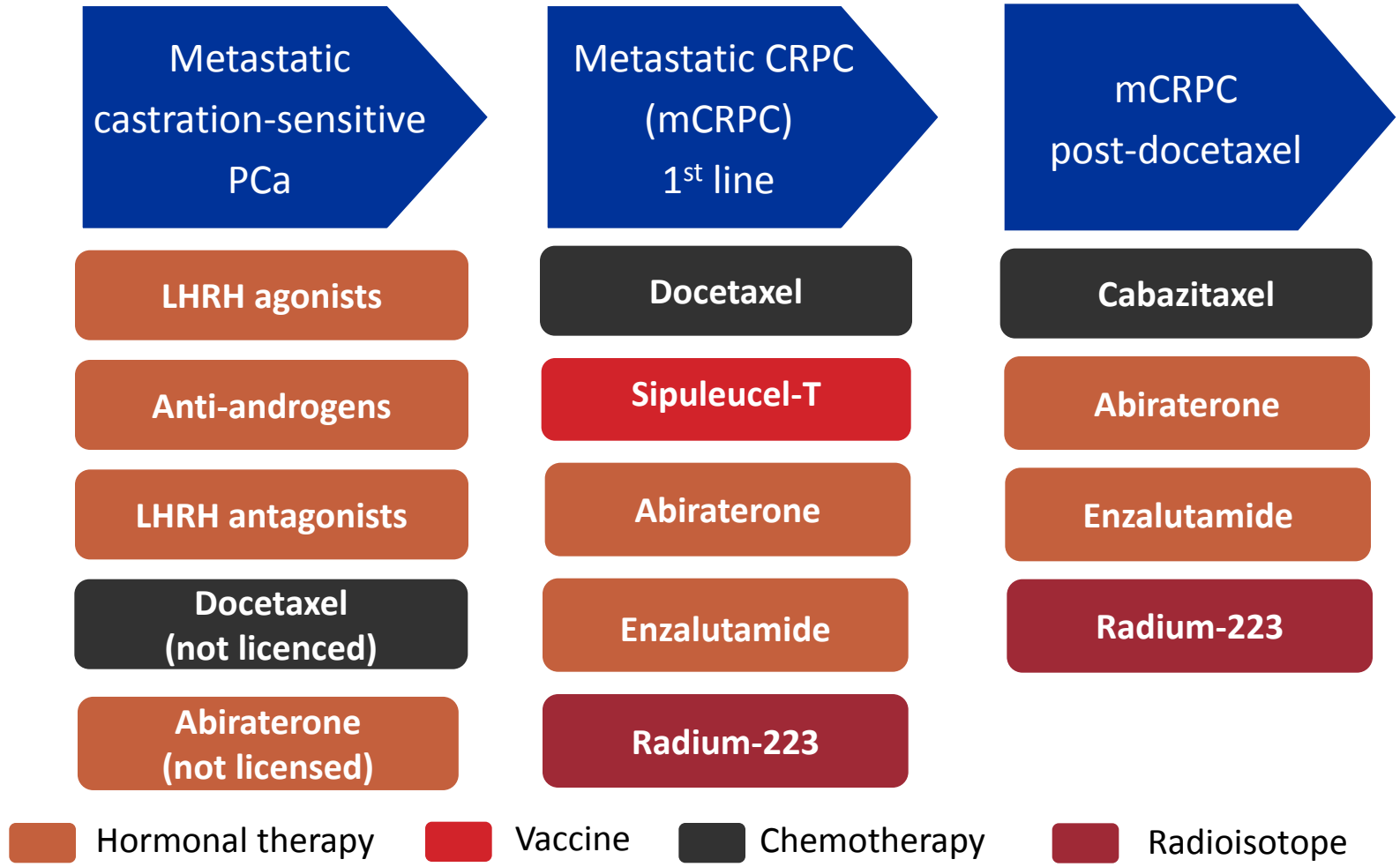
Median OS in Advanced Prostate Cancer

1990s	Prednisone (P) alone (mCRPC):	**12.6** mo[1]
2004	TAX327 (DOC/P – mCRPC):	**18.9** mo[2]
2010	TROPIC (DOC/P → CAB/P – mCRPC)*:	**29.4** mo[3-4]
2011	COU-AA-301 (DOC/P → ABI/P – mCRPC)*:	**32.6** mo[5]
2013	COU-AA-302 (ABI/P pre-DOC – mCRPC):	**34.7** mo[6]
2014	PREVAIL (ENZA pre-DOC – mCRPC):	**35.3** mo[7]
2015	STAMPEDE – M1 (DOC/P + ADT – mHSPC):	**65.0** mo[8]
2016	CHAARTED – M1 (DOC/P + ADT – mHSPC):	**57.6** mo[9]

*Median OS calculated from first DOC cycle

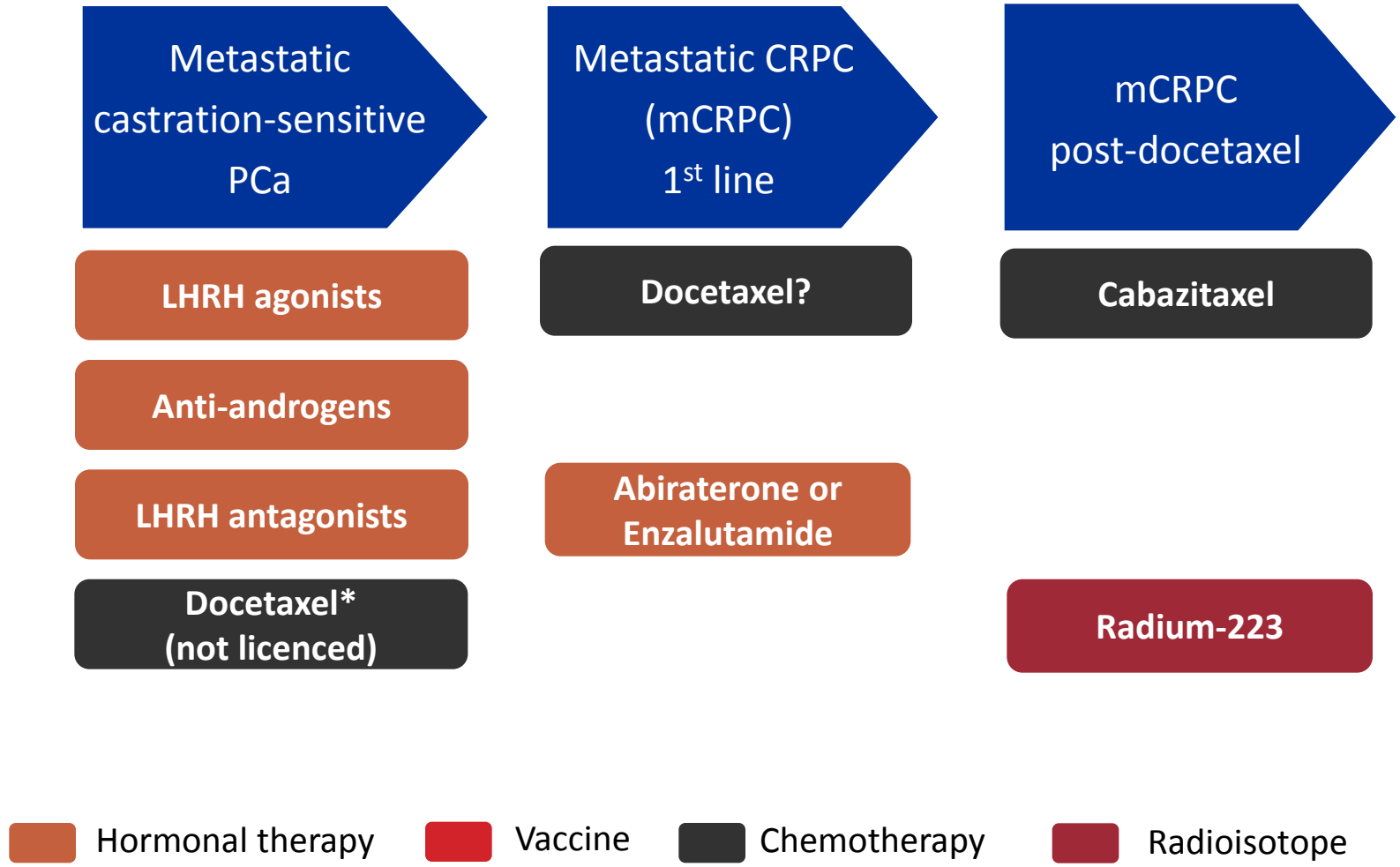
1. Kantoff PW. *J Clin Oncol*. 1999;7:2506–13; 2. Tannock IF. *N Engl J Med*. 2004;351:1502–12; 3. de Bono JS et al. *Lancet*. 2010;376:1147–54; 4. Sartor O. *J Clin Oncol*. 2011;29(S15):abstract 4525 (podium presentation); 5. Fizazi K . *Lancet Oncol*. 2012;13:983–92 (supplementary appendix); 6. Ryan CJ. *Lancet Oncol*. 2015;16:152–60; 7. Beer TM. *Eur Urol*. 2017;71:151–54; 8. James ND et al. *Lancet*. 2016;387:1163–77; 9. Sweeney C et al. Ann Oncol. 2016;27(suppl 6):

Management of Advanced Prostate Cancer (PCa): Current Options Available



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

Management of Advanced Prostate Cancer (PCa): Current Options Available



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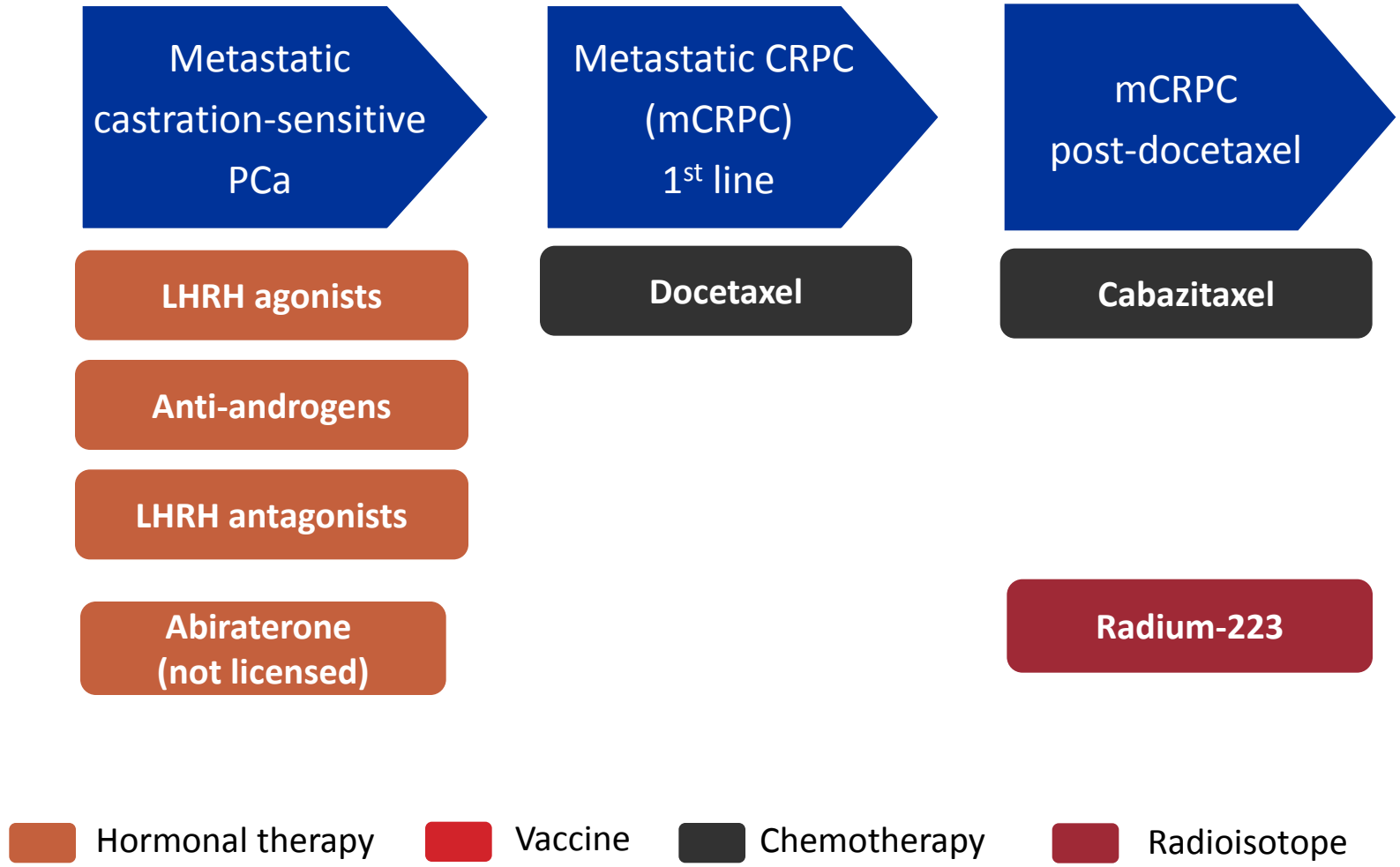
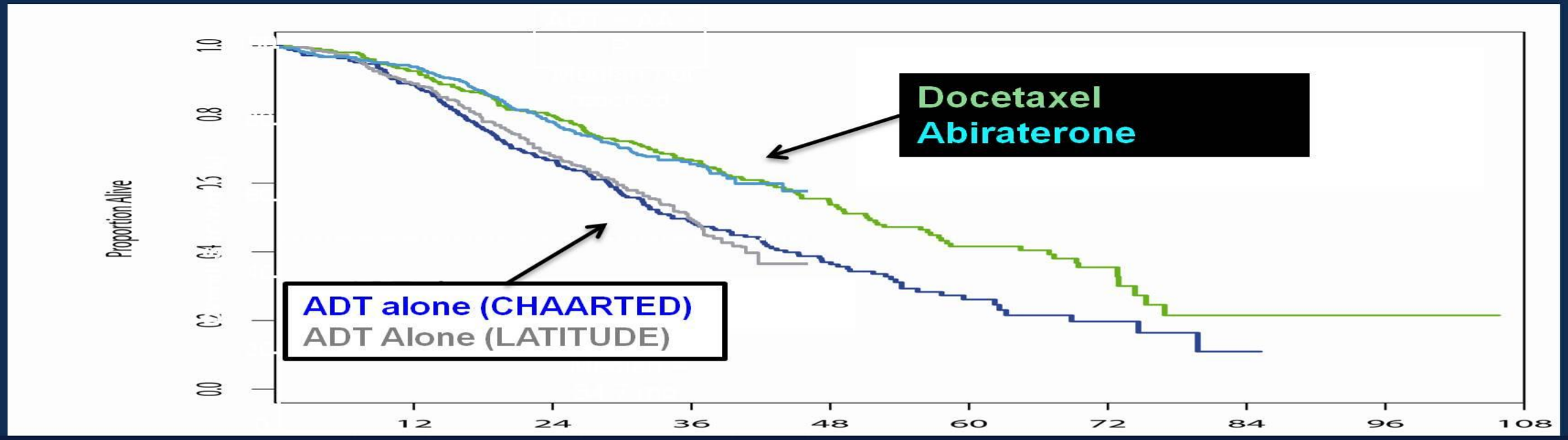


CRPC: castration-resistant prostate cancer; LHRH: luteinising hormone-releasing hormone

In MHSPC, for a patient who is fit to receive docetaxel chemotherapy

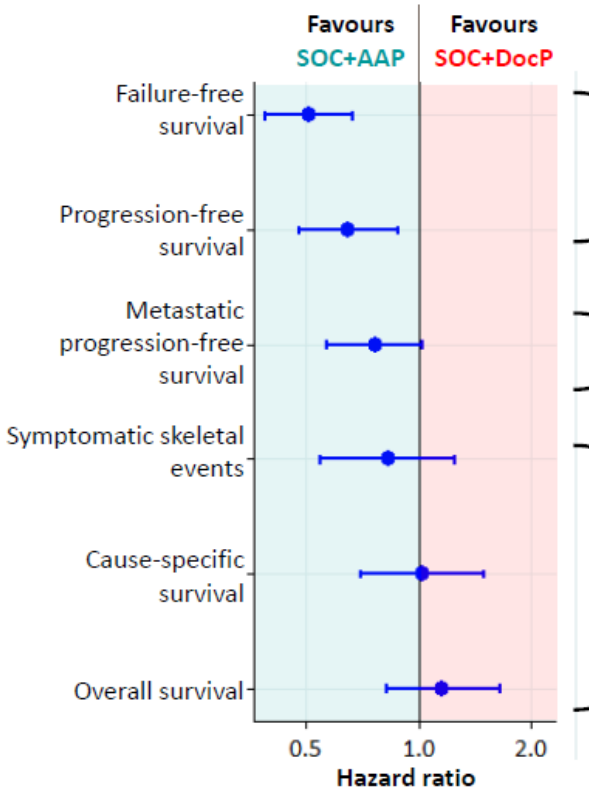
- If there was approval and funding available to treat an eligible MHSPC individual with either ADT+Docetaxel or ADT+Abiraterone

- What would you choose?



Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

Adding abiraterone acetate plus prednisolone (AAP) or docetaxel for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): directly randomised data from STAMPEDE



Summary

Head-to-head data in 566 pts (Nov-2011 to Mar-2013)

Strong evidence favouring AAP

Weak evidence favouring AAP

No good evidence of a difference

→ Proportionately different time spent in each disease state

Toxicity profiles quite different and well known

Changing paradigm of MHSPC treatment will result in two new scenarios

- Progression post upfront Docetaxel

- Progression post upfront Abiraterone

Progression Post-Upfront Docetaxel

- No reliable evidence available
- New area of disease based on recent changes with upfront docetaxel being incorporated
- Pragmatic decision making
  - Based on time to progression
  - Trajectory of disease
  - Patient fitness
- Overall prognosis is unfortunately not good

Progression Post-Upfront Docetaxel

- Pragmatic decision making
  - Based on time to progression
  - Trajectory of disease
  - Patient fitness
- My treatment strategy:
  - If progression <6 months post-upfront docetaxel- Cabazitaxel
  - If progression between 6-12 months then cabazitaxel preferred and individual case based strategy
  - If progression > 1 year then the same aspects as mCRPC treatment strategy

Progression Post-Upfront Abiraterone

- No robust data available
- It is likely treatment paradigm will involve earlier use of Docetaxel for MCRPC and subsequent post-docetaxel therapies
  - Potentially earlier use of Doc-Cabazitaxel
  - Further ART would probably not be meaningfully beneficial
  - Rad223 would probably have the same role as now

Switching Treatment Scenarios in MCRPC

Progression on ART (abiraterone/Enzalutamide)

Progression on Docetaxel

Cross-Resistance Between AR-Targeted Agents

- Poor response to Enza if progression on Abi
- Poor response to Abi if progression on Enza

- NICE (UK) does not permit use of sequential ART if there is progression on first ART

Cross-Resistance Between AR-Targeted Agents

Table 3. Completed retrospective studies of sequencing abiraterone acetate and enzalutamide (Enza) in patients with metastatic castration-resistant prostate cancer in the post-chemotherapy setting.

Authors	Year published	Number of patients	Duration of second treatment	≥ 50% decline in PSA	Median PFS
Enzalutamide → Abiraterone Acetate					
Loriot *et al.*	2013	38	3 months	3%	2.7 months
Noonan *et al.*	2013	30	13 weeks	3%	3.8 months
Abiraterone Acetate → Enzalutamide					
Schrader *et al.*	2013	35	4.9 months	29%	
Badrising *et al.*	2014	61	3 months	21%	
Bianchini *et al.*	2014	39	2.9 months	23%	
Schmid *et al.*	2014	35	2.8 months	10%	
Brasso *et al.*	2014	137	3.2 months	18%	

AA: Abiraterone acetate; PFS: Progression-free survival; PSA: Prostate-specific antigen.

Retrospective trials based on a small number of patients

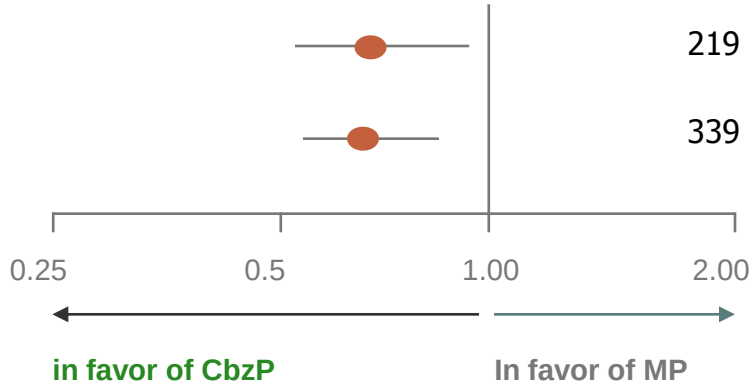
Zhang T et al. *Expert Opin Pharmacother*. 2014;16:1–9.

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

- Cabazitaxel also acts in cases of resistance to docetaxel

Sub-groups analysis of the TROPIC trial (overall survival)

	N	HR (95% CI)
Progression during treatment with docetaxel	219	0.71 (0.53-0.96)
Progression < 3 months after the last docetaxel cycle	339	0.70 (0.56-0.89)

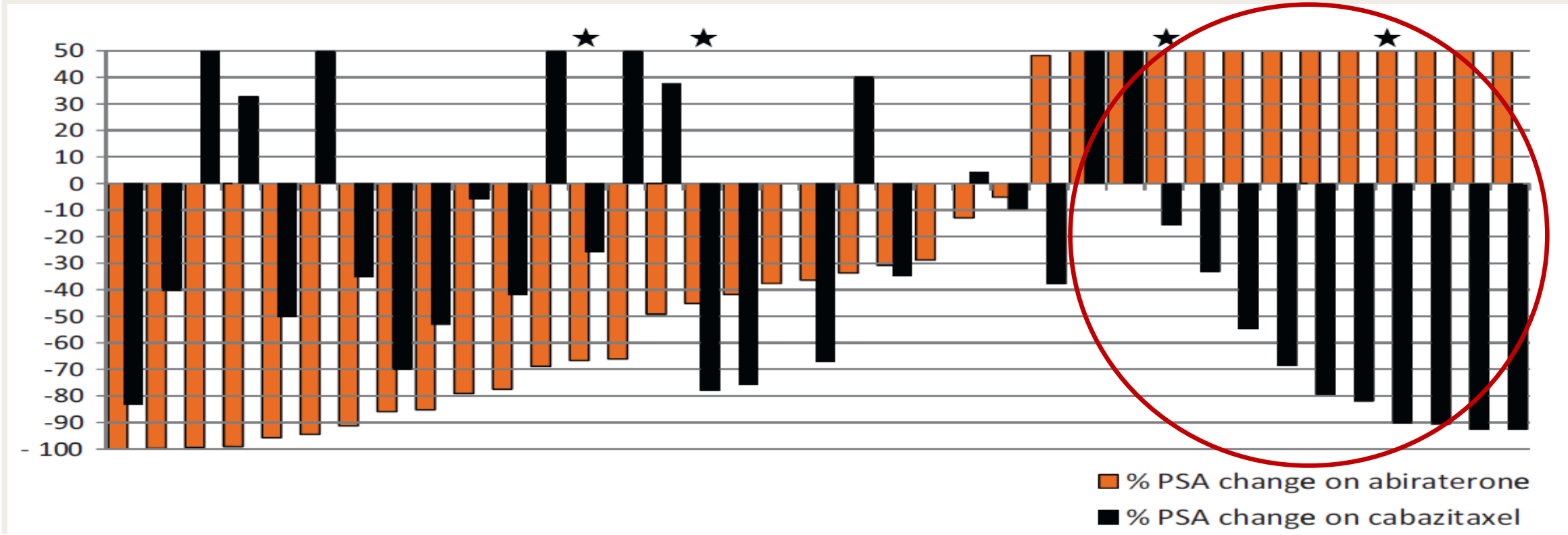


- HR = Hazard Ratio,
CbzP = Cabazitaxel + prednisone/prednisolone,
MP = Mitoxantrone + prednisone/prednisolone

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).

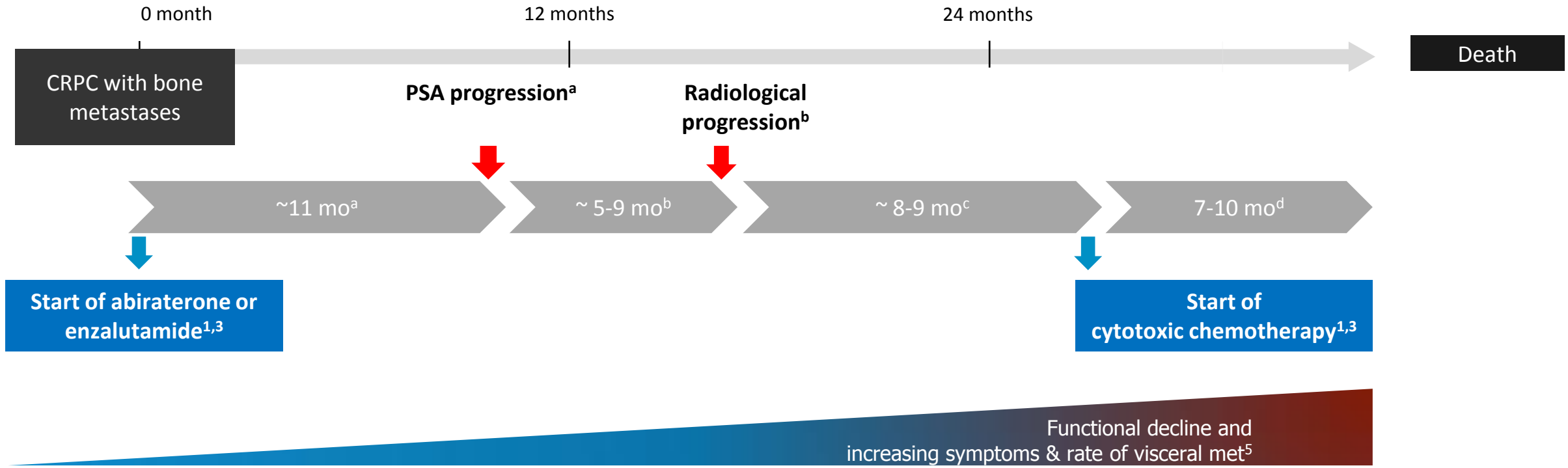
PSA response with cabazitaxel does not seem influenced by prior AR-targeted agents



- 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

A closer look at time to events in the COU-AA-302[1,2] and PREVAIL[3,4] studies



	Median time to … (months)			
	a: PSA progression	b: Radiological PFS	c: Start of cytotoxic chemotherapy	d: Death
COU-AA-302	11.1[1]	16.5[1]	25.2[1]	34.7[2]
PREVAIL	11.2[3]	20.0[4]	28.0[3]	35.3[4]

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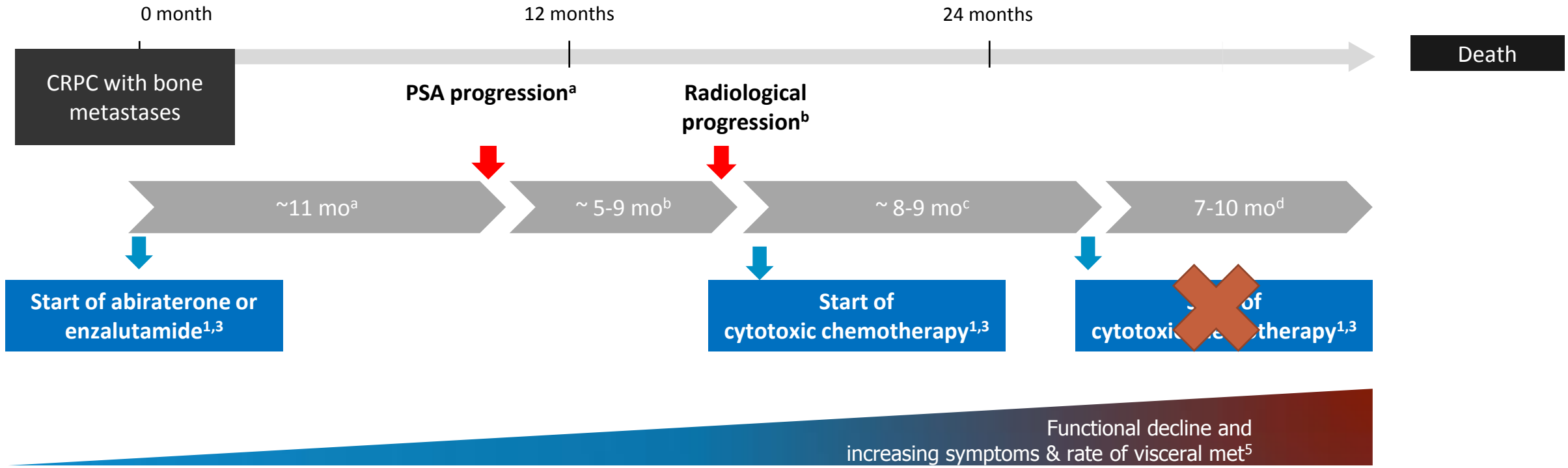

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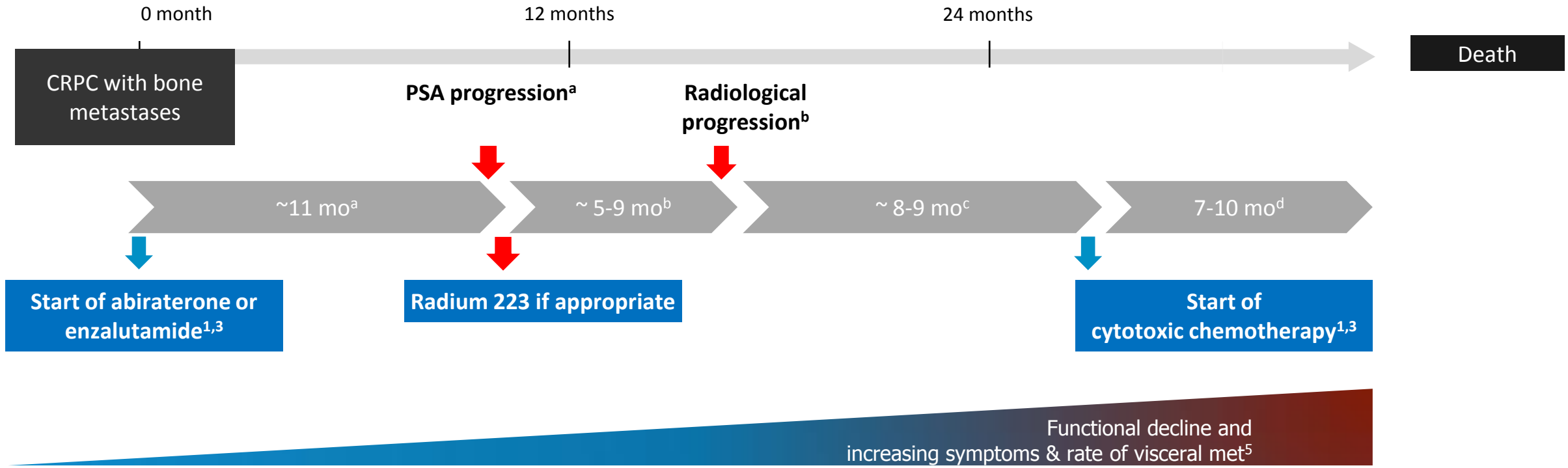

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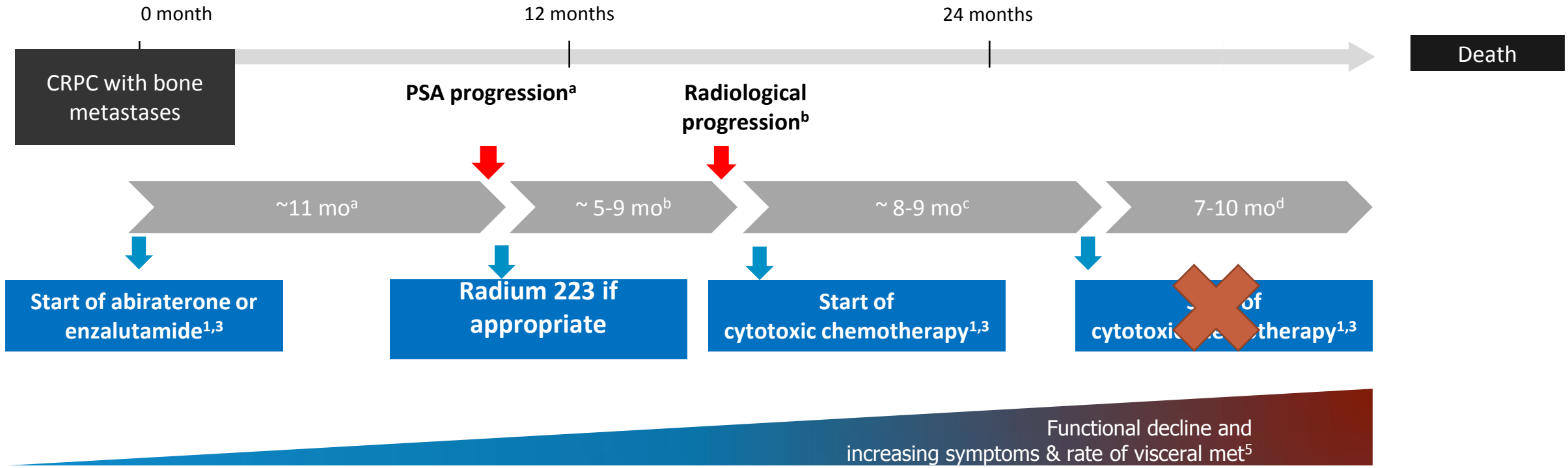

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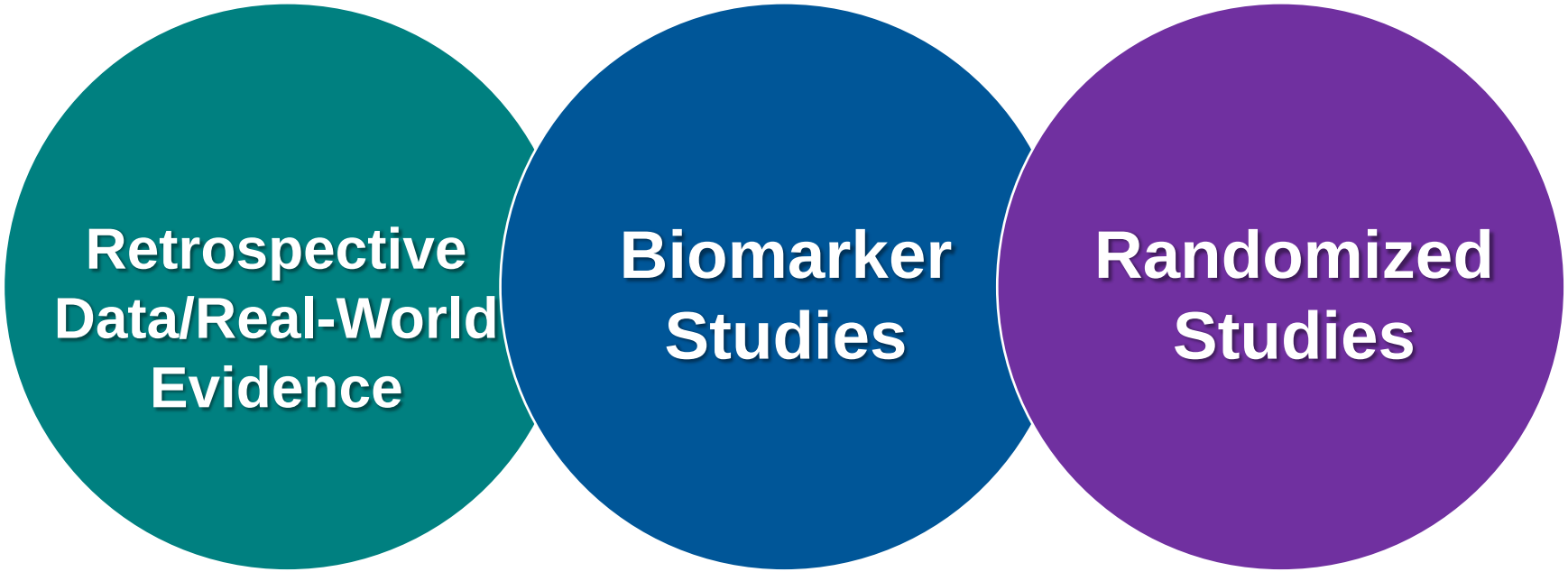
Evidence to Help Determine Optimal Sequence

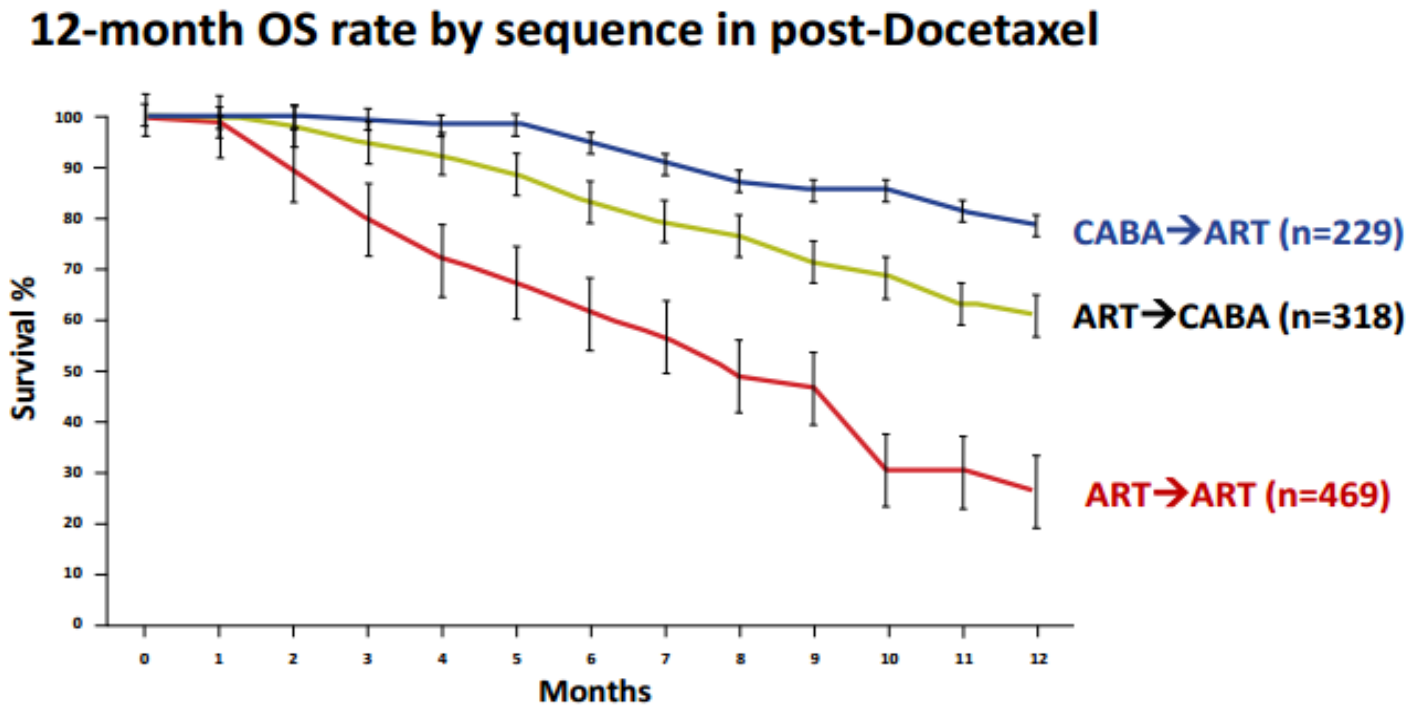


…until results of a randomized trial answering the question are available…

Evidence to Help Determine Optimal Sequence

Is There an Optimal Sequence of Life-Extending Therapies Post-Docetaxel?

Systematic Review of 13 Published Retrospective Studies in mCRPC (n=1016)



Poor outcome when ART are prescribed in sequence

ART: Androgen receptor targeted agents; CABA: cabazitaxel
Mayne F et al. Crit Rev Hematol Oncol 2015; 96: 498-506

2 chemotherapy and 1 ART seem to give better overall survival than

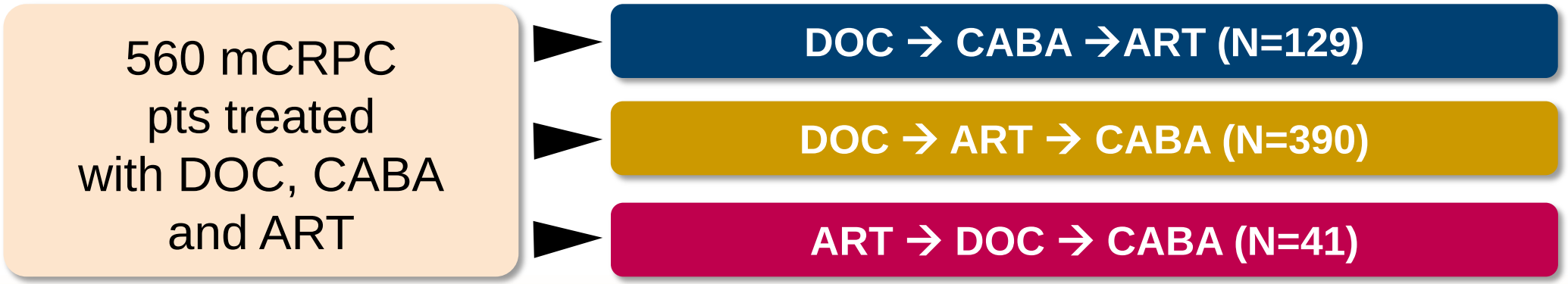
2 ART and 1 chemotherapy

…..despite this majority of MCRPC cases get maximum of 1 chemotherapy

ART=androgen receptor therapy; CABA=cabazibaxel; mCRPC=metastatic castrate-resistant prostate cancer.

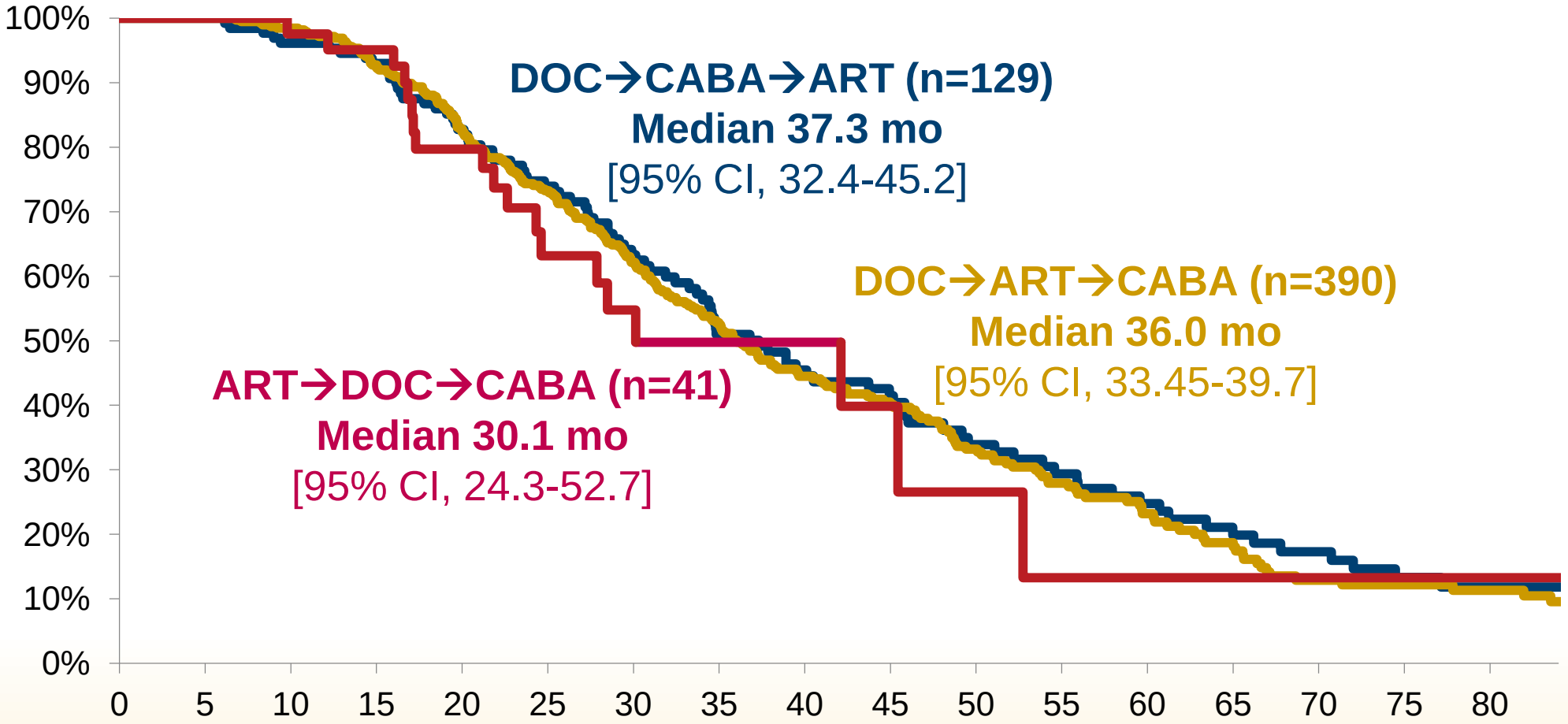
CATS International Database

- Retrospective analysis of 560 consecutive patients treated with DOC, CABA and one ART in 31 centers in 7 countries (France, Austria, Greece, Italy, Israel, Spain, UK)



Angelergues A et al. *Ann Oncol*. 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS: OS from First Life-Extending Therapy Initiation by Sequence (n=560)



Angelergues A et al. *Ann Oncol*. 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS: Conclusions and Considerations

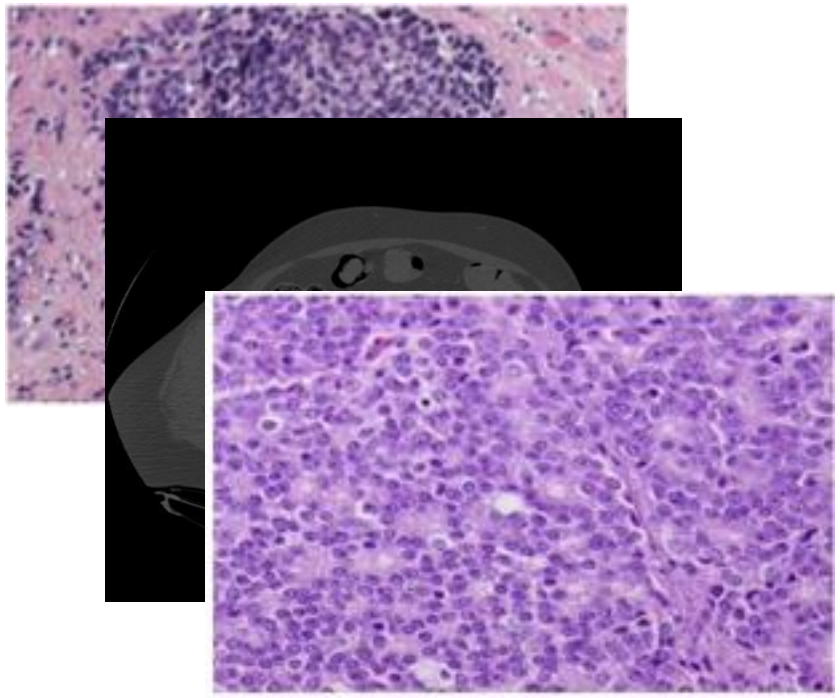
- Retrospective analysis
- No significant difference in OS between the 3 sequences
- Limitations: (1) patients were ‘fit’ enough to receive 3 life-extending therapies; (2) ART→DOC→CABA arm underpowered & may reflect patients progressing rapidly with novel ART

Angelergues A et al. *Ann Oncol*. 2016;27 (suppl 6):abstract 744P (poster presentation)

Is There an Optimal Sequence of Therapies for Metastatic Castration Resistant Prostate Cancer?

- Retrospective registries suggest that OS increases with the number of life-extending therapies
  - Best outcome with 3 therapies (DOC, CABA and an AR-targeted agent)
  - Worse outcome with 2 AR-targeted agents in sequence
- More biomarker data are required
- Randomized prospective trials needed to confirm these data
- The window of opportunity for chemotherapy should not be missed

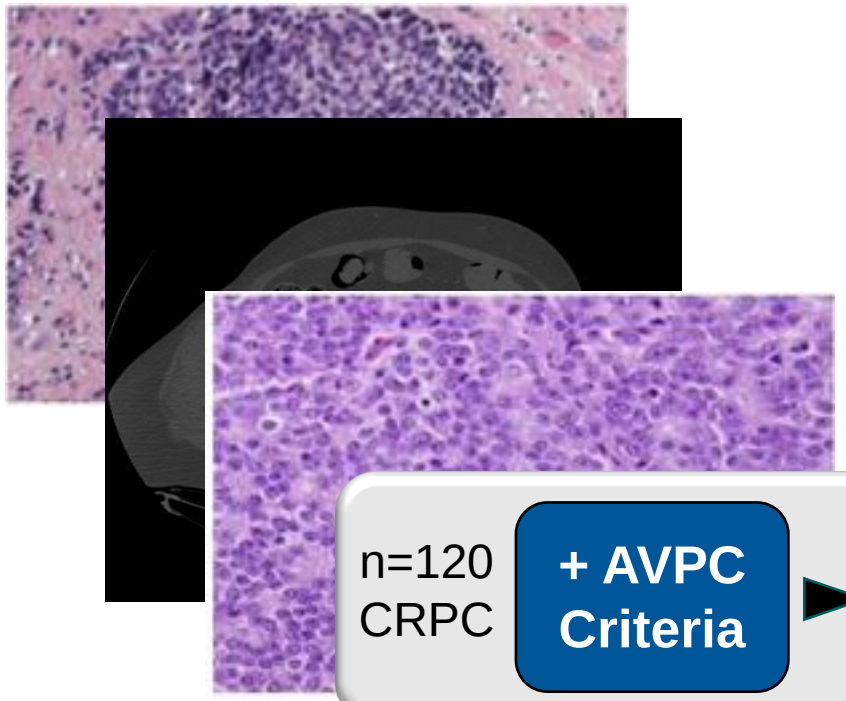
Aggressive Variant Prostate Cancers (AVPC):
Shared Clinical Features With Small Cell Prostate Carcinomas



AVPC Criteria:

1) Small cell prostate carcinoma
2) Visceral metastases only
3) Lytic bone metastases
4) Bulky nodes or prostate mass
5) Low PSA relative to volume
6) NE markers & serum CEA or LDH
7) *Early castration-resistance*

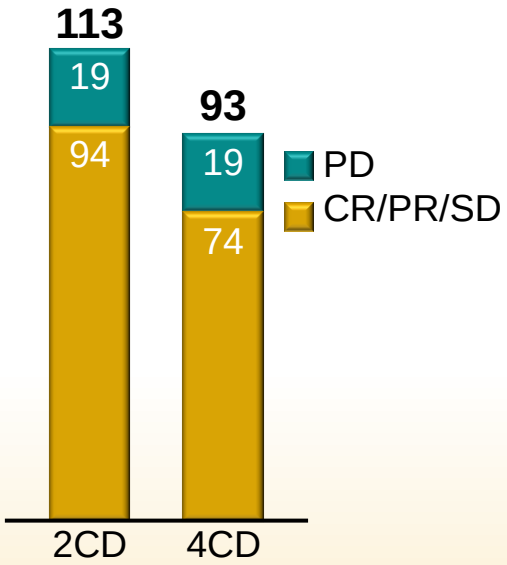
Aggressive Variant Prostate Cancers (AVPC):
*Shared **Chemotherapy Sensitivity** with the Small Cell Prostate Carcinomas*



n=120 CRPC → **+ AVPC Criteria** → Docetaxel + Carboplatin → Etoposide + Cisplatin

AVPC Criteria:
1) Small cell prostate carcinoma; 2) Visceral metastases only;
3) Lytic bone metastases; 4) Bulky nodes or prostate mass;
5) Low PSA relative to volume; 6) NE markers *&* serum CEA or LDH;
7) Early castration-resistance.

Response to 1st-Line Carboplatin and Docetaxel
(Number of Patients)



CEA, carcinoembryonic antigen; CR, complete response; LDH, lactate dehydrogenase; NE, neuroendocrine; PD, progressive disease; PR, partial response; SD, stable disease.

Aparicio AM et al. *Clin Cancer Res.* 2013;19(13):3621-30.

The 'Laws' of Sequencing: My Adaptation of Newton's Laws

- Every selection has a reason
- 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!

Philosophical approach

- Would you give the potentially less toxic agent first ?
- Would you give the potentially more toxic agent first ?

Caution: To stimulate discussion only!

The ‘Concern Factors’ With Chemotherapy

- Impact on Quality of Life
- Impact on Survival
- Elderly Patient
- Patient acceptance

The 'Concern Factor' With Chemotherapy: QOL

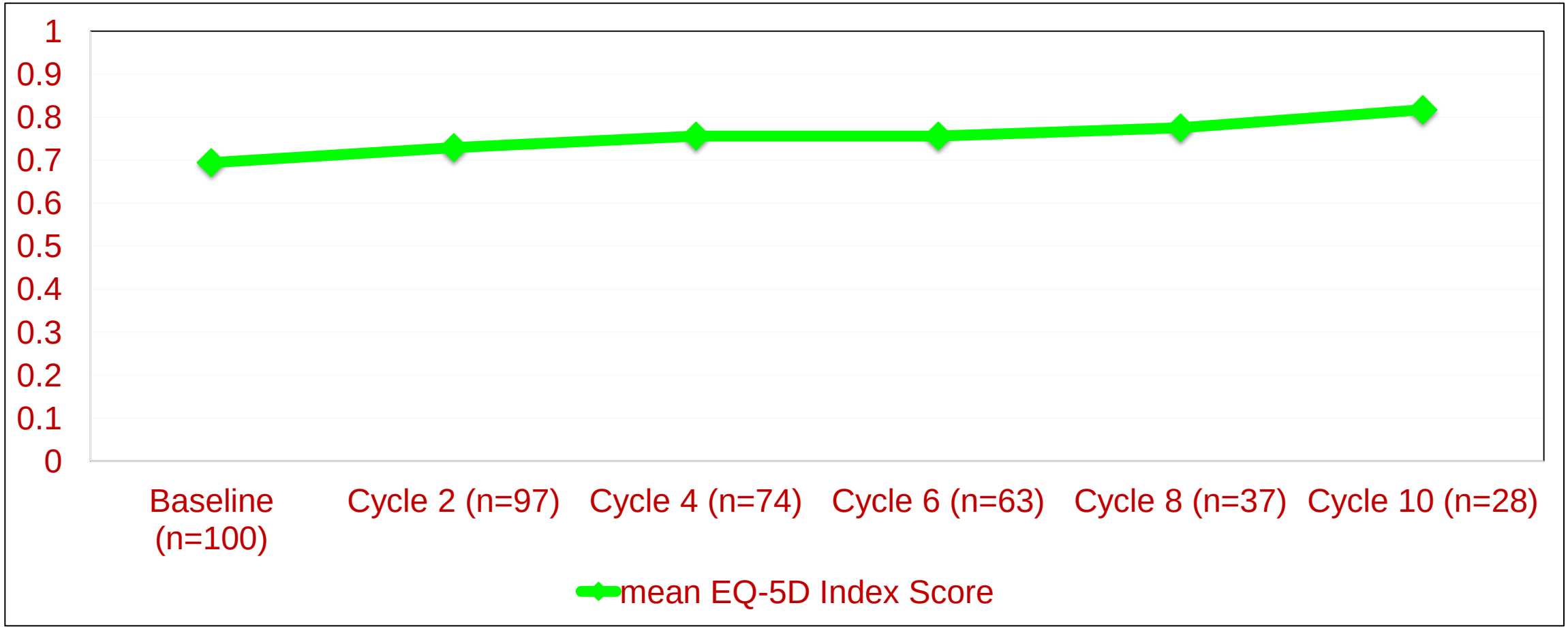
- Impact on Quality of Life

- Pain control improved in comparison to Mitoxantrone
  - In MCRPC – 1st line chemotherapy with Docetaxel (TAX327 study)
  - In MCRPC- post-docetaxel chemotherapy with Cabazitaxel (TROPIC study)

- QOL improved with chemotherapy:
  - In MHSPC by Docetaxel (CHAARTED study)
  - In MCRPC – 1st line Docetaxel chemotherapy (TAX327 study)
  - In MCRPC- 2nd line post-docetaxel Cabazitaxel chemotherapy (Global EAP including UK EAP)

MCRPC=metastatic castrate-resistant prostate cancer; MHSPC=metastatic hormone sensitive prostate cancer; RCT=randomized clinical trial.

QOL Data on Cabazitaxel in MCRPC: UK EAP Study



Bahl A et al. BJU Int. 2015;116:880-7.

The 'Concern Factor' With Chemotherapy: Impact on Survival

- Overall Survival improved in Phase III RCT:
  - In MHSPC- CHAARTED and STAMPEDE
  - In MCRPC- 1st line chemotherapy with Docetaxel (TAX327 and SWOG trials)
  - In MCRPC- post docetaxel 2nd line Cabazitaxel chemotherapy (TROPIC trial)

MCRPC=metastatic castrate-resistant prostate cancer; MHSPC=metastatic hormone sensitive prostate cancer; RCT=randomized clinical trial.

The Concern Factor With Chemotherapy: Elderly Patient

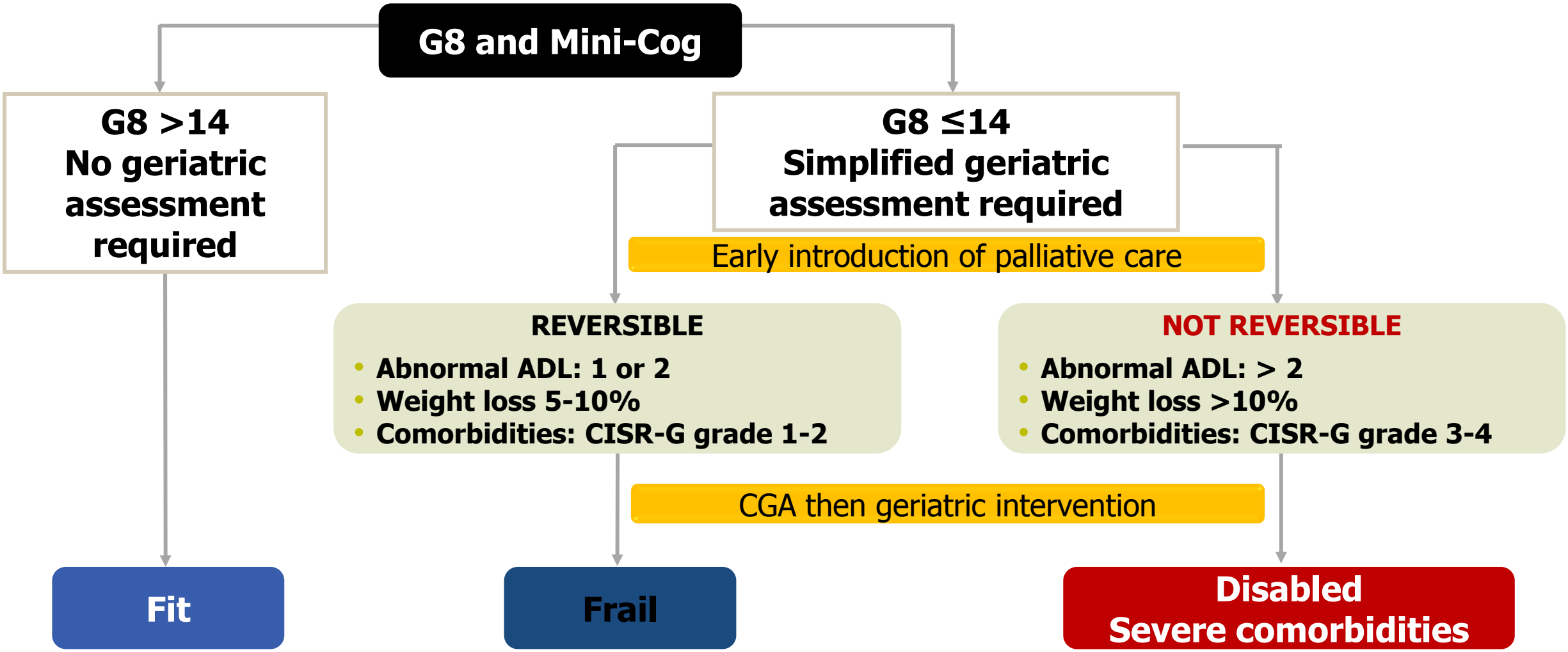
- Patient selection is critical
- Patient education is critical
- Screening with G8 and mini-COG or equivalent validated tool

G8 Screening Tool

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: > 85
		1: 80-85
		2: < 80
	Total score	0-17

Droz JP et al. Lancet Oncol 2014;15:e404-14

Health status evaluation



CGA: complete geriatric assessment

Droz JP et al. Eur Urol 2017;doi: 10.1016/j.eururo.2016.12.025

The 'Concern Factor' With Chemotherapy: Patient Acceptance

- Important to establish the goals for long term
- Remember it is NOT ***'one OR the other'*** it is ***'one AFTER the other'***
- It appears that earlier use of chemotherapy will be potentially advantageous
  - Also likely to be better tolerated
  - Two basic questions to consider
    - 1. Is the patient likely to die from his Metastatic Prostate Cancer?
    - 2. Is the patient fit and willing to have chemotherapy?

My View:
If the answer to both these questions is 'YES' then preferable to use chemotherapy earlier rather than as a last resort

The Challenge For The Uro-Oncology Teams in mCRPC

- **To identify mCRPC patients with poor response to enzalutamide or abiraterone**
  … and to offer them first-line chemotherapy
- **To identify disease progression on first-line treatment at an early time point**
  … and to offer subsequent therapy before performance status deteriorates
- **To pro-actively manage adverse events of new treatment options**
  … to optimize treatment outcomes (QoL, survival)
- **Multidisciplinary care a key to success!!**

mCRPC=metastatic castrate-resistant prostate cancer; QoL=quality of life.

- *My Personal View and Hope…*

‘All Eligible Patients should avail the benefits of all proven and effective treatments……..To MAXIMISE SURVIVAL WITH PRESERVED/IMPROVED QOL’

THANK YOU