Optimal strategies for patients progressing on AR-pathway inhibitors

Amit Bahl
Consultant Oncologist
Bristol Cancer Institute, University Hospitals Bristol
Clinical Director, Spire Oncology Centre
UK

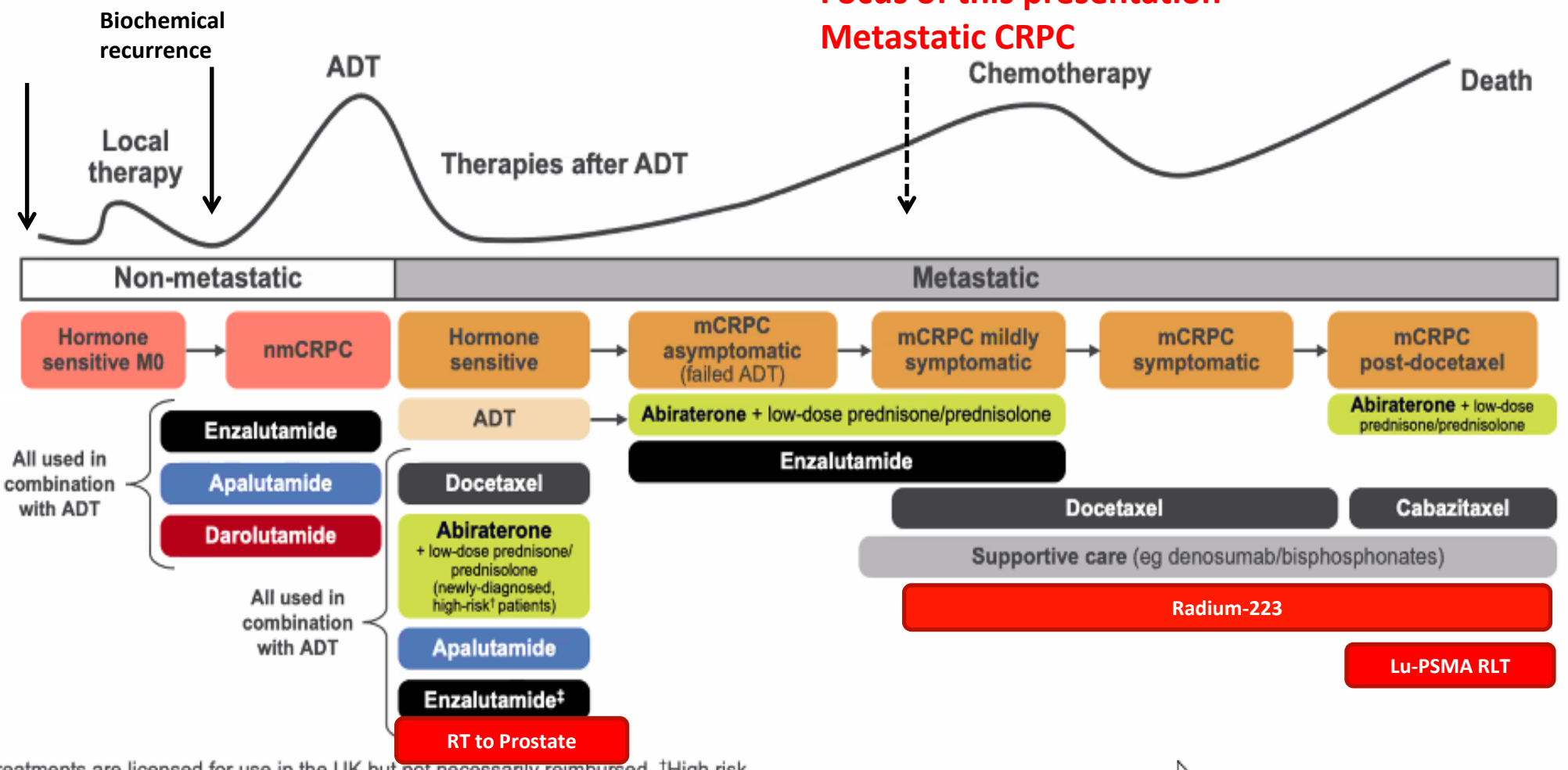
NHS
University Hospitals Bristol
NHS Foundation Trust

Disclosure

- Advisory boards and honoraria
  - Amgen, Astellas, Bayer, Ipsen, Janssen, MSD, Novartis, Sanofi Genzyme
- Research grants (To Instituion)
  - Sanofi Genzyme, Bayer, Janssen
- Meeting sponsorship
  - Astellas, Bayer, Ipsen, Janssen, MSD, Roche, Sanofi Genzyme

Current Management of Prostate Cancer*

Focus of this presentation
Metastatic CRPC



* These treatments are licensed for use in the UK but not necessarily reimbursed. †High risk defined as patients with at least two of following: a Gleason score of ≥8; ≥3 bone lesions; the presence of measurable visceral metastasis. ‡ **Enzalutamide is not licensed for mHSPC in the UK. Interim access has been approved during COVID period in England and Wales.**
ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Merseburger AS, et al. Onco Targets Ther. 2016;9:7263–74.

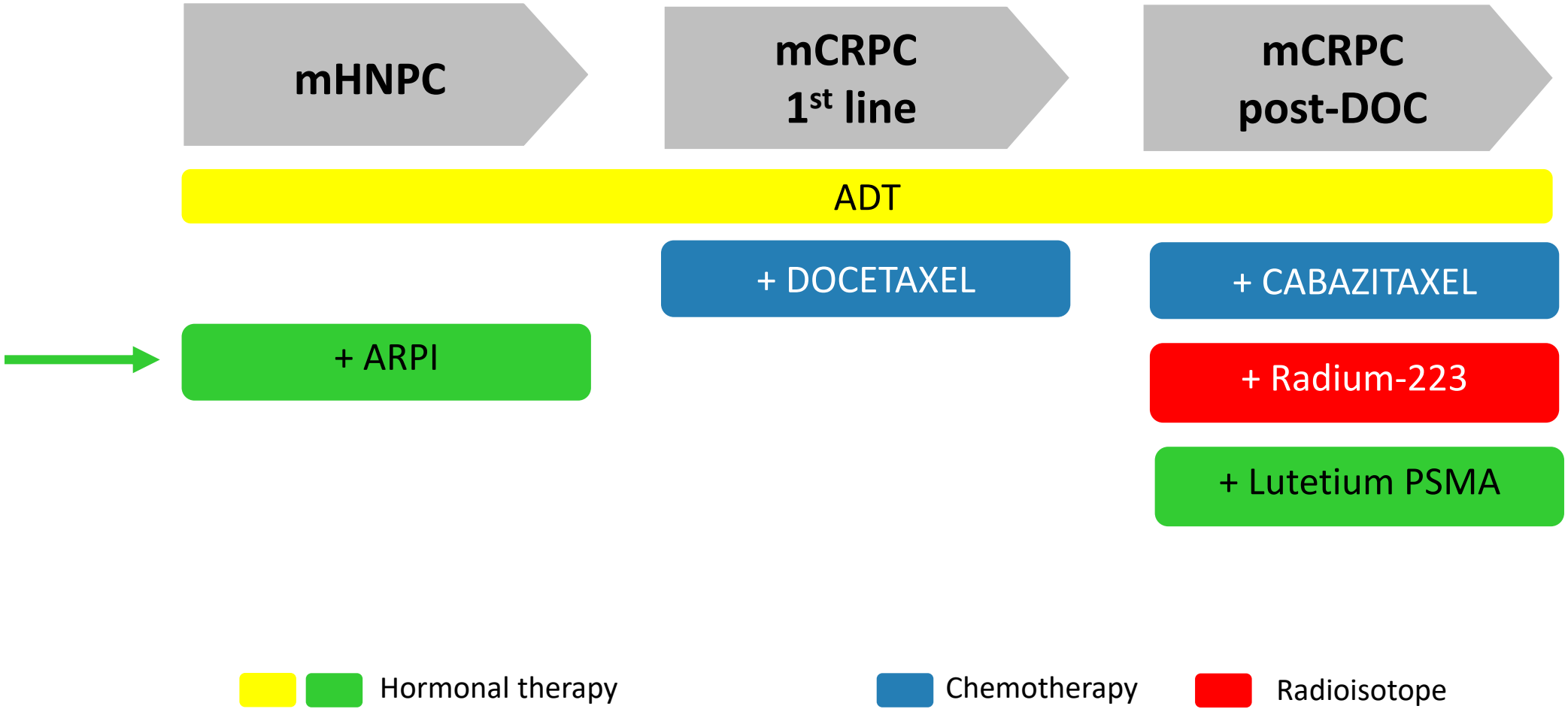
TREATMENT OPTIONS FOR mHSPC

2015	2017	2019	2021	2022
DOCETAXEL	ABIRATERONE	ENZALUTAMIDE	DOCETAXEL PLUS ABIRATERONE	DOCETAXEL PLUS DAROLUTAMIDE
CHAARTED STAMPEDE-C	LATITUDE STAMPEDE-G	ENZAMET ARCHES	PEACE-1	ARASENS
		APALUTAMIDE TITAN		

+IO? (pembrolizumab?)
+PARP inhibitor? (BRCAmut)
+^{177}Lu-PSMA-617

Kyriakopoulos CE et al. J Clin Oncol. 2018 Apr 10;36(11):1080-1087. Clarke NW et al. Annals of Oncology30:1992-2003, 2019. Fizazi K et al. Lancet Oncol 2019 May; 20(5):686-700. James N et al. 2020 ESMO. Davis IA et al. N Engl J Med 2019;381:121-131. Armstrong AJ et al. Annal Oncol 2021;32(5):S1283-S1346, LBA25. Chi KN et al. J Clin Oncol. 2021 39:2294-2303.

Management of Metastatic PCa
Current Options Available



PCa, prostate cancer; mHNPC, metastatic hormone-naive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; ADT: androgen deprivation therapy
DOC: docetaxel; CABA: cabazitaxel; ARPI: Androgen Receptor Pathway Inhibitors
EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2022 (http://uroweb.org)

Changing Paradigm of MHSPC Treatment Results in 3 New Scenarios and 1 Old Scenario

- Progression post upfront Docetaxel
- Progression post upfront ARTA
- Progression post upfront Docetaxel+ARTA
- Progression post ADT

Progression Post Upfront ARPI

- No robust data available
- It is likely the treatment paradigm will involve earlier use of DOC for mCRPC and subsequent post-DOC therapies
  - Potentially earlier use of DOC-CABA
  - Further ART would probably not be meaningfully beneficial[1]
  - Radium-223 would probably have the same role as now- bone only metastatic disease
  - Lutetium PSMA has license in Taxane ineligible patients but no evidence in this setting

Monitoring Treatment

Monitoring Treatment

- Monitoring in real life practice often is dictated by practical considerations including the radiological modalities available

- Guidelines usually recommend:
  - **Frequency and modality**
    - Clinical: every cycle
    - Biochemical: PSA every 4 weeks
    - **Radiological: every 3 months if other parameters stable, otherwise earlier**

Monitoring Treatment

- **Aim of monitoring**
  - Ensure appropriate switching if not benefitting from current treatment
  - Prevent significant decline in performance status before offering subsequent treatment
- **If the patient is eligible for a subsequent treatment option then monitoring should be done methodically and as per schedule**
- Therefore, aim of monitoring is to ensure that patient is able to have the next treatment if progression confirmed

mCRPC Patient on ARTA (ABI or ENZA)

- Is it important to do radiological monitoring if the patient is symptomatically doing well and PSA is controlled on ARTA?

YES

Prostate Cancer and Prostatic Diseases (2017) 00, 1–7
www.nature.com/pcan

ORIGINAL ARTICLE

Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce[1], JJ Alumkal[2], A Armstrong[3], CS Higano[4], P Iversen[5], CN Sternberg[6], D Rathkopf[7], Y Loriot[8], J de Bono[9], B Tombal[10], S Abhyankar[11,15], P Lin[12], A Krivoshik[13], D Phung[14] and TM Beer[2]

BACKGROUND: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested.

METHODS: Chemotherapy-naive asymptomatic or mildly symptomatic men ($n=872$) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed *post hoc* for rising versus nonrising PSA (empirically defined as >1.05 vs $\leqslant 1.05$ times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups.

RESULTS: Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26–2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar.

CONCLUSIONS: Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results demonstrate that disease progression on enzalutamide can occur without rising PSA levels. Therefore, a disease monitoring strategy that includes imaging not entirely reliant on serial serum PSA measurement may more accurately identify disease progression.

Prostate Cancer and Prostatic Diseases advance online publication, 24 January 2017; doi:10.1038/pcan.2016.71

Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients

Bryce AH et al. Prostate Cancer Prostatic Dis. 2017;20:221-7.

Switching Treatment

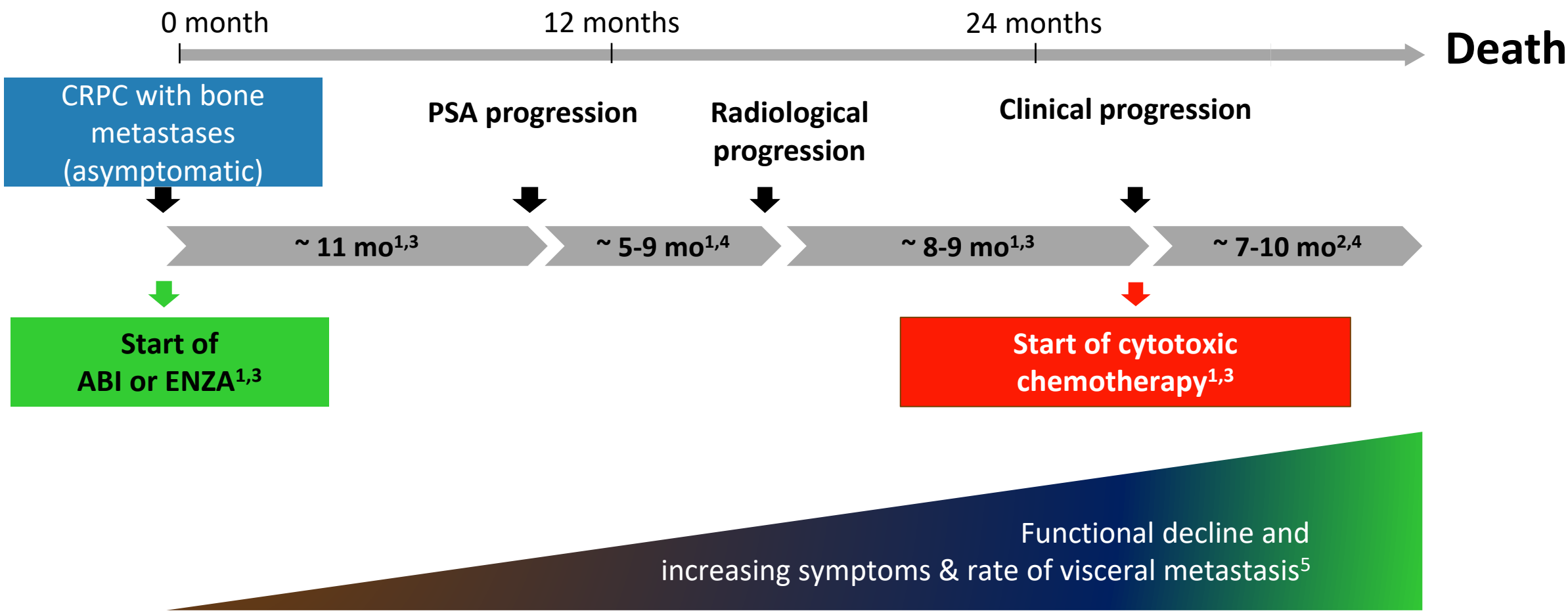
When to Switch Treatment?

- Generally accepted view is that 2 out of the following 3 factors should be met[1]:
  - PSA progression
  - Radiological progression
  - Symptomatic progression

- However, unequivocal radiological progression which is clinically meaningful on its own warrants change in therapy

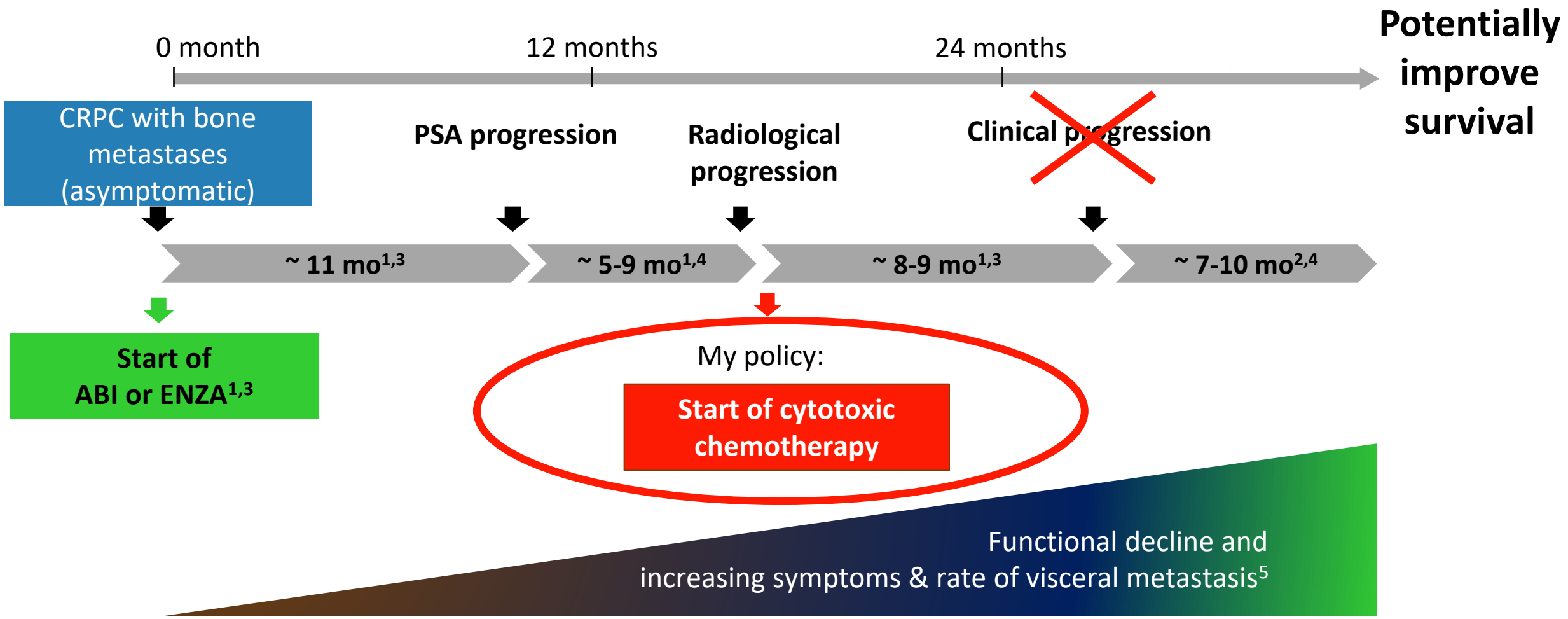
1. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018. (http://uroweb.org).

A Closer Look at Time to Events in COU-AA-302 and PREVAIL Studies



1. Ryan CJ et al. N Engl J Med. 2013;368:138-48; 2. Ryan CJ et al. Lancet Oncol. 2015;16:152-60; 3. Beer TM et al. N Engl J Med. 2014;371:424-33;
4. Beer TM et al. Eur Urol. 2017;71:151-4; 5. Pezaro CJ et al. Eur Urol. 2014;65:270-3.

A Closer Look at Time to Events in COU-AA-302 and PREVAIL Studies



1. Ryan CJ et al. N Engl J Med. 2013;368:138-48; 2. Ryan CJ et al. Lancet Oncol. 2015;16:152-60; 3. Beer TM et al. N Engl J Med. 2014;371:424-33;
4. Beer TM et al. Eur Urol. 2017;71:151-4; 5. Pezaro CJ et al. Eur Urol. 2014;65:270-3.

Switching Treatment Scenarios in mCRPC

- Progression on ART (ABI/ENZA)
- Progression on DOC

Progression on ART in mCRPC: Cross-Resistance Between ART

- Poor response to ENZA if progression on ABI[1]
- Poor response to ABI if progression on ENZA[1-2]

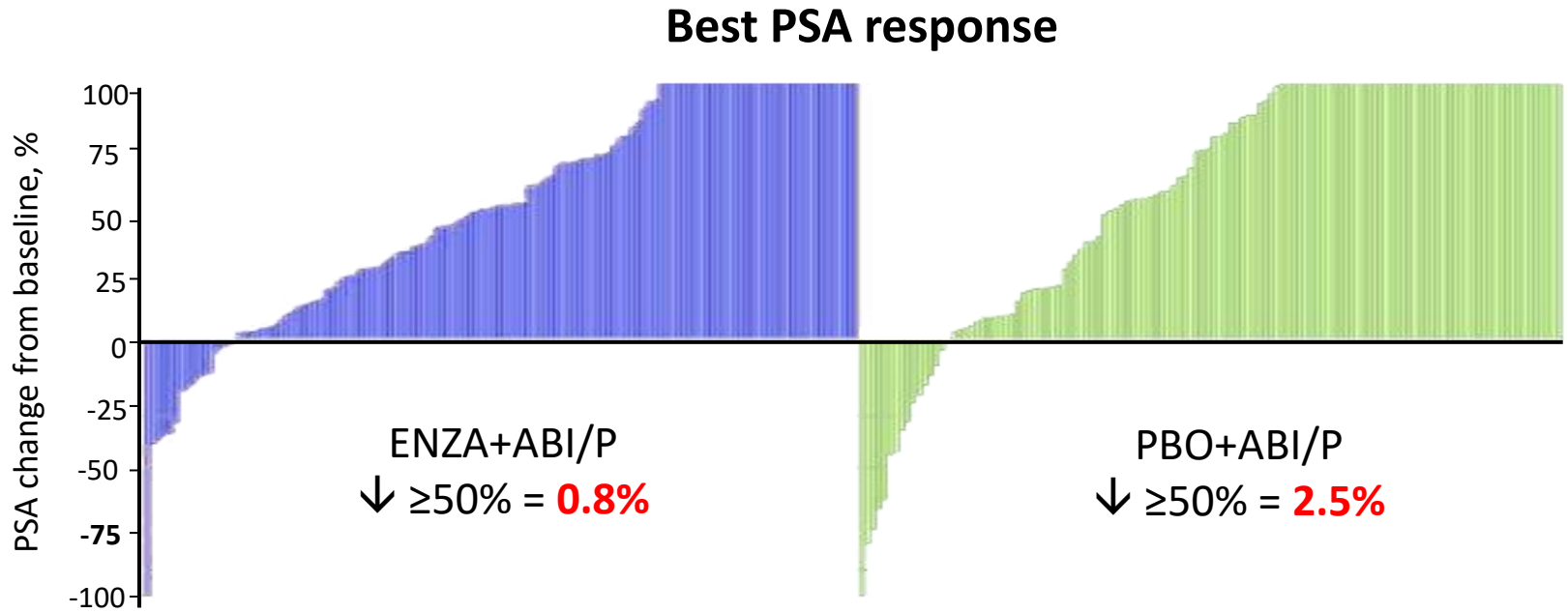
- **NICE (UK) does not permit use of sequential ART if there is progression on first ART[3]**

- Preferred treatment option if patient fit → chemotherapy

1. Expert Opin Pharmacother. 2015;16:473-85; 2. Attard G et al. J Clin Oncol. 2017;35(suppl):abstract 5004 (podium presentation);
3. https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer

Cross-Resistance Between ABI and ENZA

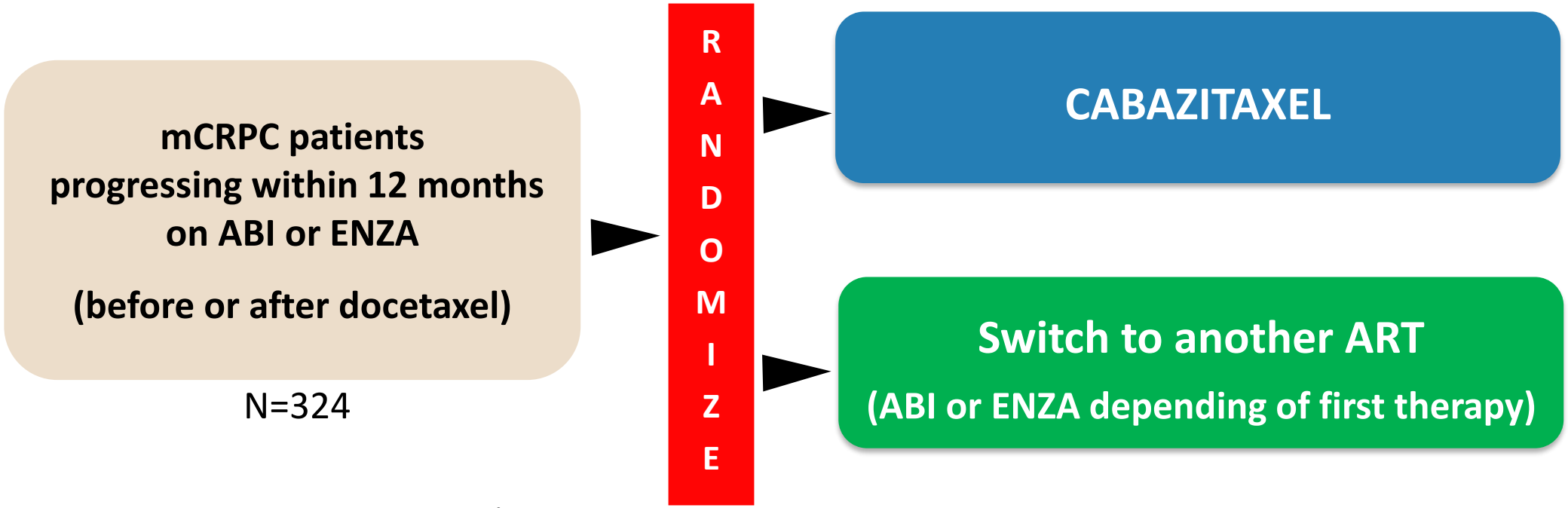
- PLATO – Prospective, phase IV, double-blind, PBO-controlled study in 251 chemo-naïve mCRPC patients with PSA response to ENZA >3 months
- Randomized at PSA progression to ENZA+ABI/P vs PBO+ABI/P
- PFS* (primary endpoint): 5.7 vs 5.6 months, *P*=0.22



**Radiological progression or unequivocal clinical progression; PBO, placebo*

Attard G et al. J Clin Oncol. 2017;35(suppl):abstract 5004 (podium presentation) - NCT01995513.

CARD Study



Stratification factors: ECOG PS (0/1 vs 2), time to progression (≤6 vs 6-12 mos), timing of ART (before vs after DOC)

Primary endpoint: radiographic PFS

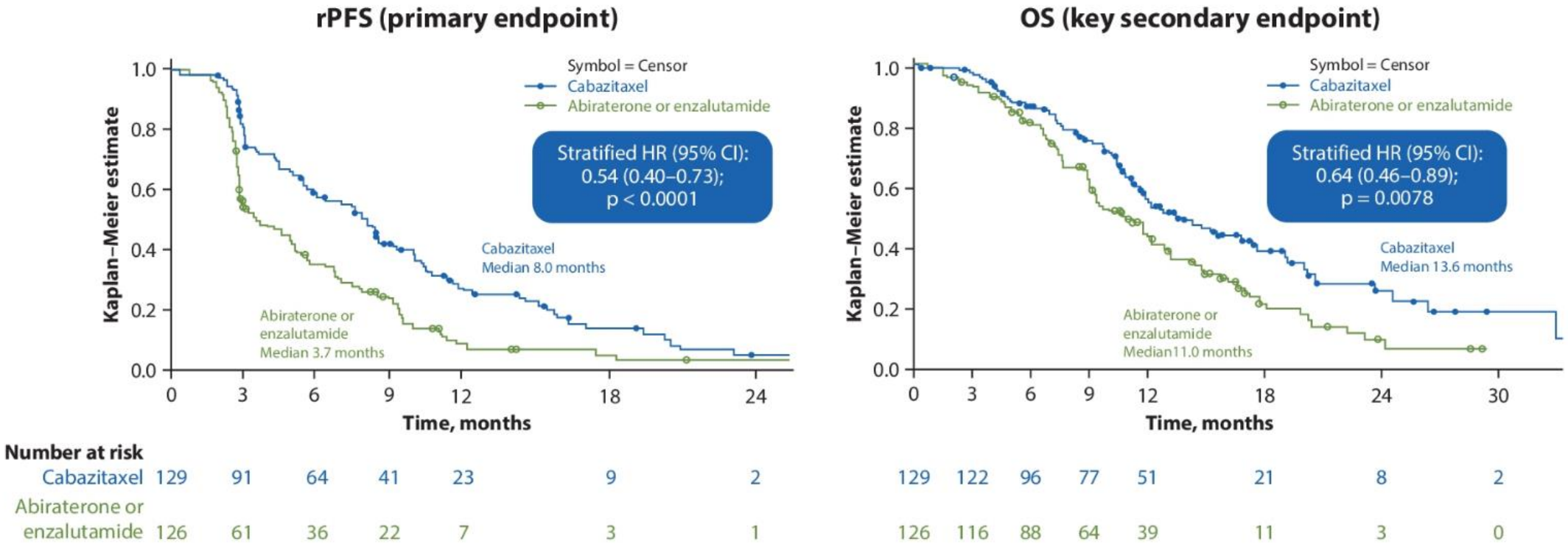
Secondary endpoints: PSA response, ECOG PS, PFS (clinical or radiological), objective tumor response, pain, QoL, time to SSEs, OS, safety biomarkers

Sponsor: Sanofi

QoL, quality of life; SSE, skeletal-related event

NCT02485691. https://clinicaltrials.gov/

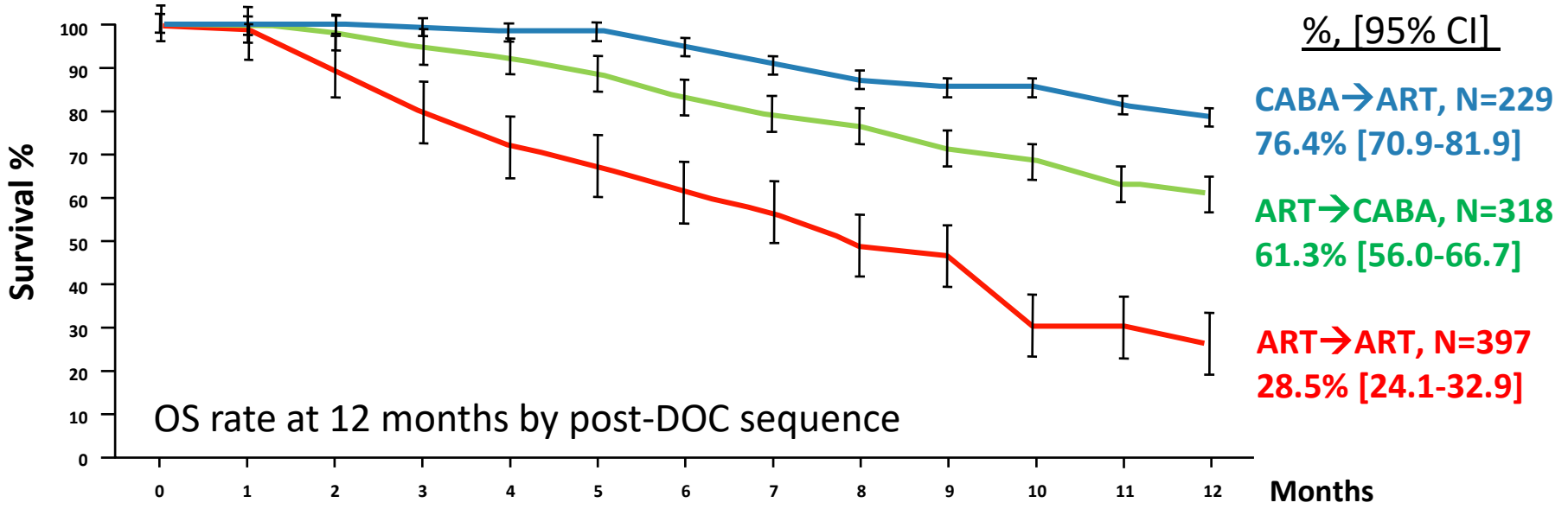
CARD: Cabazitaxel vs. an androgen receptor targeted agent (ART; abiraterone/enzalutamide) in mCRPC



Tombal B, et al. Virtual poster presentation at ASCO 2020; abstract 5569.

Is There an Optimal Treatment Sequence in mCRPC?

Systematic Review of 13 Published Retrospective Studies in mCRPC (N=1,016)



2 taxanes (DOC, CABA) and 1 ART seem to give better OS than 1 taxane (DOC) and 2 ART in sequence

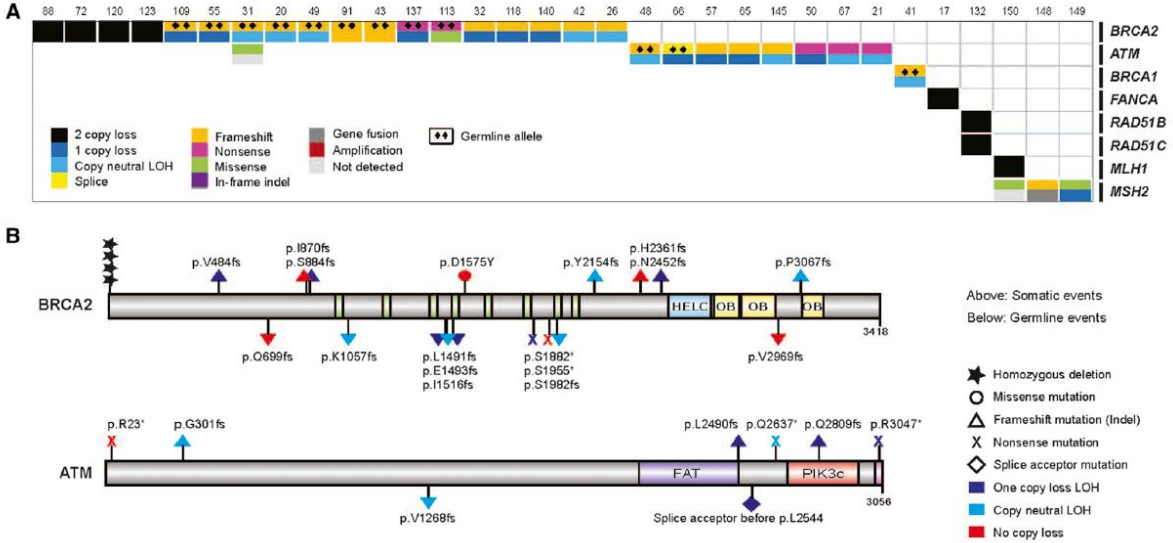
Maines F et al. Crit Rev Hematol Oncol. 2015;96:498-506.

Biomarker Driven Strategy

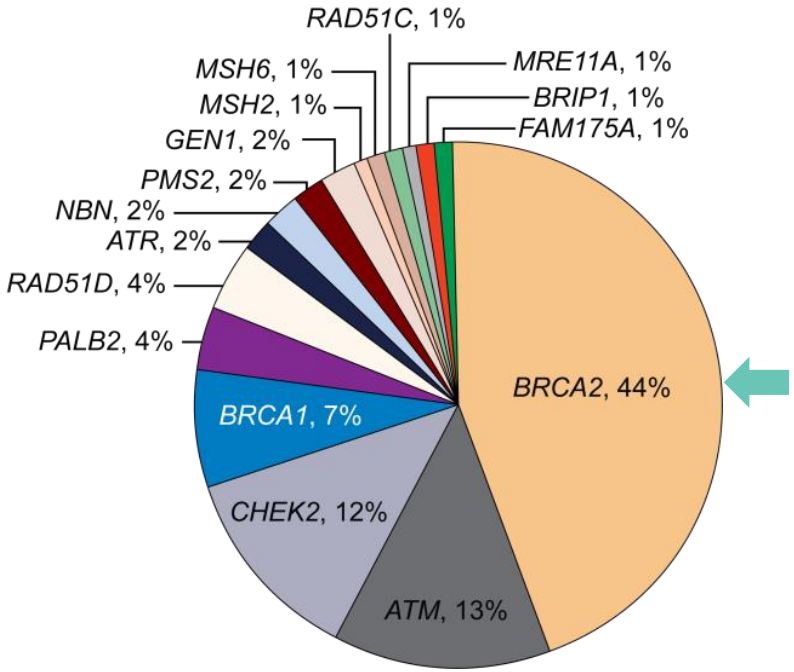
DNA Repair Gene Alterations (Somatic and Germline) Are Common in Metastatic prostate cancer

SOMATIC

- **~23%** of men with mCRPC have DNA repair pathway aberrations
- The incidence of DNA repair alterations is higher in men with **metastatic prostate cancer** than those with **localised disease**



GERMLINE

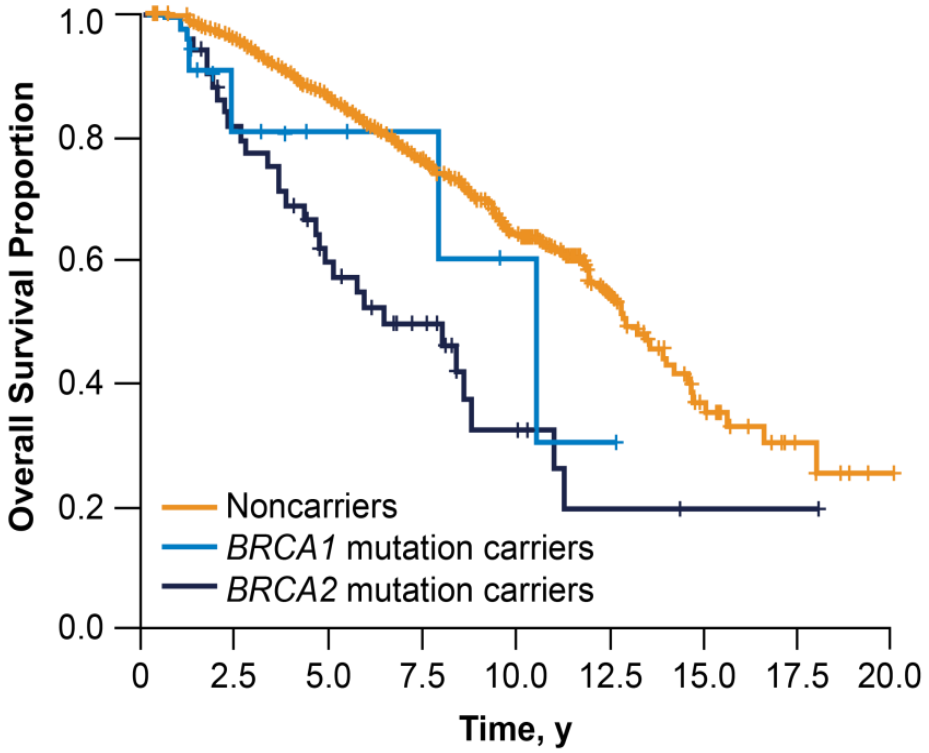


- **~12%** of men with metastatic prostate cancer have germline mutations in one or more of the 16 DNA repair genes

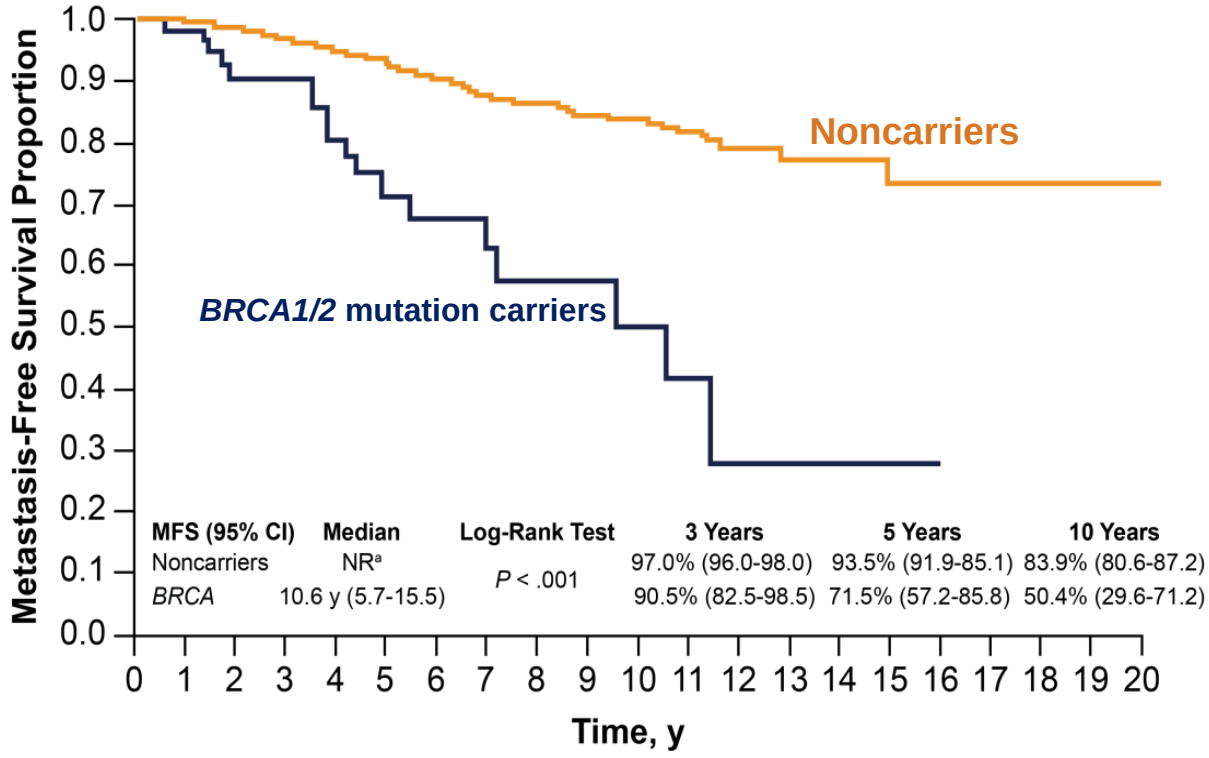
LOH, loss of heterozygosity; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer

1. Robinson D, et al. Cell. 2015;161:1215-28; 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-53; 3. Antonarakis ES, et al. Eur Urol. 2018;74:218-25

BRCA2 Carriers With Prostate Cancer Have Worse Prognosis[1,2]



No. at Risk									
Noncarriers	1,940	1,394	896	467	186	68	22	6	1
BRCA1 mutation carriers	18	12	5	4	2	1	0	0	0
BRCA2 mutation carriers	61	40	28	16	6	3	1	1	0



MFS (95% CI)	Median	Log-Rank Test	3 Years	5 Years	10 Years
Noncarriers	NR[a]	*P* < .001	97.0% (96.0-98.0)	93.5% (91.9-85.1)	83.9% (80.6-87.2)
BRCA	10.6 y (5.7-15.5)		90.5% (82.5-98.5)	71.5% (57.2-85.8)	50.4% (29.6-71.2)

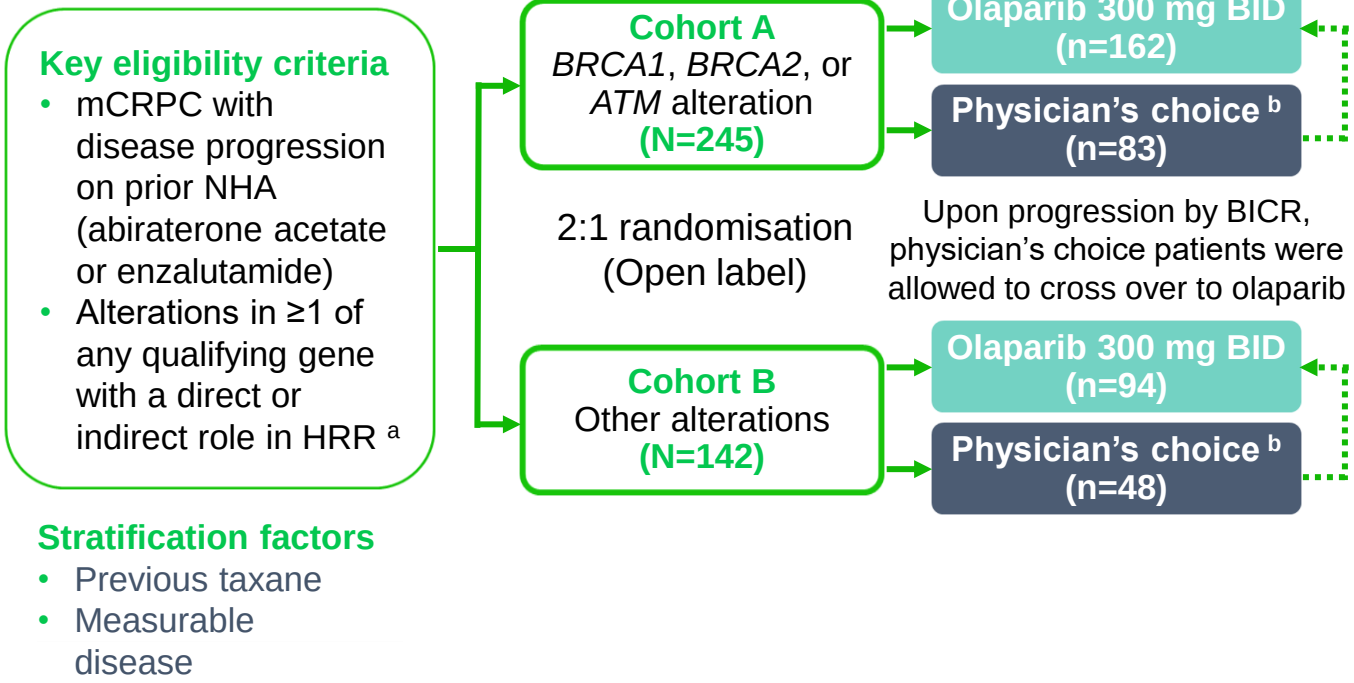
No. at Risk	Baseline	3 years	5 years	8 years	10 years	12 years	15 years	20 years
Noncarriers	1,235	865	646	285	140	57	18	1
BRCA	67	39	20	12	7	2	1	0

[a] Median survival not reached after a median of 64 months of follow-up

BRCA1/2, breast cancer type 1/2 susceptibility protein; CI, confidence interval; MFS, metastasis-free survival; NR, not reached; y, years

1. Castro E, et al. J Clin Oncol. 2013;31:1748-57; 2. Castro E, et al. Eur Urol. 2015;68:186-93

PROfound: phase 3 data with Olaparib in mCRPC



Primary endpoint

rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)

Key secondary endpoints

- rPFS in cohorts A and B (by BICR)
- Confirmed radiographic objective response rate in cohort A (by BICR)
- Time to pain progression in cohort A
- OS in cohort A

[a] An investigational clinical trial assay, based on the FoundationOne® CDx next-generation sequencing test, used to prospectively select patients with alteration of *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* in their tumour tissue

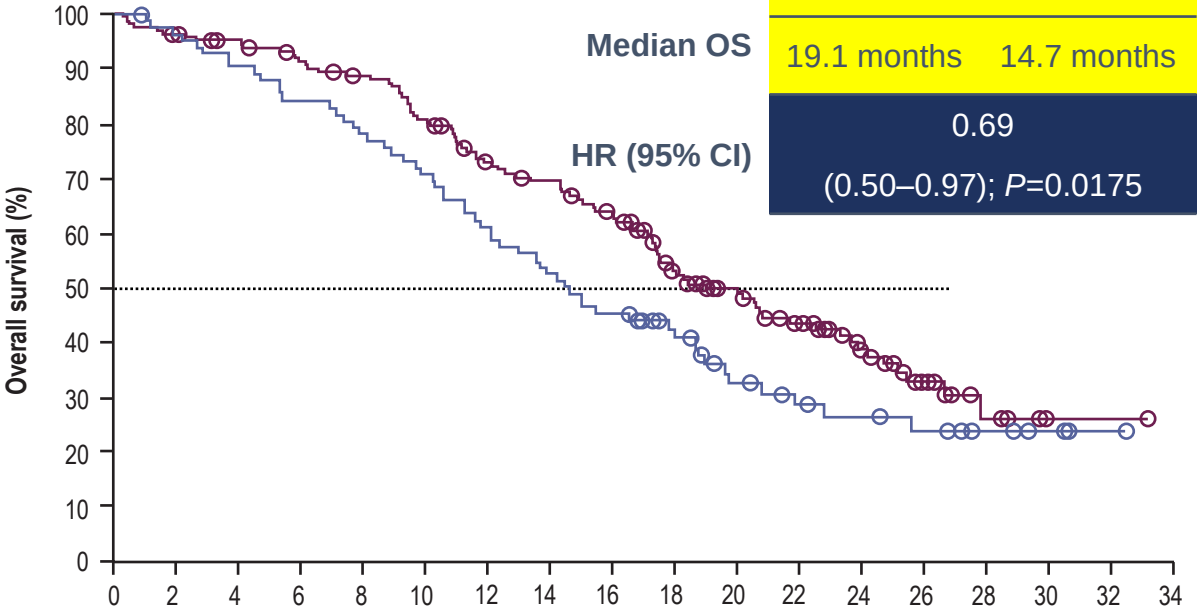
[b] Physician's choice: enzalutamide 160 mg/day, or abiraterone 1,000 mg/day + prednisone 5 mg BID

ATM, ataxia telangiectasia mutated; BICR, blinded independent central review; BID, twice daily; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; QD, once daily

de Bono J, et al. N Engl J Med. 2020;382:2091-2102; Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

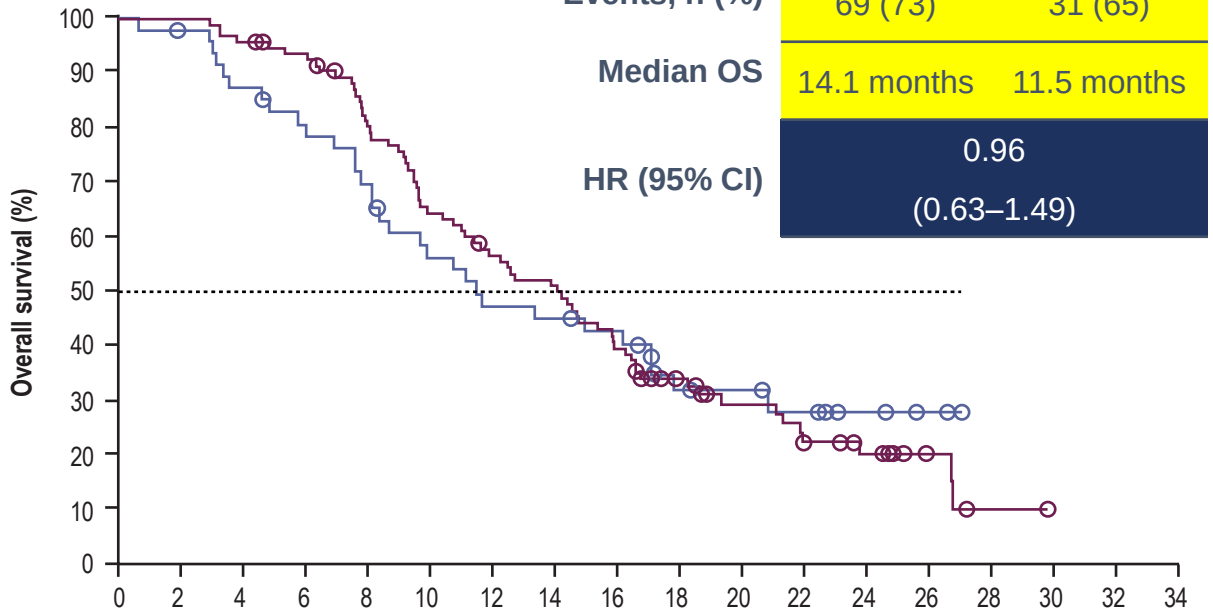
PROfound: Olaparib improved OS in Cohort A (BRCA1, BRCA2 or ATM) and Cohort B (12 genes* other than BRCA1, BRCA2 or ATM) Prespecified ITT (final prespecified analysis)

Cohort A



	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50–0.97); *P*=0.0175	

Cohort B



	Olaparib (N=94)	Control (N=48)
Events, n (%)	69 (73)	31 (65)
Median OS	14.1 months	11.5 months
HR (95% CI)	0.96 (0.63–1.49)	

Median follow-up duration for censored patients was 21.9 months for the olaparib arm and 21.0 months for the control arm.
*Re-censored; conducted using RPSFTM to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy. †Patients receiving olaparib at any time.

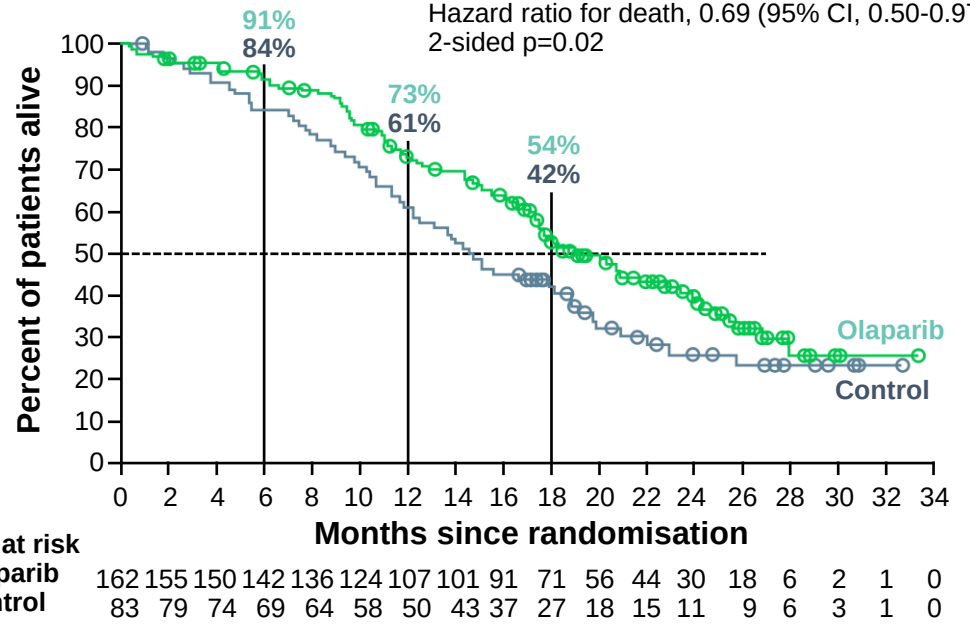
Joaquin Mateo. Oral presentation at ESMO 2020; abstract 610O

PROFOUND: FINAL OVERALL SURVIVAL

OS IN COHORT A (*BRCA1&2, ATM*)

	No. of Deaths/ No. of Patients	Median OS (95% CI), months
Olaparib	91/162	19.1 (17.4-23.4)
Control	57/83	14.7 (11.9-18.8)

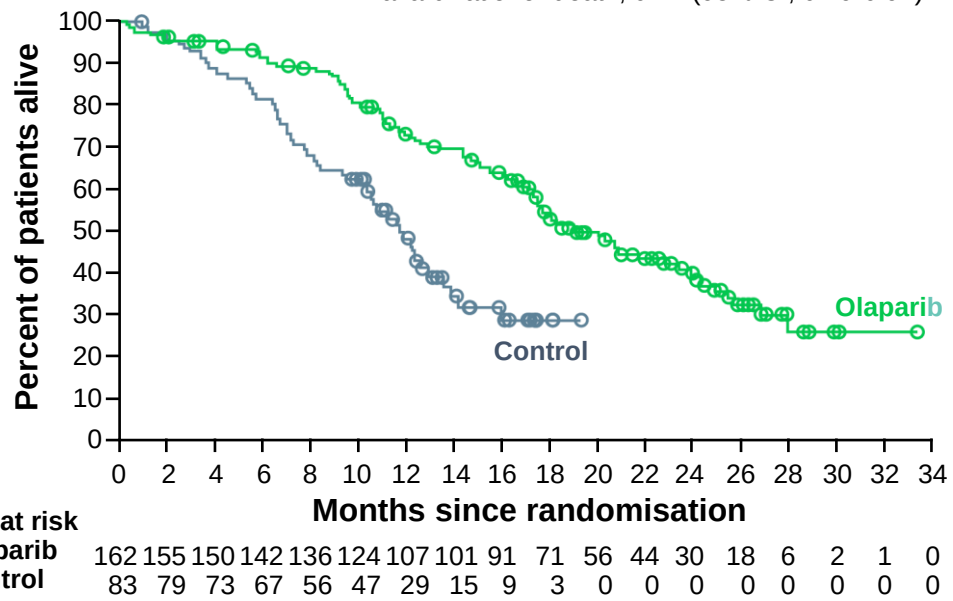
Hazard ratio for death, 0.69 (95% CI, 0.50-0.97)
2-sided p=0.02



No. at risk																	
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

CROSSOVER-ADJUSTED OS IN COHORT A

Patients who crossed over, 67% (56/83)
Hazard ratio for death, 0.42 (95% CI, 0.19-0.91)



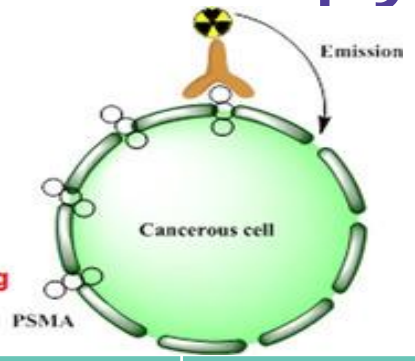
No. at risk																	
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

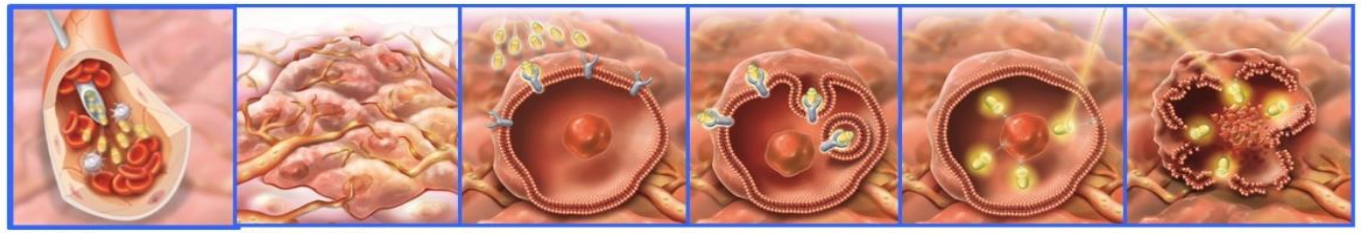
- >80% crossover!

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer type 1/2 susceptibility protein; CI, confidence interval; HR, hazard ratio; OS, overall survival
Hussain M, et al. N Engl J Med. 2020;383(24):2345-57

Radioligand Therapy (RLT)

PSMA–Ligands for Targeted Tumor Imaging





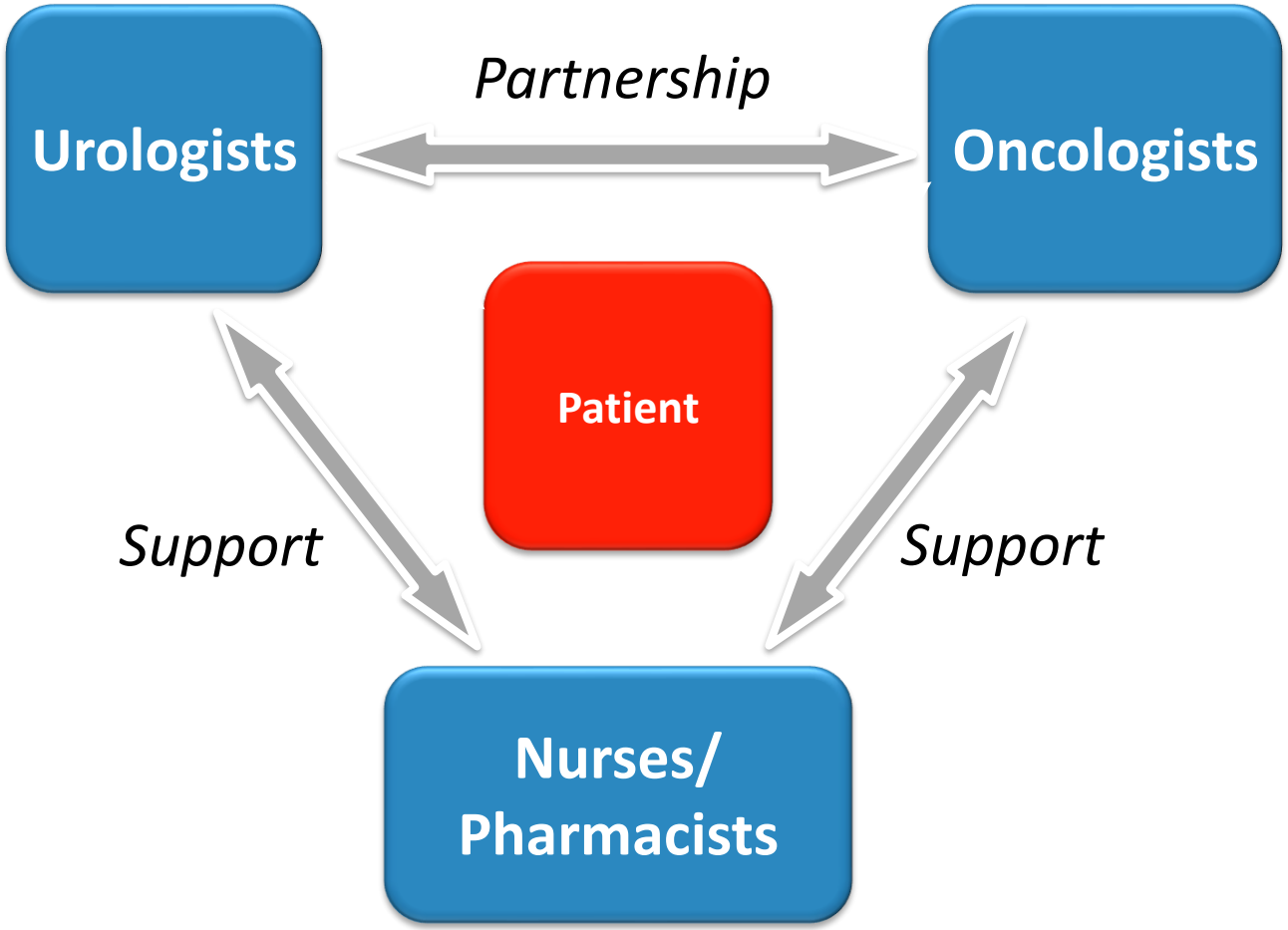
	TheraP	VISION
Trial	Phase 2 RCT (1:1 randomisation)	Phase 3 RCT (2:1 randomisation)
Control Arm	Cabazitaxel	Protocol defined SOC, excl SACT
Primary Endpoint	PSA decline ≥50%	OS, rPFS
^{177}Lu-PSMA-617	8.5GBq (↓0.5GBq) per cycle Up to 6 cycles, guided by SPECT/CT	7.5GBq per cycle Up to 6 cycles: 4 cycles ± 2
Median cycles	5	5
Post therapy SPECT/CT	✓	x
Selection criteria: PSMA	PSMA SUVmax ≥ 20 SUVmax >10 for all measurable lesions	PSMA >Liver
Selection criteria: FDG	FDG+PSMA positive - excluded	FDG not performed
PSA response	66%	46%

Cimadamore et al, Front Oncol 2018, Lowick et al, Radboud university

The Challenge for the Uro-oncologist in mCRPC

- **To identify mCRPC patients with poor response to ENZA or ABI**
  … and to offer them first-line chemotherapy
- **To identify disease progression on 1L therapy 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 (quality of life, survival)
- **Multidisciplinary care a key to success!!**

Patient Management: A Patient-Centered Partnership



My Personal View and Hope

‘All eligible patients should be offered the benefits of all proven and effective treatments to…

MAXIMIZE SURVIVAL WITH PRESERVED/IMPROVED QUALITY OF LIFE’

Thank you