

# Cancer de la Prostate Résistant à la Castration:

## RECOMMANDATIONS

**S.ZAIDI M.OUKKAL**  
**Oncologie Médicale**  
**CHU BENI MESSOUS**



### 2<sup>ème</sup> FORUM DES CANCERS UROLOGIQUES

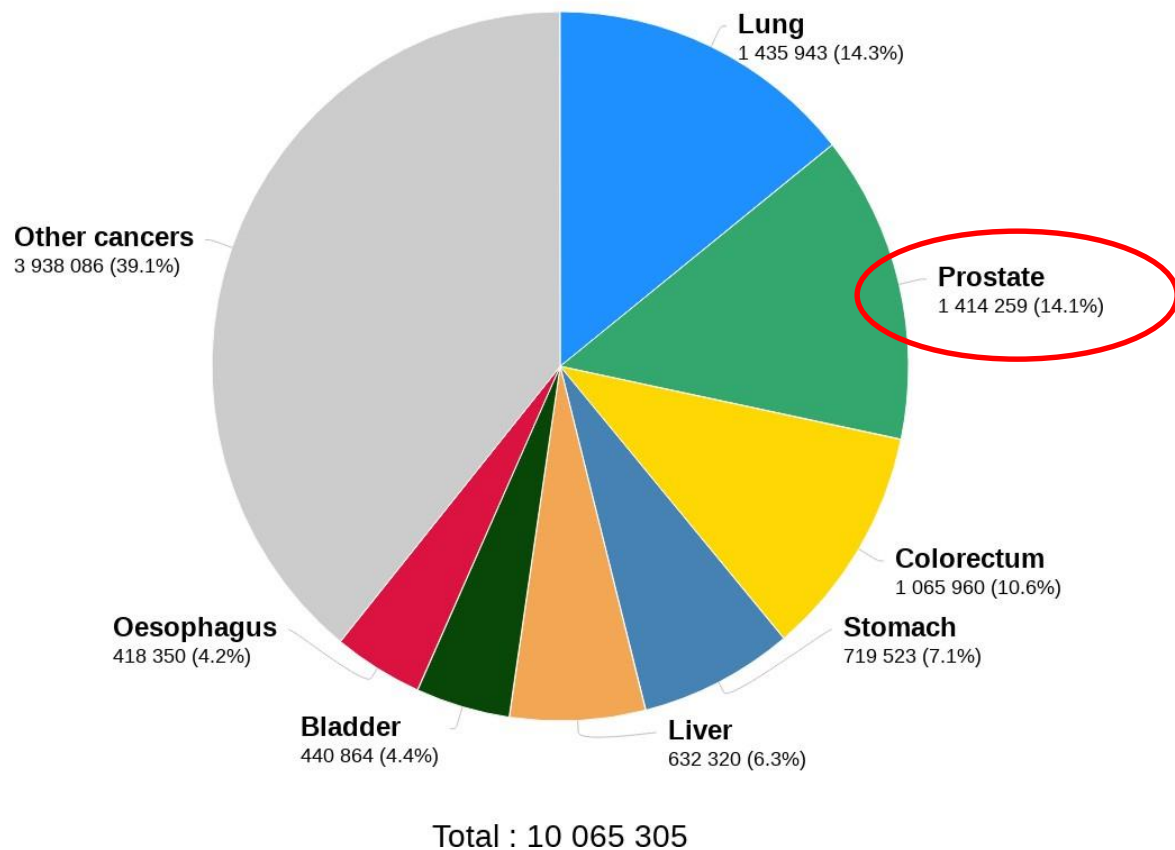
Thèmes :

- Epidémiologies et dépistage
- Diagnostic
- Etudes anatomo-pathologies
- Examen radiologique et bilan d'extension
- Prise en charge thérapeutique

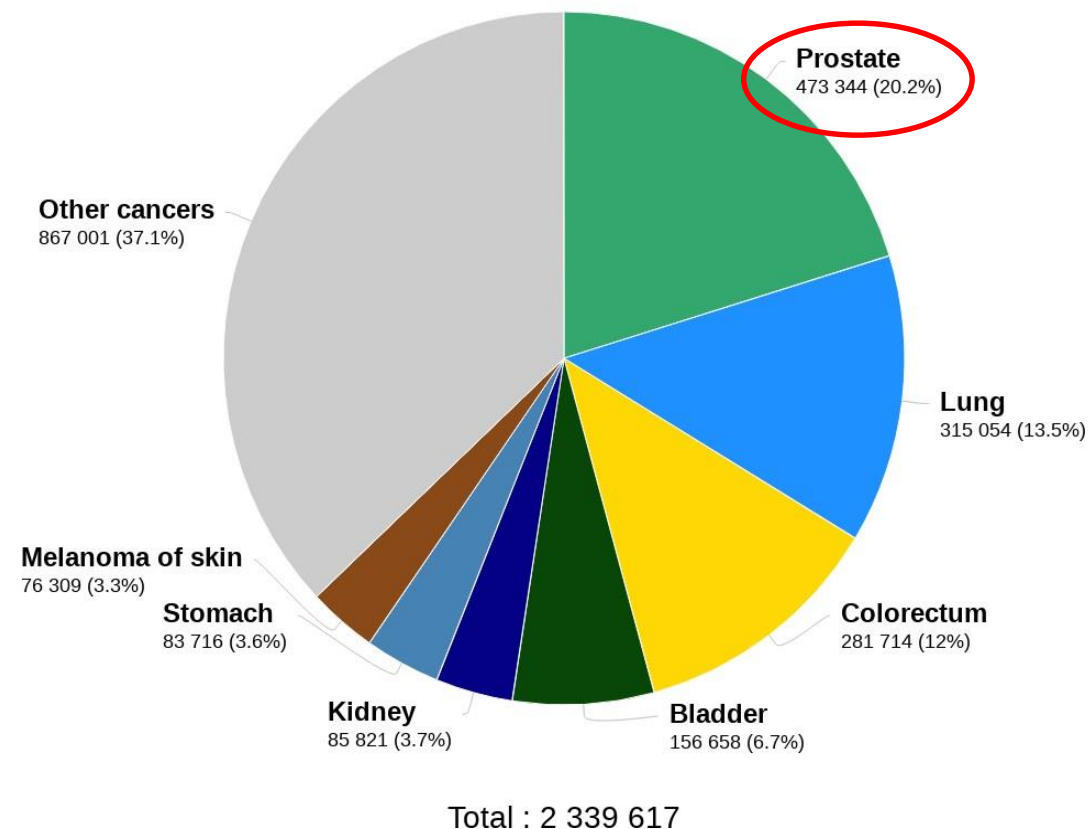
09 et 10 juin 2022, Hôtel Mercure, Alger

# Le Cancer de la Prostate est le 2<sup>ème</sup> cancer le plus fréquent chez l'homme dans le monde

Estimated number of new cases in 2020, worldwide, males, all ages

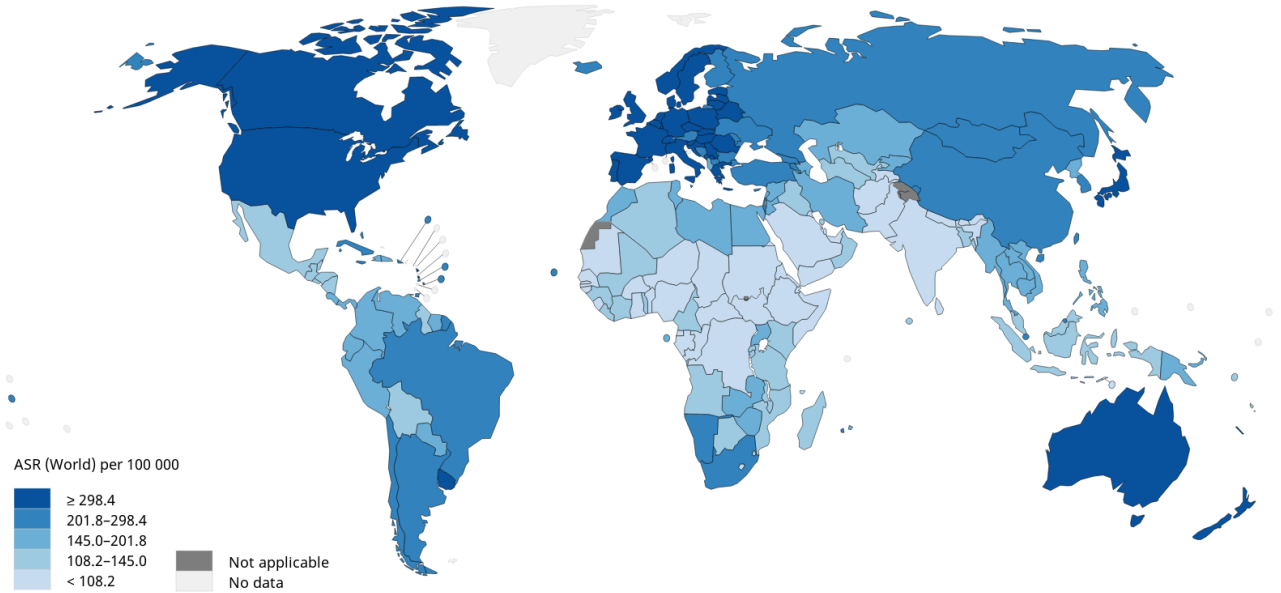


Estimated number of new cases in 2020, Europe, males, all ages

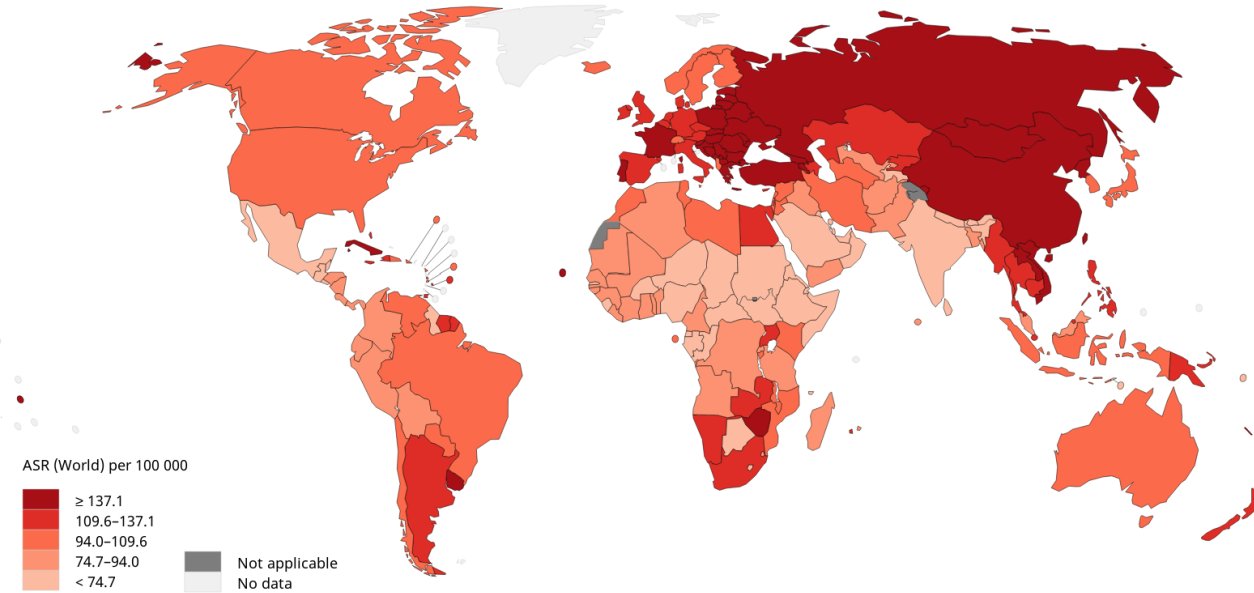


# Incidence et mortalité varient largement à travers le monde

Estimated age-standardized incidence rates (World) in 2020, all cancers, males, all ages



Estimated age-standardized mortality rates (World) in 2020, all cancers, males, all ages



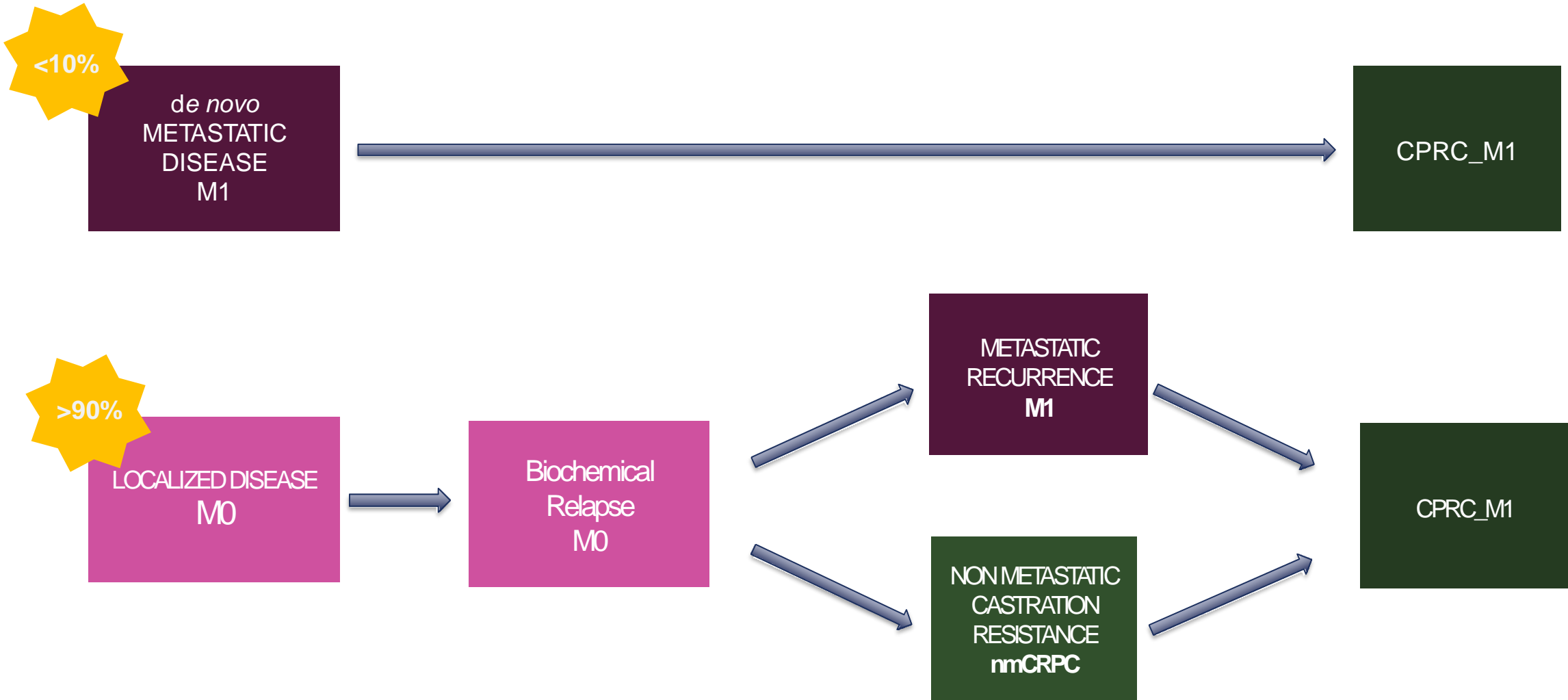
<https://gco.iarc.fr/> accessed March, 2021.

<https://gco.iarc.fr/> accessed March, 2021.

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Data source: GLOBOCAN 2020  
Graph production: IARC  
(<http://gco.iarc.fr/today>)  
World Health Organization

# NATURAL HISTORY OF PROSTATE CANCER

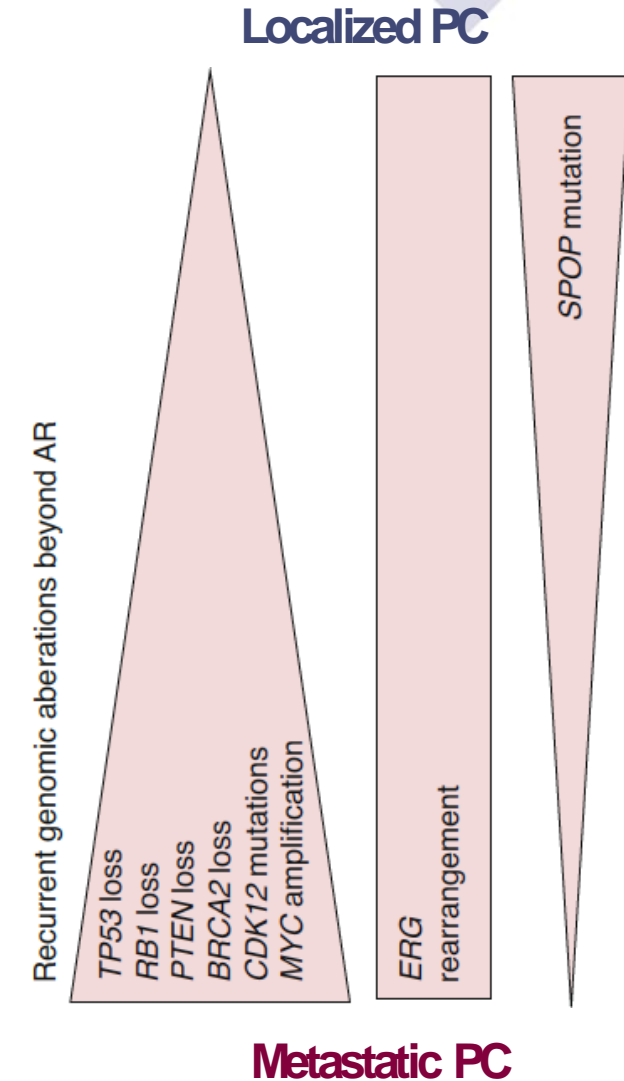


# IMPORTANCE DE LA PREVALENCE DES ALTERATIONS GÉNOMIQUES DANS LE CANCER DE LA PROSTATE LA

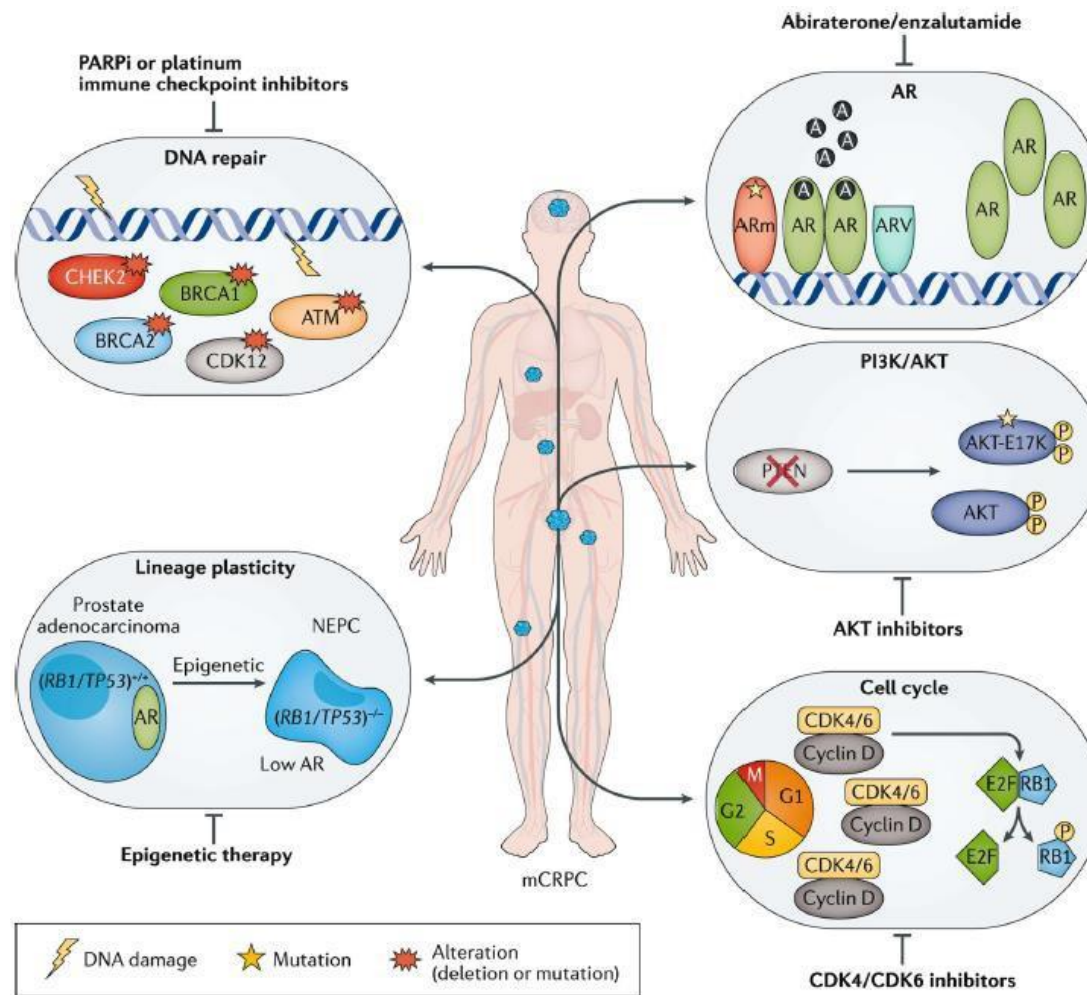


**Table 1 | Prevalence of recurrent genomic alterations across prostate cancer disease states in published cohorts**

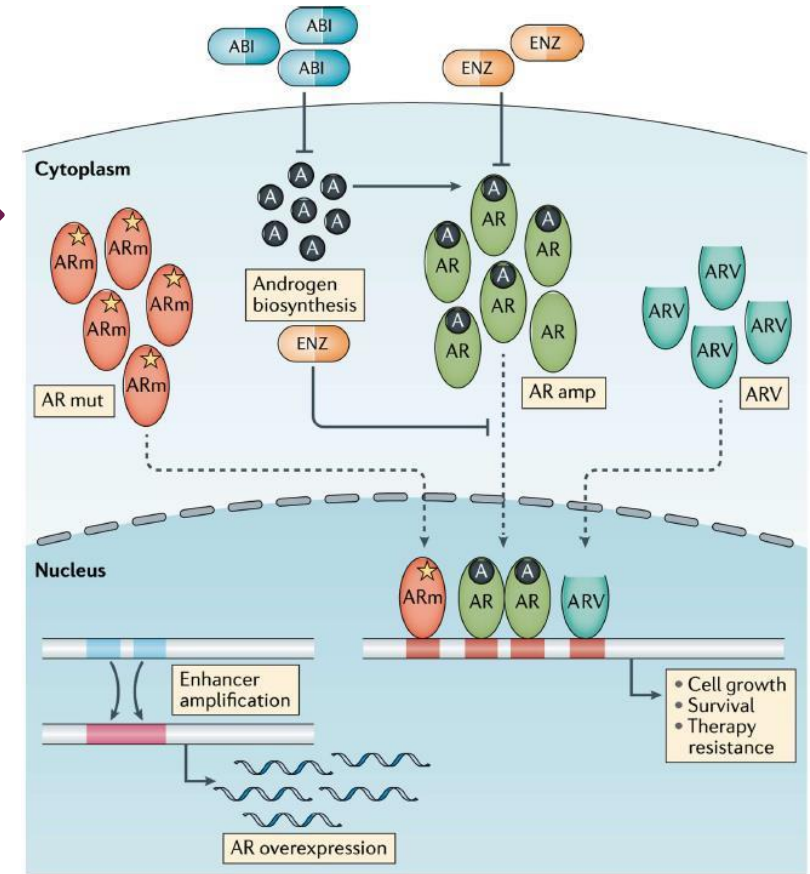
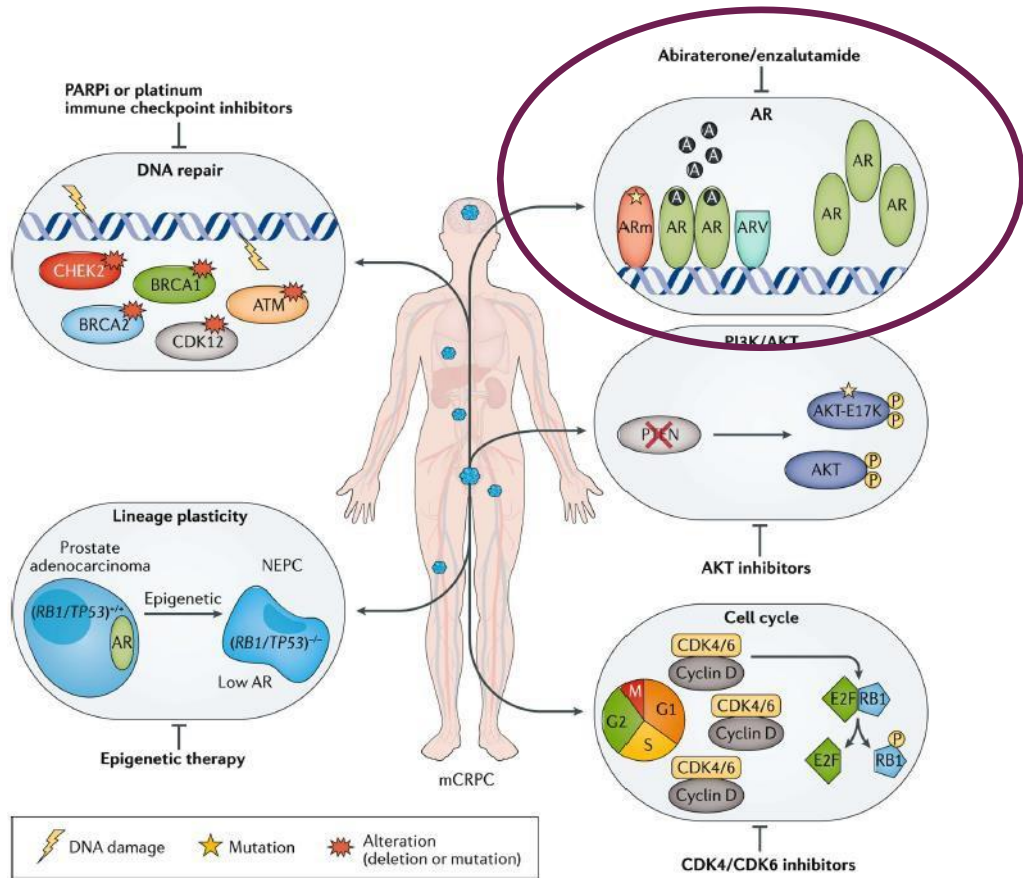
		80	129			36	48	
Ref.		333	200	140	164	444 <sup>a</sup>	101	
NGS assay		WES	Panel (MSK-IMPACT)	Panel (MSK-IMPACT)	Panel (MSK-IMPACT)	WES	WGS	
Population		Locoregional PC	Locoregional PC	Hormone-sensitive metastatic PC	mCRPC	mCRPC	mCRPC	
Gene	Alterations			Percentage altered				
AR and ERG	AR	Mut, Amp	1	2	4	51	59	70
	ERG	Mut, HomDel	2	0	0	0	5	N/A
	ERG	Fusion	46	N/A	N/A	N/A	41	43
	ETV1	Fusion	9	N/A	N/A	N/A	6	10
	ETV4	Fusion	5	N/A	N/A	N/A	4	5
	ETV5	Fusion	0	N/A	N/A	N/A	0,4	2
	FOXA1	Mut	4	15	10	10	9	19
Cell cycle	CDK1NB	Mut	2	1	2	7	5	7
	CDKN2A	Mut	2	2	2	2	3	4
	RB1	Mut, HomDel	1	2	7	18	13	12
	TP53	Mut, HomDel	8	27	30	48	40	57
DNA repair	ATM	Mut, HomDel	6	2	2	11	7	6
	BRCA1	Mut, HomDel	1	1	1	2	2	1
	BRCA2	Mut, HomDel	3	6	7	10	11	10
	CDK12	Mut, HomDel	2	4	6	10	7	3
	FANCA	Mut, HomDel	8	1	3	7	1	N/A
	MLH1	Mut, HomDel	0,3	1	2	1	1	1
	MSH2	Mut, HomDel	1	0	2	3	2	2
	MSH6	Mut, HomDel	1	0	1	1	2	1
	PALB2	Mut, HomDel	0,3	1	0	3	1	N/A
PI3K	AKT1	Mut	1	0	2	1	1	2
	PIK3CA	Mut	2	3	4	3	3	1
	PIK3CB	Mut	1	0	1	3	2	N/A
	PTEN	Mut, HomDel	17	11	17	27	32	45
Wnt	APC	Mut, HomDel	5	3	13	14	8	9
	CTNNB1	Mut	2	2	6	3	4	6
Other	ARID1A	Mut	1	1	1	2	3	N/A
	BRAF	Mut	4	2	2	3	7	4
	CHD1	Mut, HomDel	7	N/A	N/A	N/A	7	9
	MYC	Amp	7	2	6	10	23	33
	SPOP	Mut	11	12	11	5	6	5



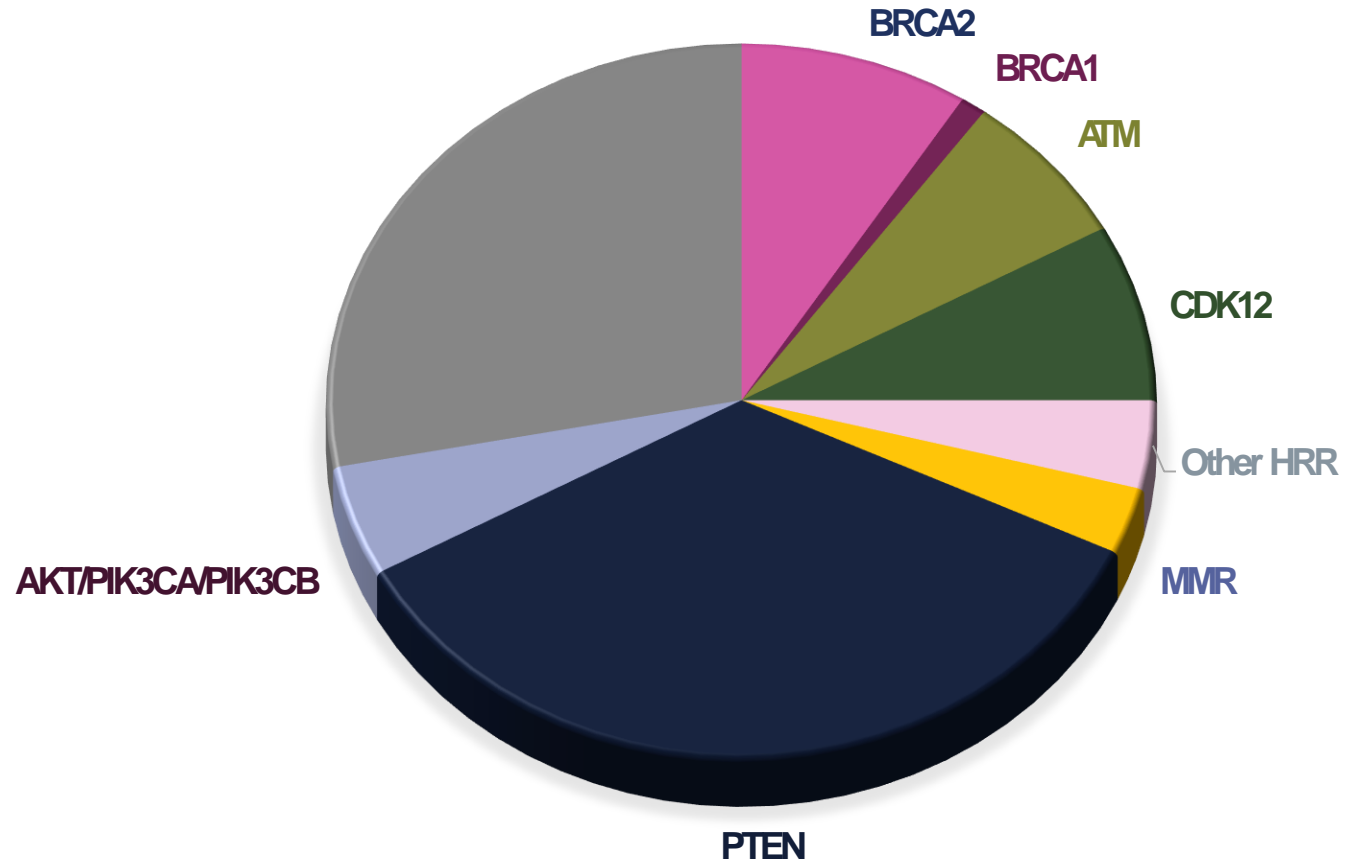
# MEDECINE DE PRECISION POUR LE CANCER LOCALEMENT ÉVOLUÉ



# L'ALTERATION DE LA VOIE DE SIGNALISATION DE L'AR REPRÉSENTE LA VOIE DE RECHERCHE LA PLUS PRÉVALENTE DANS LE MCRPC



# PREVALENCE DE CERTAINES ALTERATIONS GENETIQUES CIBLES DANS LE LA CRPC



# NON-METASTATIC CRPC

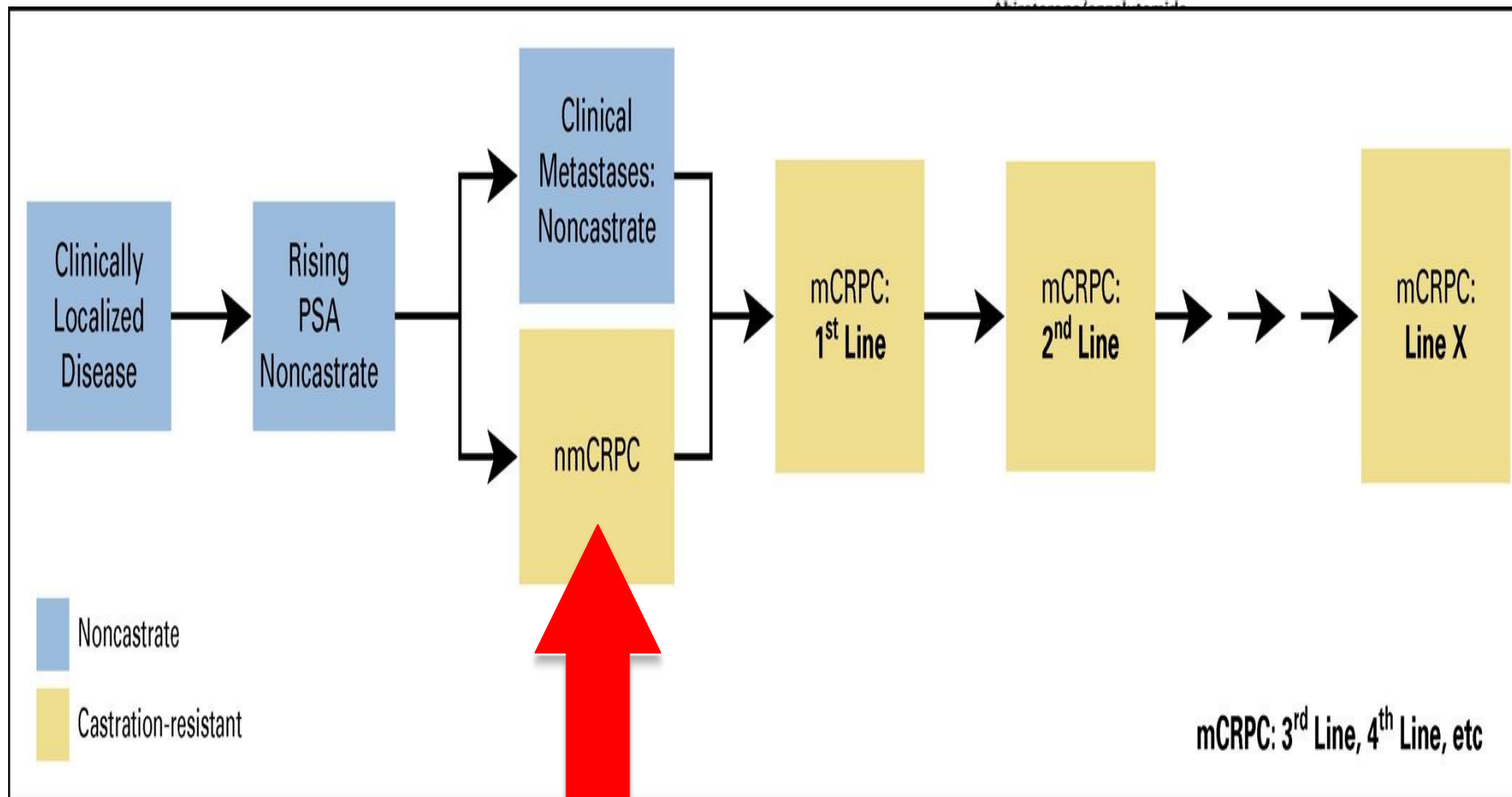


**Le nmCRPC (M0 CRPC) est défini par l'augmentation des PSA sous ADT avec une testostéronémie de castration en l'absence de détection de métastases à distance avec l'imagerie conventionnelle**

**Représente 3-9% de tous les cas de cancer**

**PSMA-PET dans le M0 CRPC détecte approximativement 50% de maladie extra-pelvienne**

# DISEASE CONTINUUM IN PROSTATE CANCER



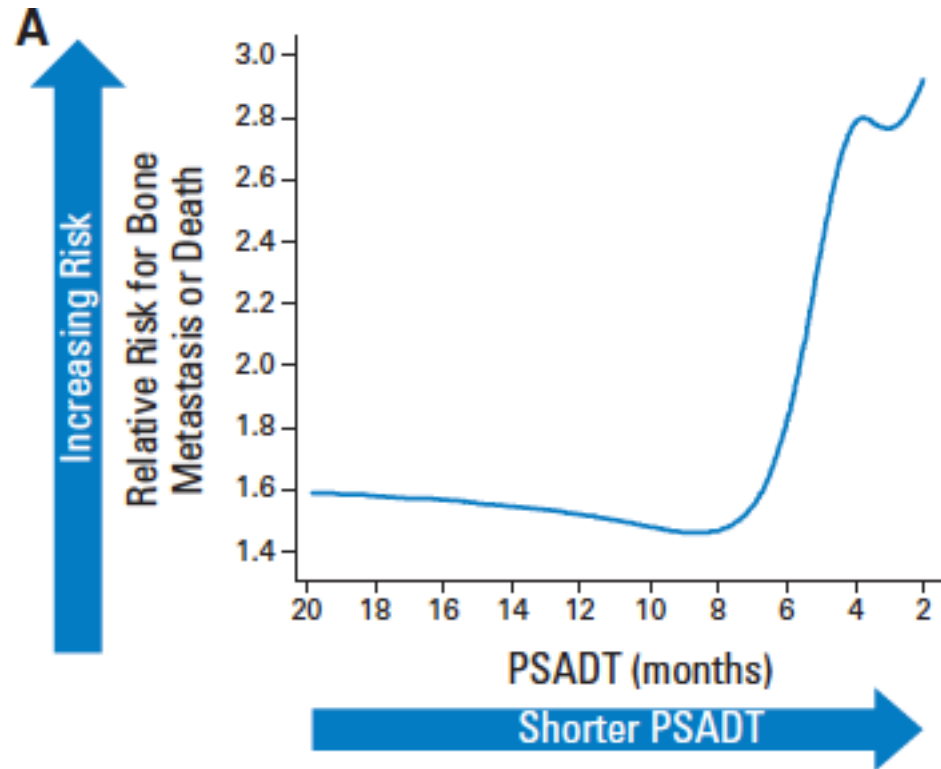
# NON-METASTATIC CRPC

## Importance of PSA doubling time

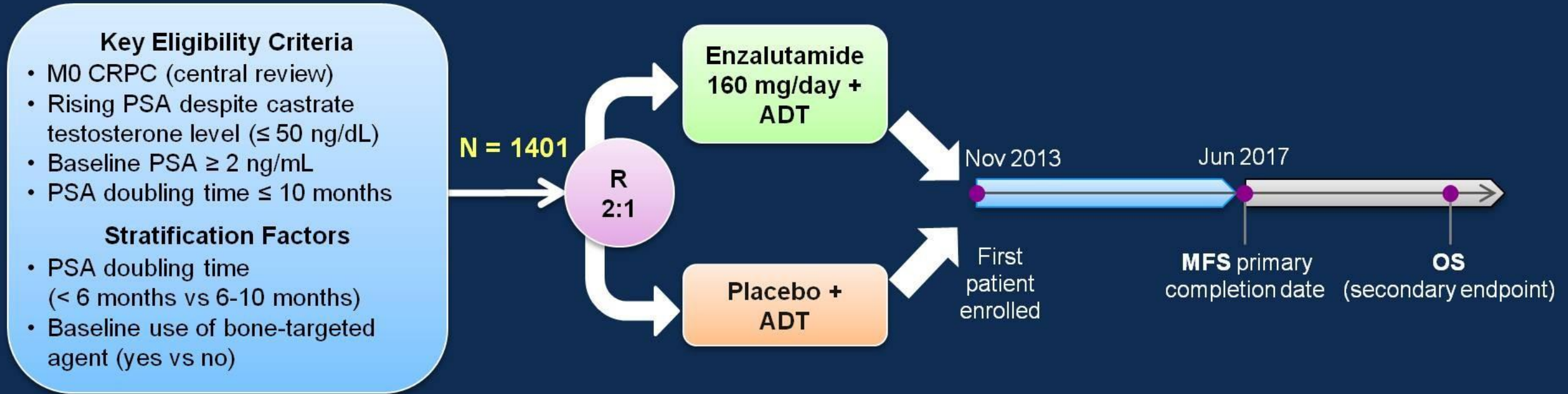
Pas de thérapies approuvées pour le nmCRPC jusqu'à un passé très proche

nmCRPC avec PSA DT < 8-10 mois corrélé à un risque significatif de développer des M+ et risque spécifique de décès par pCA

Développement de métastases=principale cause de morbidité



# PROSPER Study Design



## Primary endpoint

- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)

## Statistical Design:

- Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
- Target of 440 events provides 90% power to detect a target HR of 0.72

## Secondary endpoints

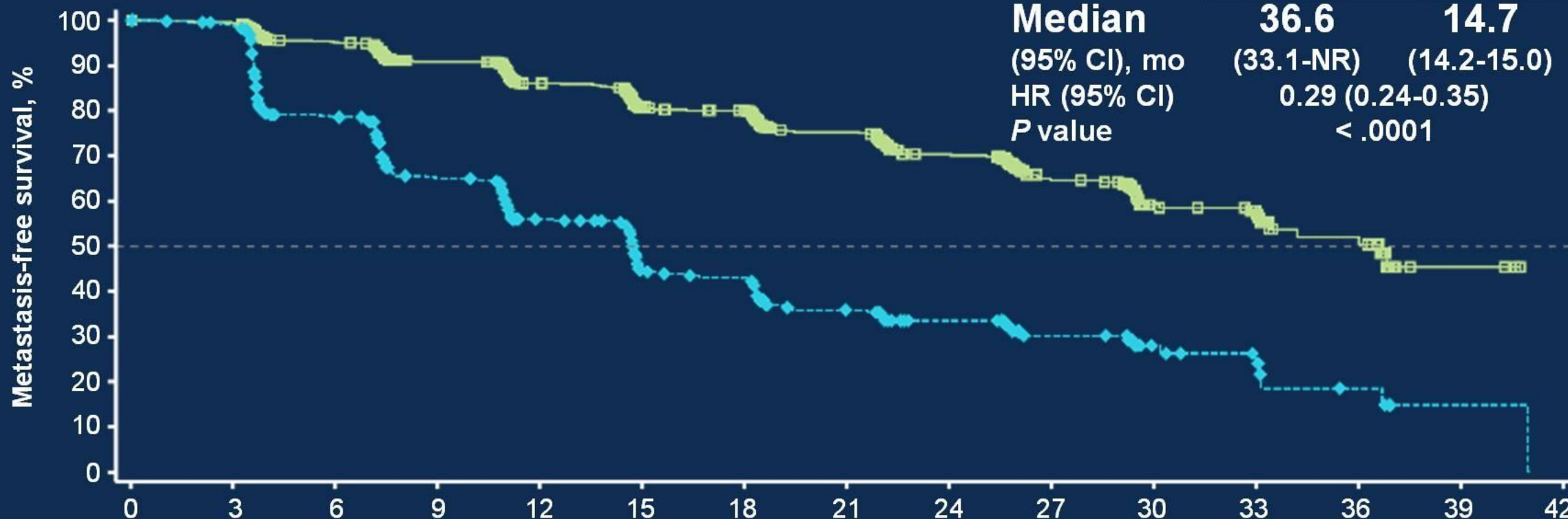
- Safety
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.

# Primary Endpoint: MFS

ENZA + ADT (n = 933)	PBO + ADT (n = 468)
-------------------------	------------------------

<b>Median</b>	<b>36.6</b>	<b>14.7</b>
(95% CI), mo	(33.1-NR)	(14.2-15.0)
HR (95% CI)	0.29 (0.24-0.35)	
P value	< .0001	



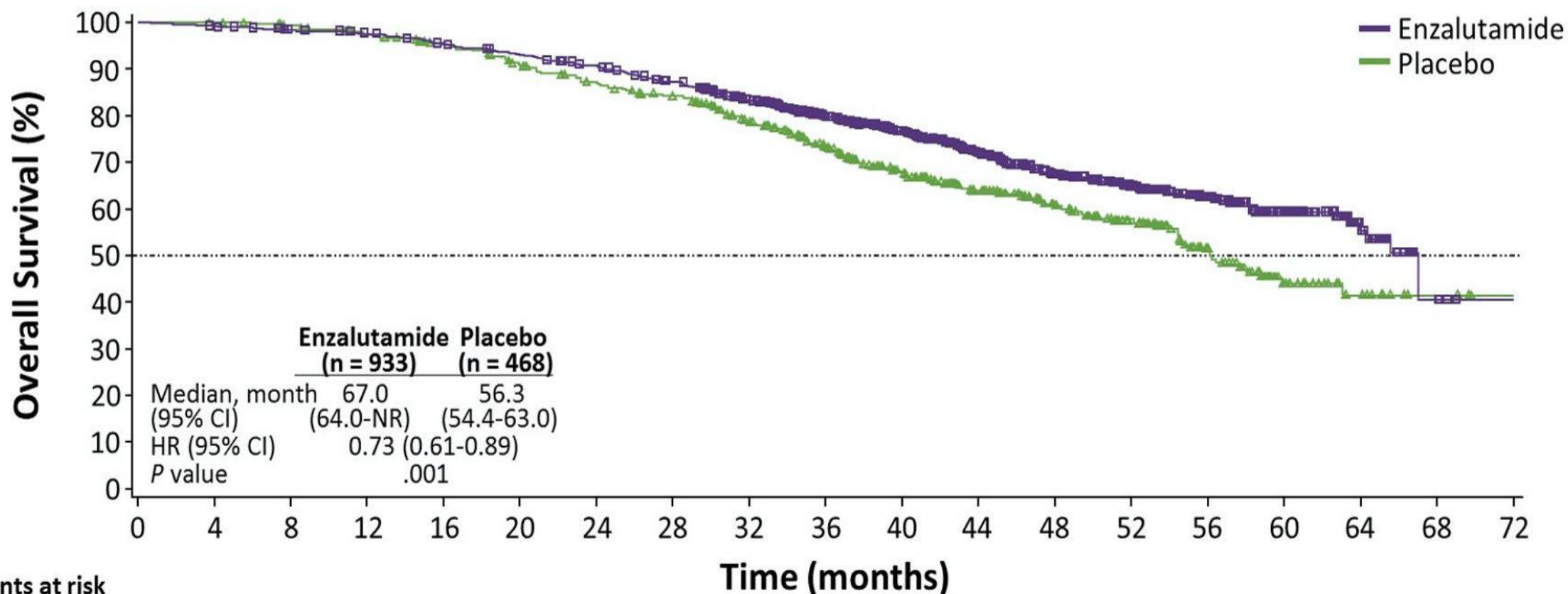
No. at risk	mo														
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
ENZA + ADT	933	865	759	637	528	431	418	328	237	159	87	77	31	4	0
PBO + ADT	468	420	296	212	157	105	98	64	49	31	16	11	5	1	0

- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.

# PROSPER Final Overall Survival Analysis

Enzalutamide was associated with a statistically significant 27% reduction in the risk of death



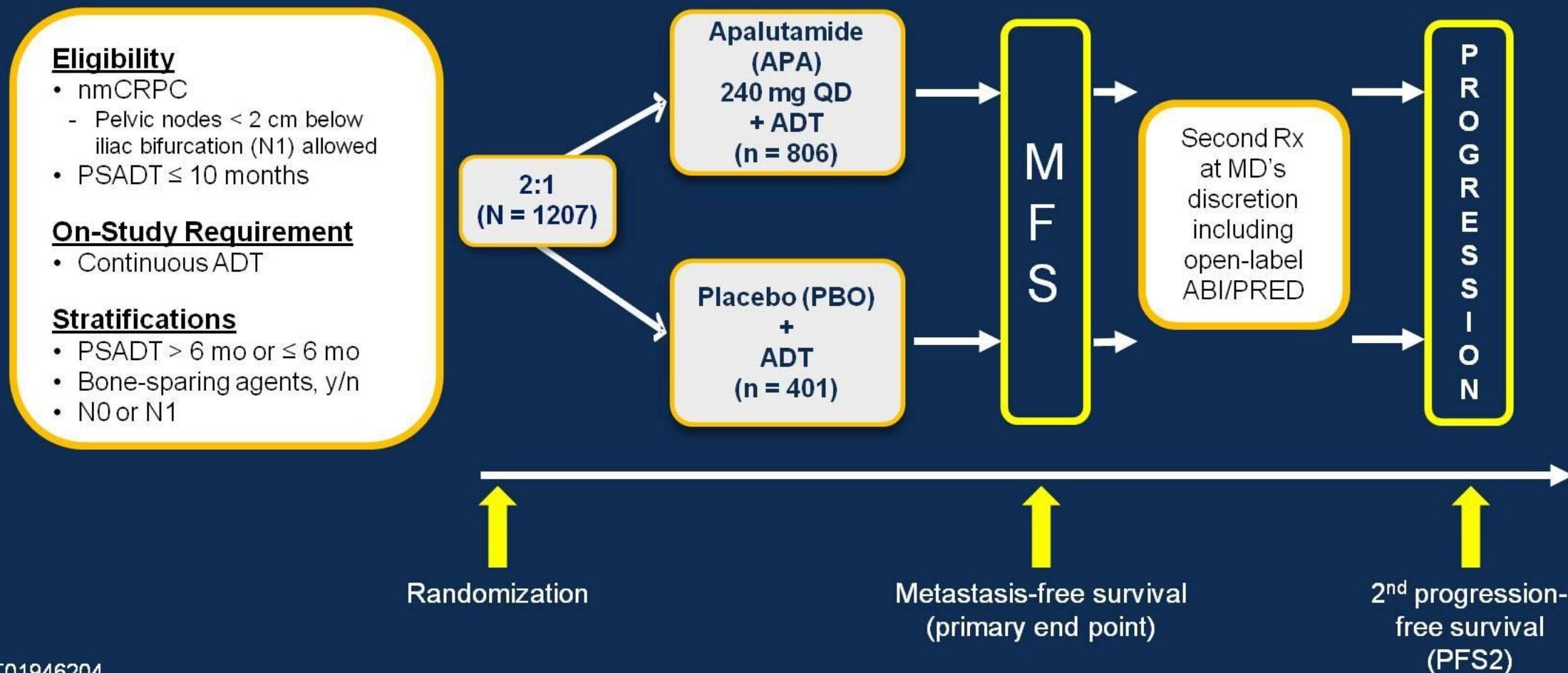
## Patients at risk

	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
Enzalutamide	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0
Placebo	468	467	459	444	428	404	381	363	321	274	219	177	140	106	64	30	16	3	0

CI, confidence interval; HR, hazard ratio; NR, not reached.

# SPARTAN – Overall Study Design

## Phase 3 Placebo-Controlled, Randomized International Study

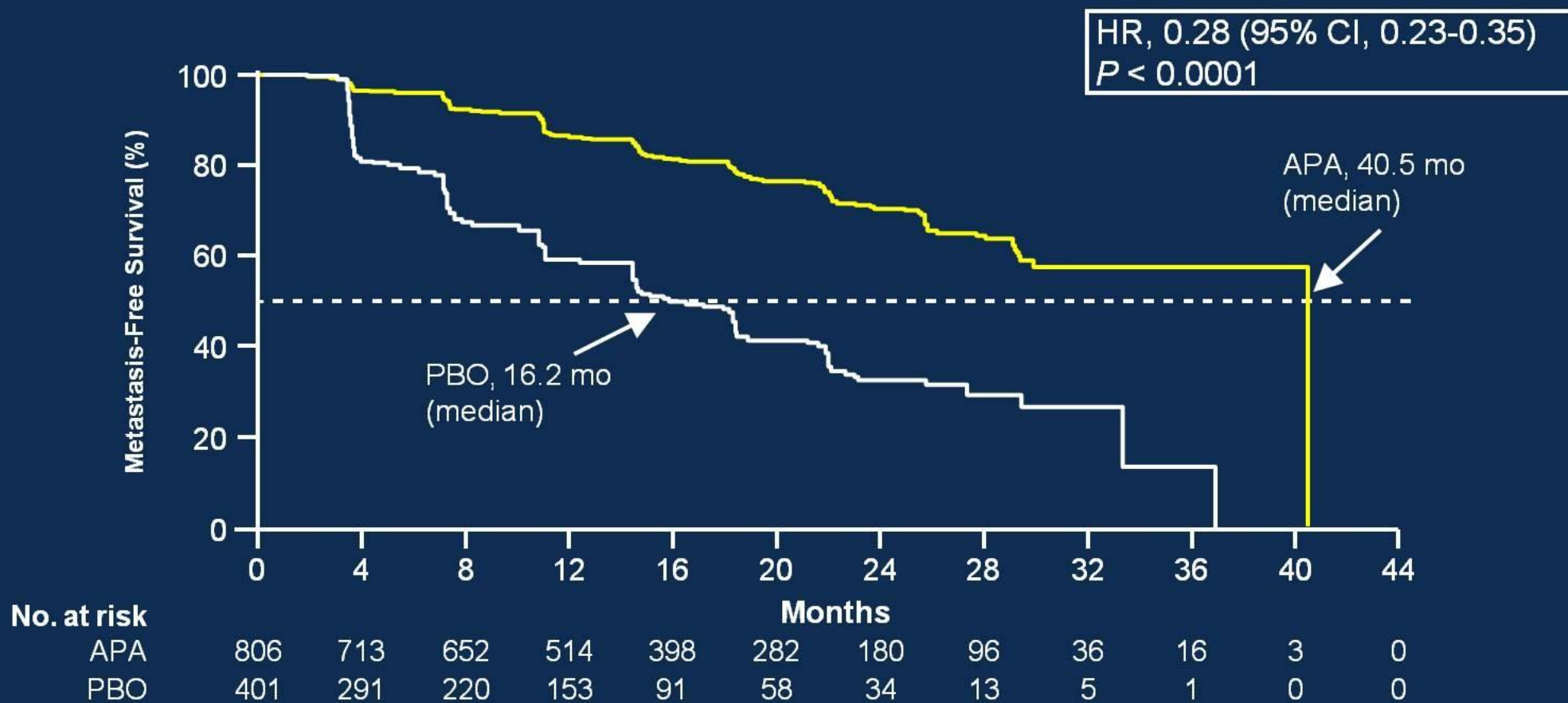


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ABI/PRED, abiraterone acetate plus prednisone; nmCPRC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.

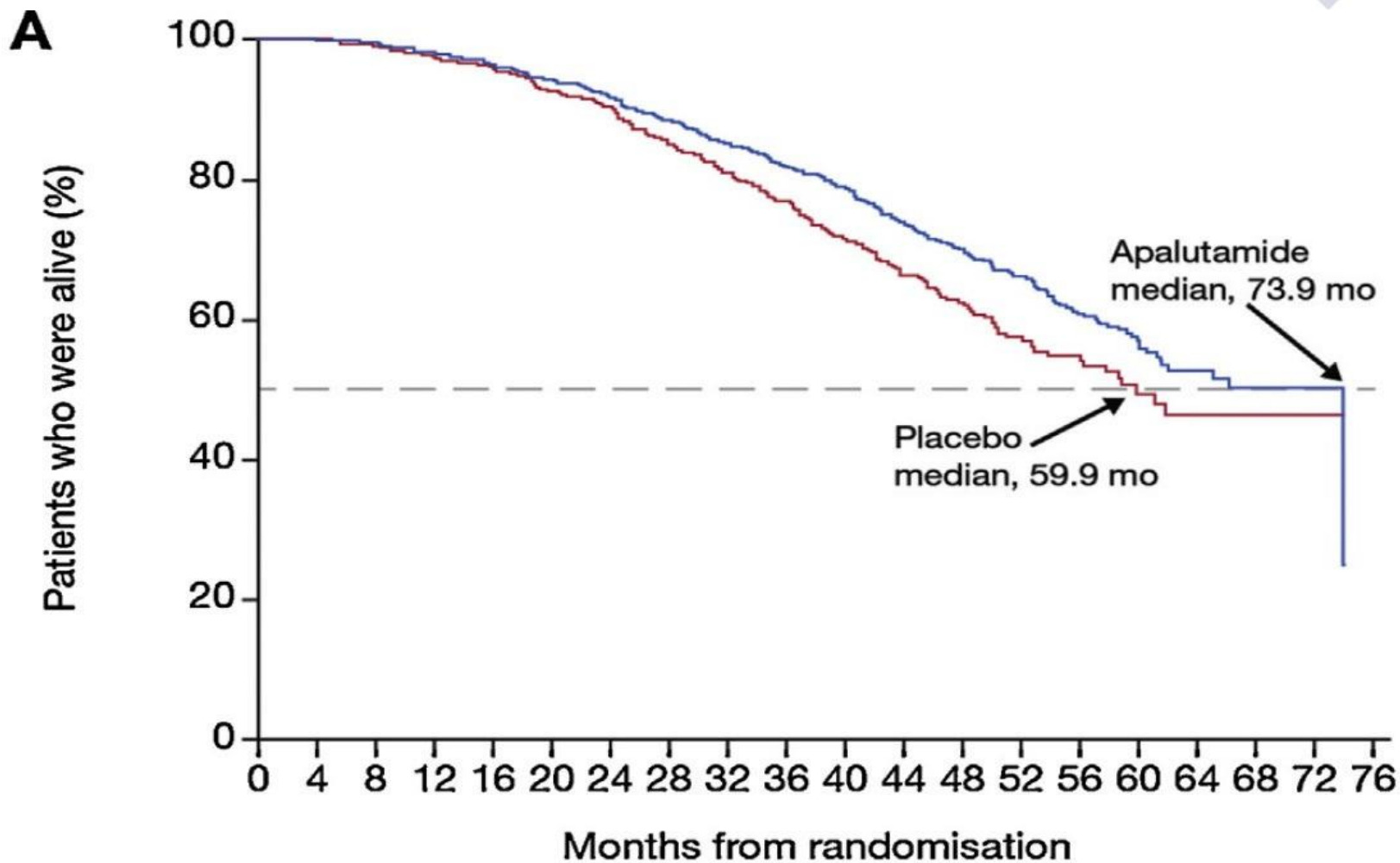
# Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death



# SPARTAN

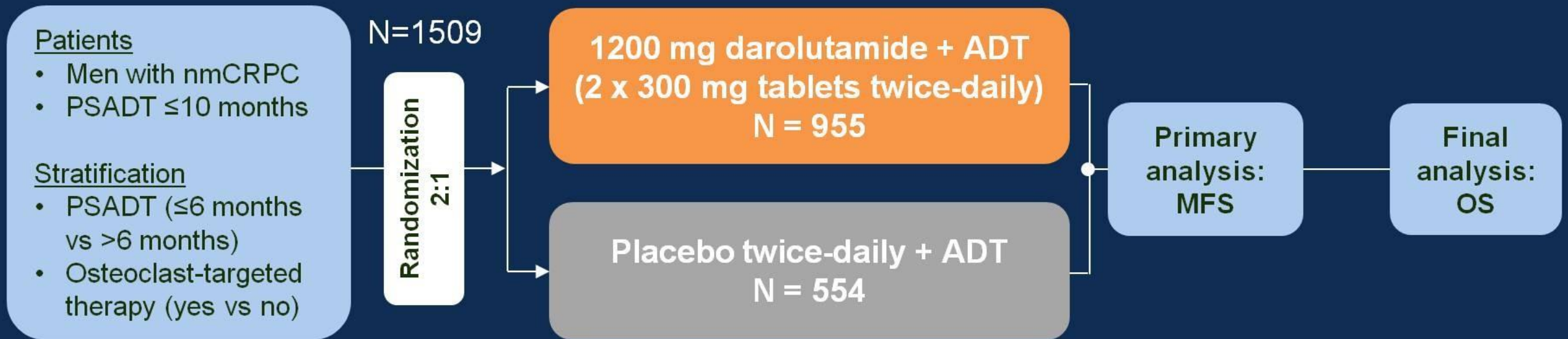
## Apalutamide in nmCRPC



Number of patients

Apalutamide	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0
Placebo	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0

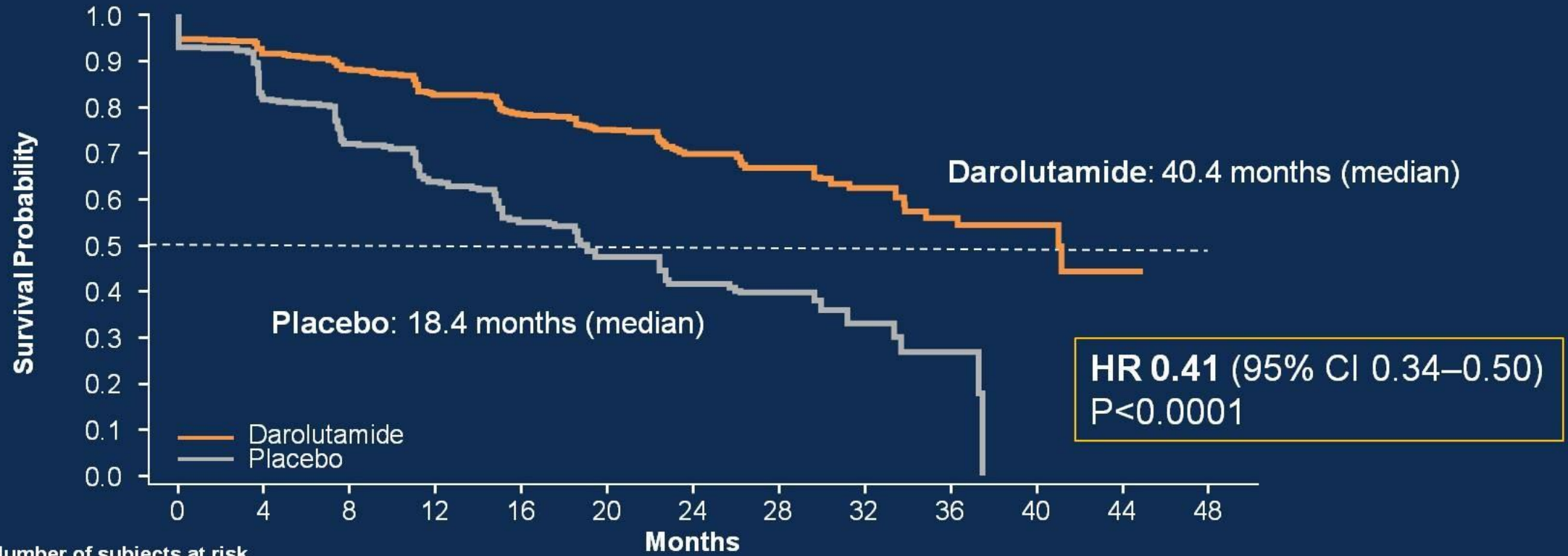
# ARAMIS trial design



ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time.

# Primary endpoint: Metastasis-free survival

59% risk reduction of distant metastases or death

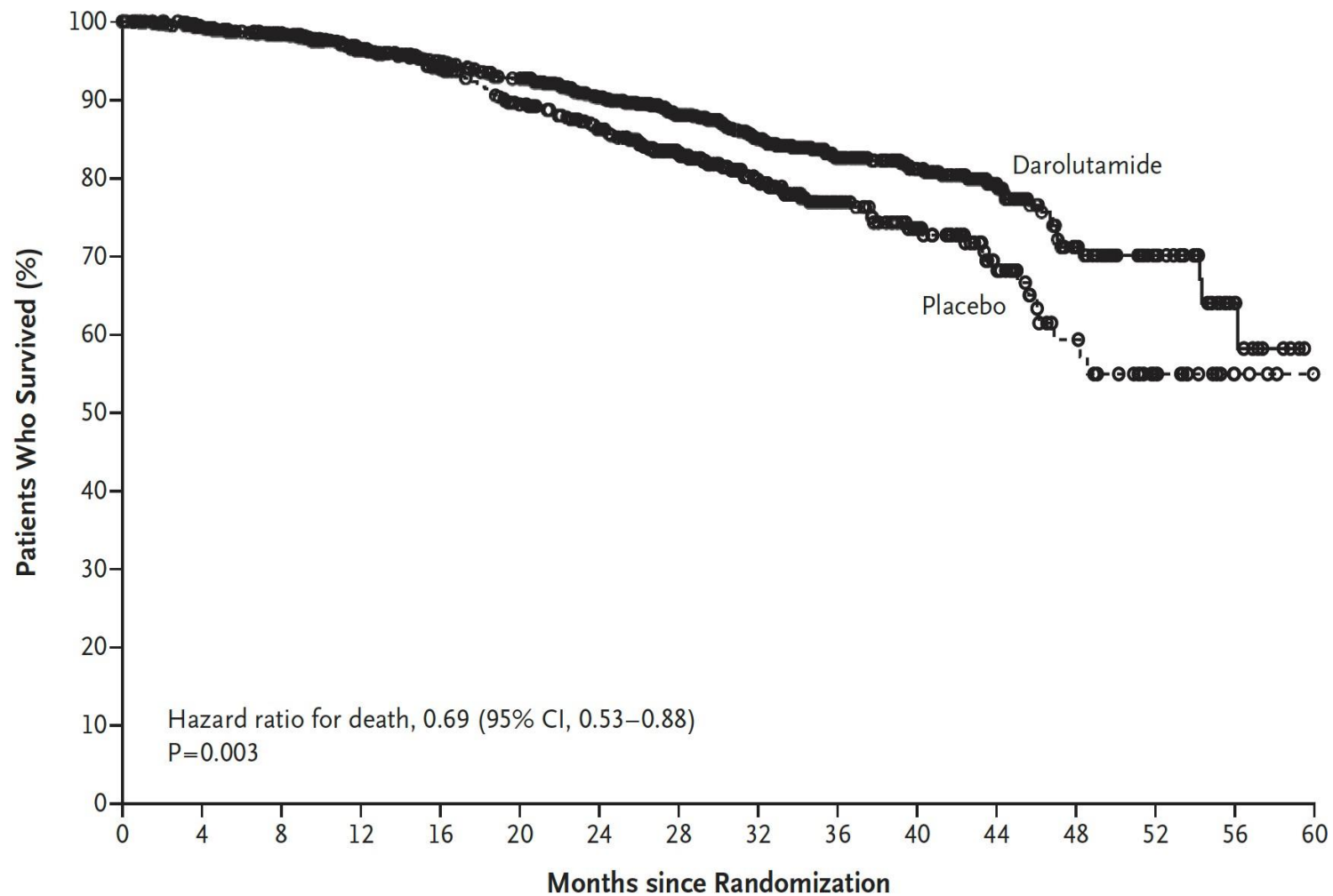


Median follow-up time at primary analysis was 17.9 months

CI, confidence interval; HR, hazard ratio.

# ARAMIS

## Darolutamide in nmCRPC



### No. at Risk

Darolutamide	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0
Placebo	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0

## SUMMARY : Pivotal nmCRPC trials

	PROSPER	SPARTAN	ARAMIS
<b>Drug</b>	Enzalutamide	Apalutamide	Darolutamide
<b>Dose</b>	160mg OD	240mg OD	600mg BD
<b>MFS (mo)</b>	36.6 vs. 14.7 HR 0.29; P<0.0001	40.5 vs. 16.2 HR 0.28; P<0.0001	40.4 vs. 18.4 HR 0.41; P<0.0001
<b>OS (mo)</b>	67 vs. 56.3 HR 0.73; P=0.001	73.9 vs. 59.9 HR 0.78; P=0.0161	NR vs. NR HR 0.69; P=0.003
<b>Gr 3 / 4 AE (%)</b>	31	45	25
<b>Falls (%) – any Gr</b>	11	16	4
<b>Fatigue (%) - any Gr</b>	33	30	16
<b>Rash (%) – any Gr</b>	NR	24	3
<b>Treatment stop due to AE (%)</b>	9	11	9

# TAKE-HOME MESSAGES

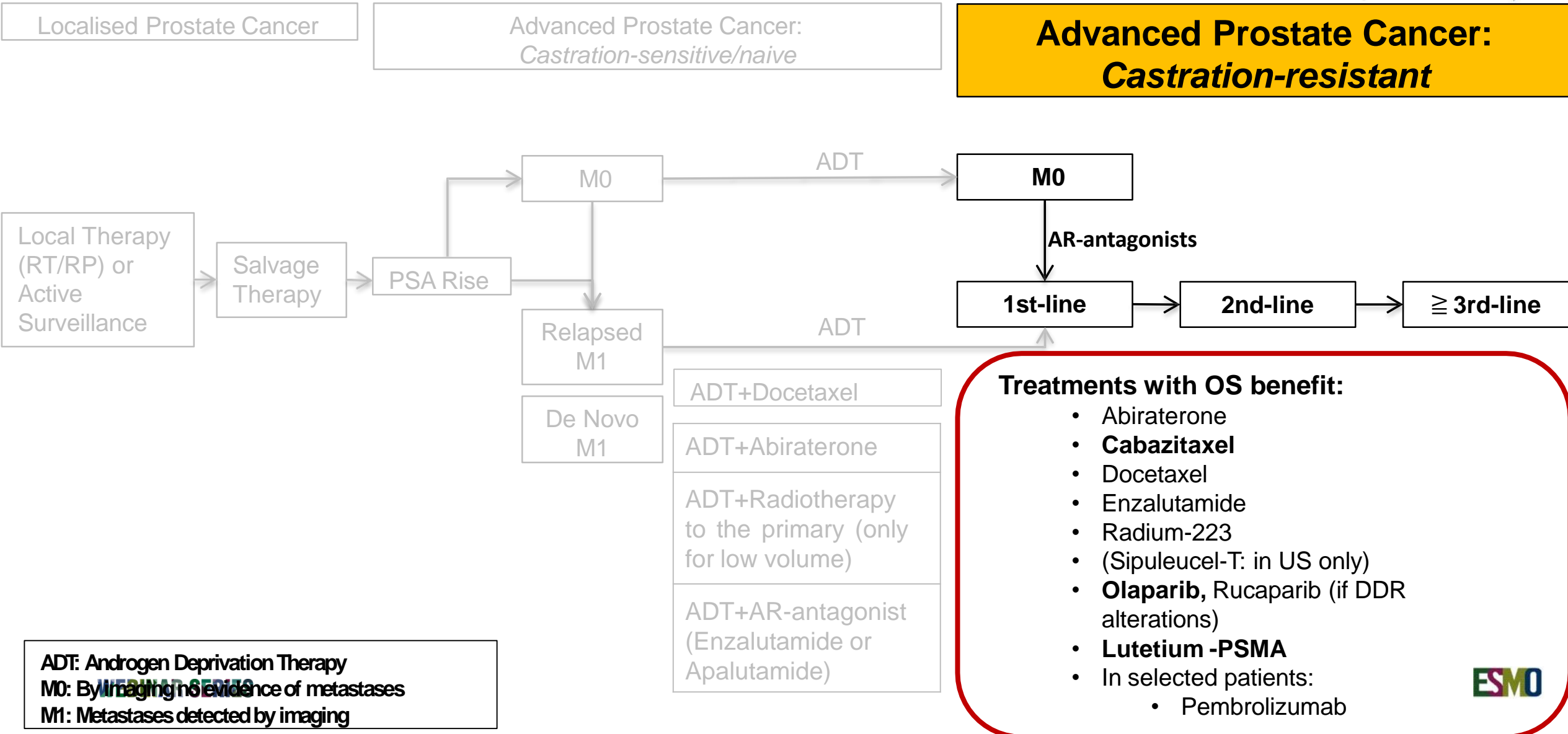
## nmCRPC

- ✓ 3 agents actifs avec amélioration significative de la OS
- ✓ Efficacité similaire
- ✓ Toxicité variable
- ✓ Vraisemblablement avec un recours moindre de l'ADT précoce mais plus de recours au PET PSMA
- ✓ D'autres sont nécessaires pour de meilleurs résultats oncologiques

# CANCER DE LA PROSTATE METASTATIQUE RESISTANT A LA CASTRATION (MCRPC): TRAITEMENTS ACTUELS



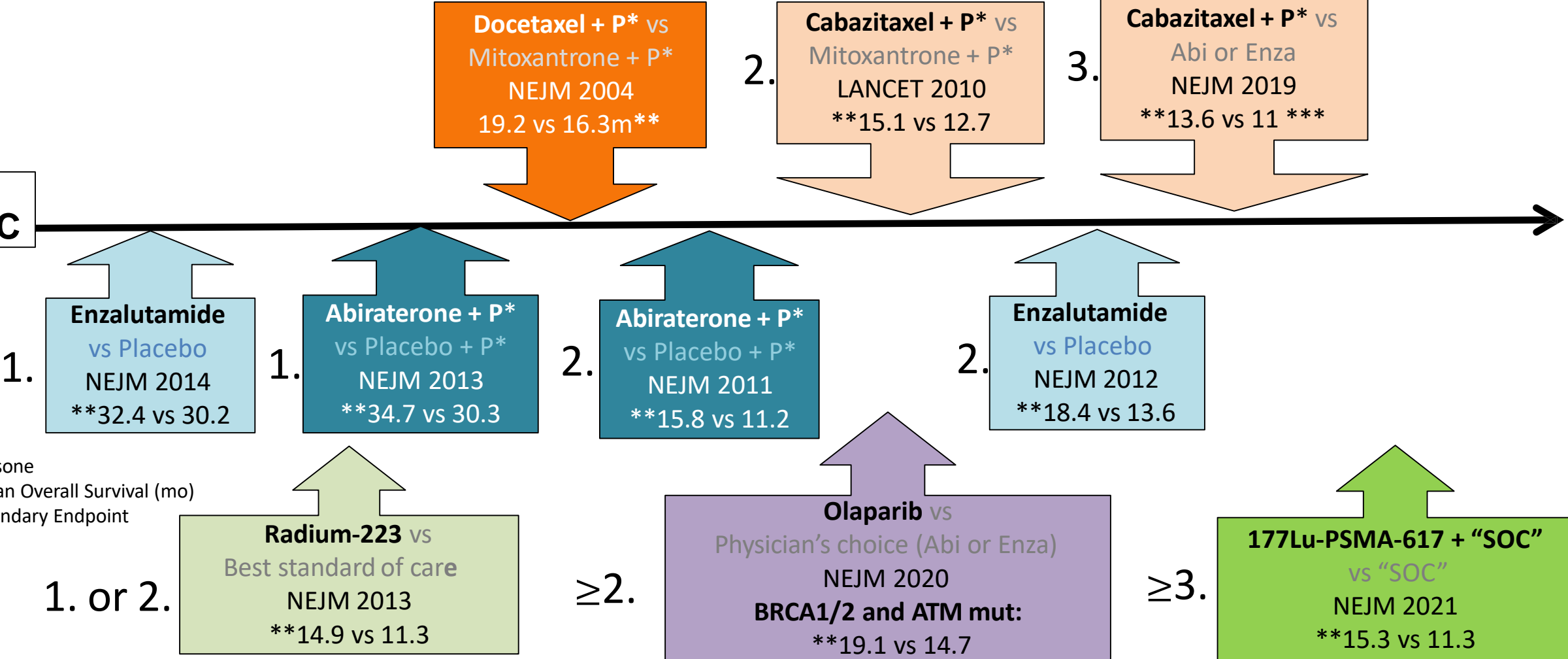
# Prostate Cancer: Castration resistant (CRPC)



# Approved systemic therapies for mCRPC



CRPC



\* Prednisone  
\*\* Median Overall Survival (mo)  
\*\*\* Secondary Endpoint

\*\*\*Zoledronate vs Placebo JNCI 2004; 16 vs 10.5m

\*\*\*Denosumab vs Zoledronate LANCET 2011; 20.7 vs 17.1m

\*\*\* Time to first skeletal event



# Several agents approved for mCRPC, but optimal sequence is unclear

# First Line Therapy mCRPC



**Abiraterone/Prednisone (COU-302):** Asymptomatic, mildly symptomatic; no visceral metastases

**Docetaxel/Prednison (TAX-327)**

**Enzalutamide (PREVAIL):** Asymptomatic, mildly symptomatic

**Radium-223 (ALSYMPCA):** Symptomatic, no lymph node bulk, no visceral metastases



# Second line mCRPC after Docetaxel for first line mCRPC

**Abiraterone/Prednisone (COU-301)**

**Cabazitaxel/Prednison (TROPIC and PROSELICA)**

**Enzalutamide (AFFIRM)**

**Radium-223 (ALSYMPCA):** Symptomatic, no lymph node bulk, no visceral metastases

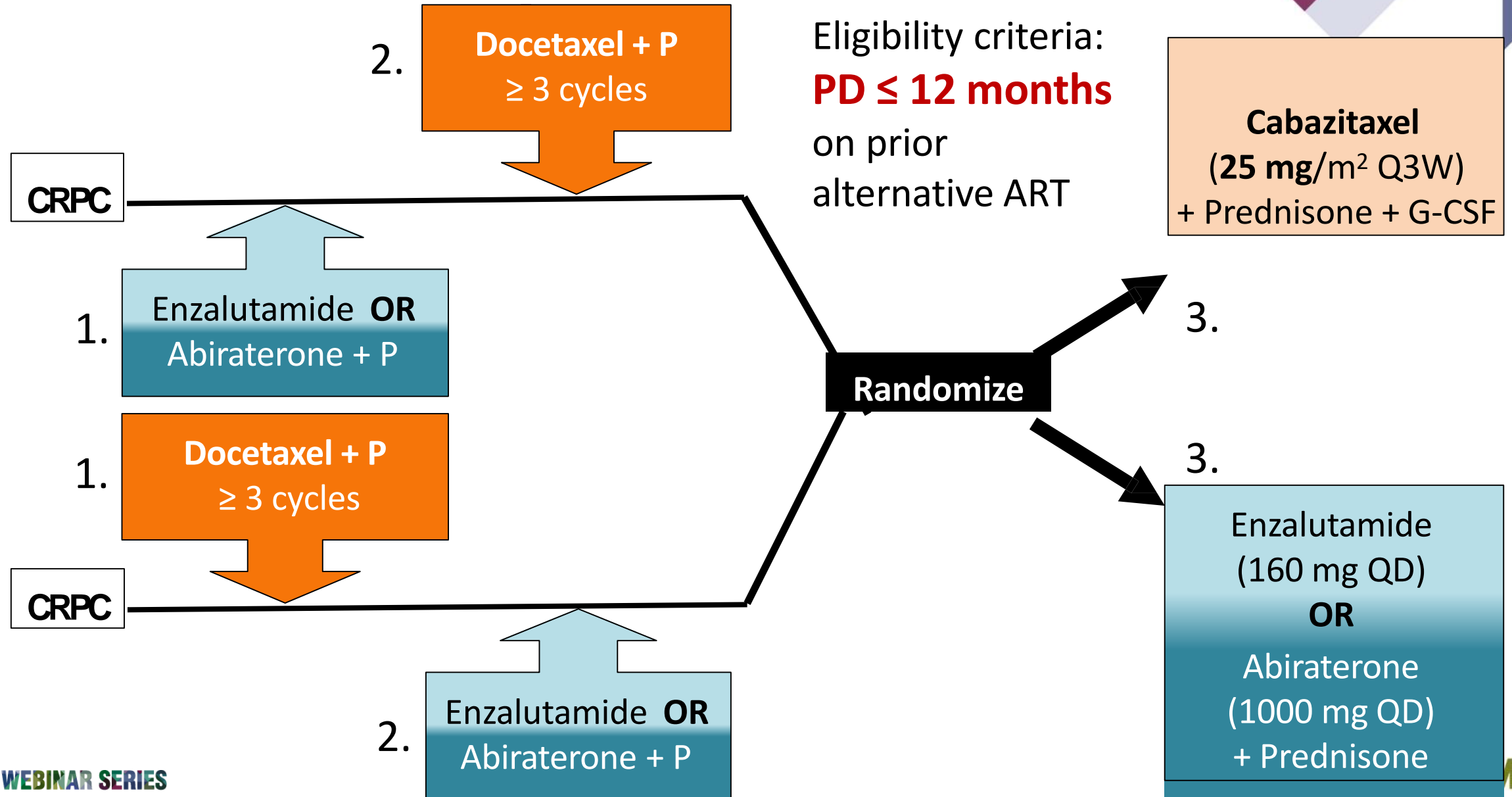
# Sequencing:

## Facteurs intervenants dans le choix thérapeutique

- Liés au patient : symptomatique versus non-symptomatique, médications, comorbidités, examen clinique
- Traitement durant la phase hormono-sensible (ADT seule ou ADT en association), durée de réponse à ce traitement
- «Staging»
  - NFS, fonction rénale et hépatique, ALP, LDH...
  - PSA (taux), PSA-DT
  - Imagerie: TDM TAP, scintigraphie osseuse, IRM corps entier, PET/CT PSMA
  - Analyse moléculaire
  - **Préférence du Patient et disponibilité**

Co

# 3rd line: CARD



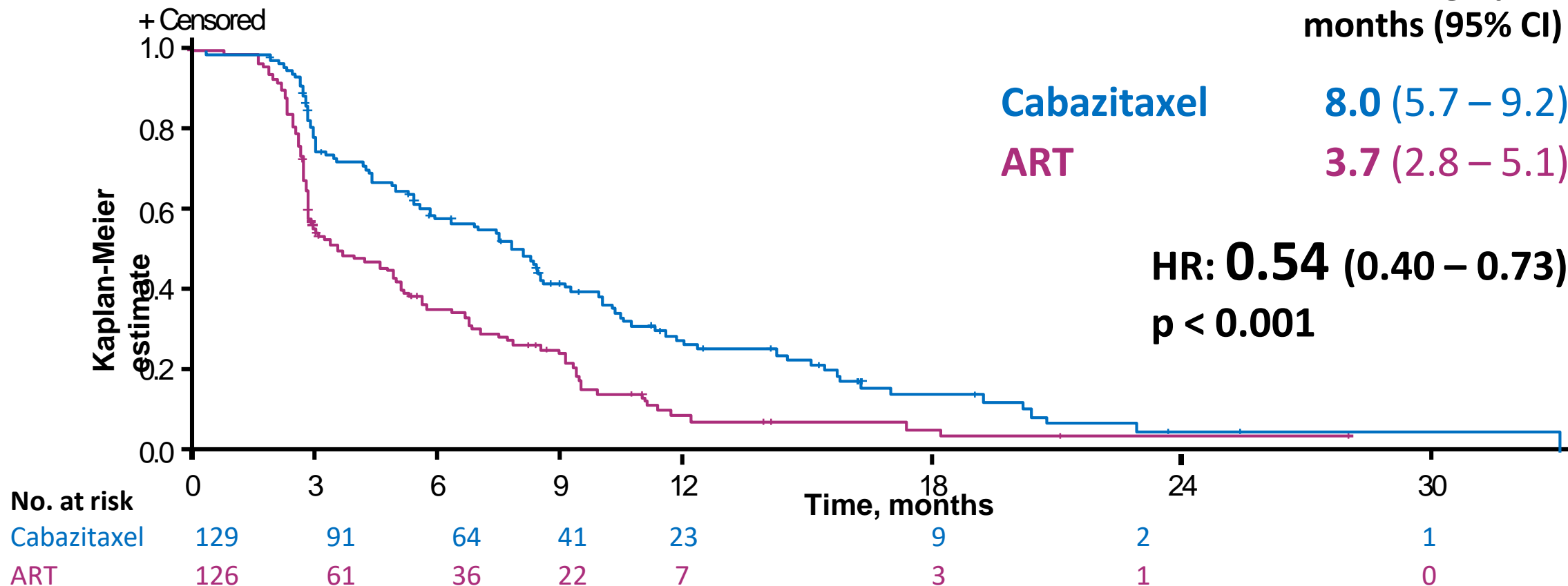
# Efficacy: rPFS (Primary endpoint)



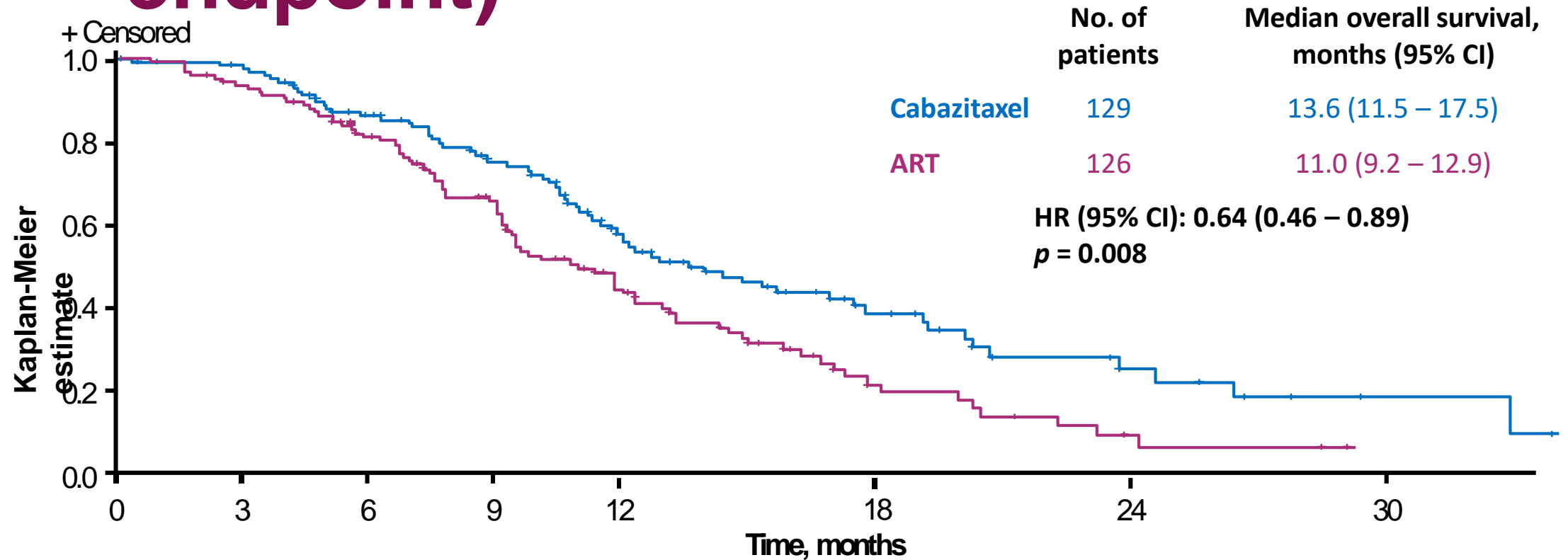
Median radiographic PFS, months (95% CI)

**Cabazitaxel** 8.0 (5.7 – 9.2)  
**ART** 3.7 (2.8 – 5.1)

**HR: 0.54 (0.40 – 0.73)**  
**p < 0.001**



# Efficacy: OS (Key secondary endpoint)



## No. at risk

Cabazitax.	129	122	96	77	51	21	8	2
ART	126	116	88	64	39	11	3	0

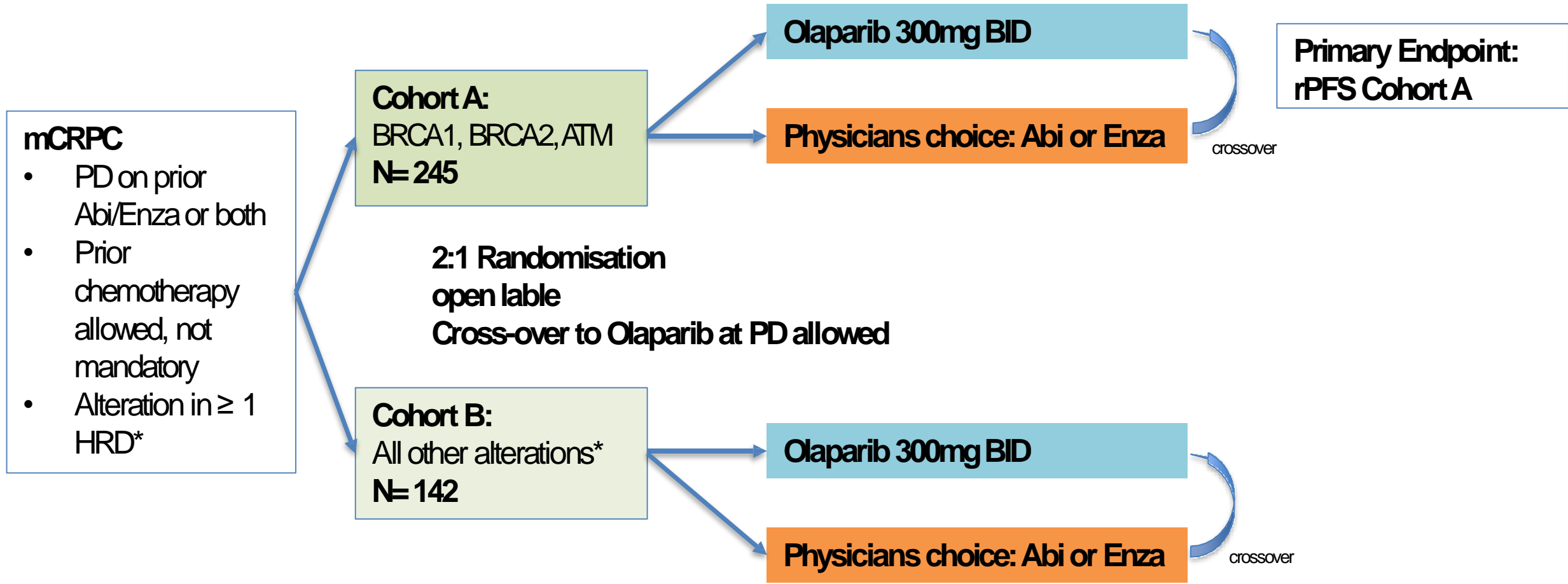
# Sequencing of AR Pathway Inhibitors



	CARD Trial Abi/Enza after Enza/Abi n=255	PLATO Trial Abi <u>after</u> Enza n=509	NCT02116582 Enza <u>after</u> Abi n=214
<b>Patient selection</b>	PD ≤ 12 months on prior NHA	251 pts with no PSA rise on ≥21 wks of Enza	≥24 wks of prior Abi (median duration 54 wks!)
<b>PSA decline ≥50%</b>	13.5%	2%	19%
<b>Time to PSA progression</b>	2.7 mo (PFS)	2.8 mo	5.7 mo
<b>rPFS (or clinical PFS for PLATO)</b>	3.7 mo 4.8 Enza after Abi 3.4 Abi after Enza	5.6 mo (rPFS or clinical PFS)	8.1 mo (rPFS)



# PROfound Trial: Design

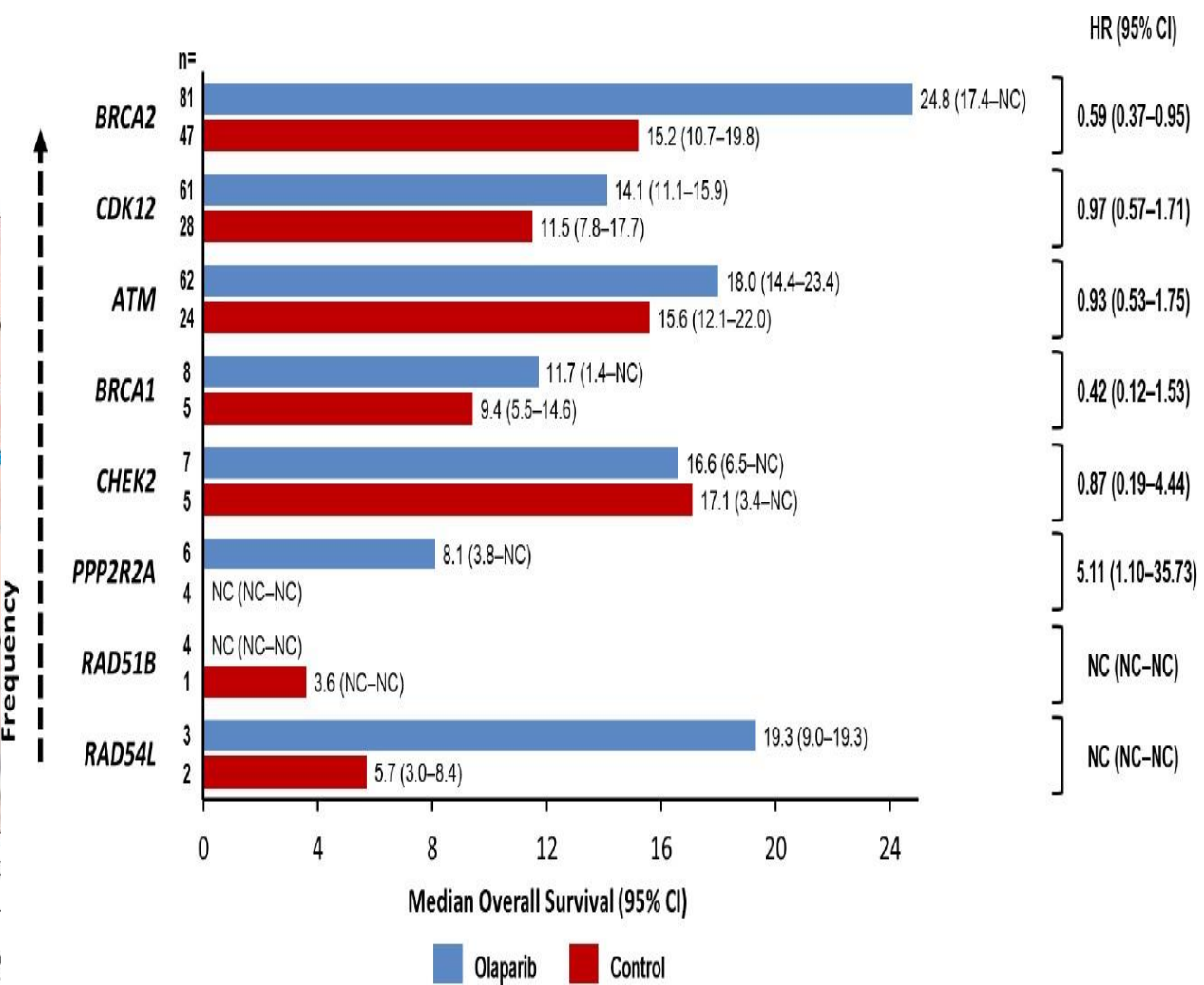
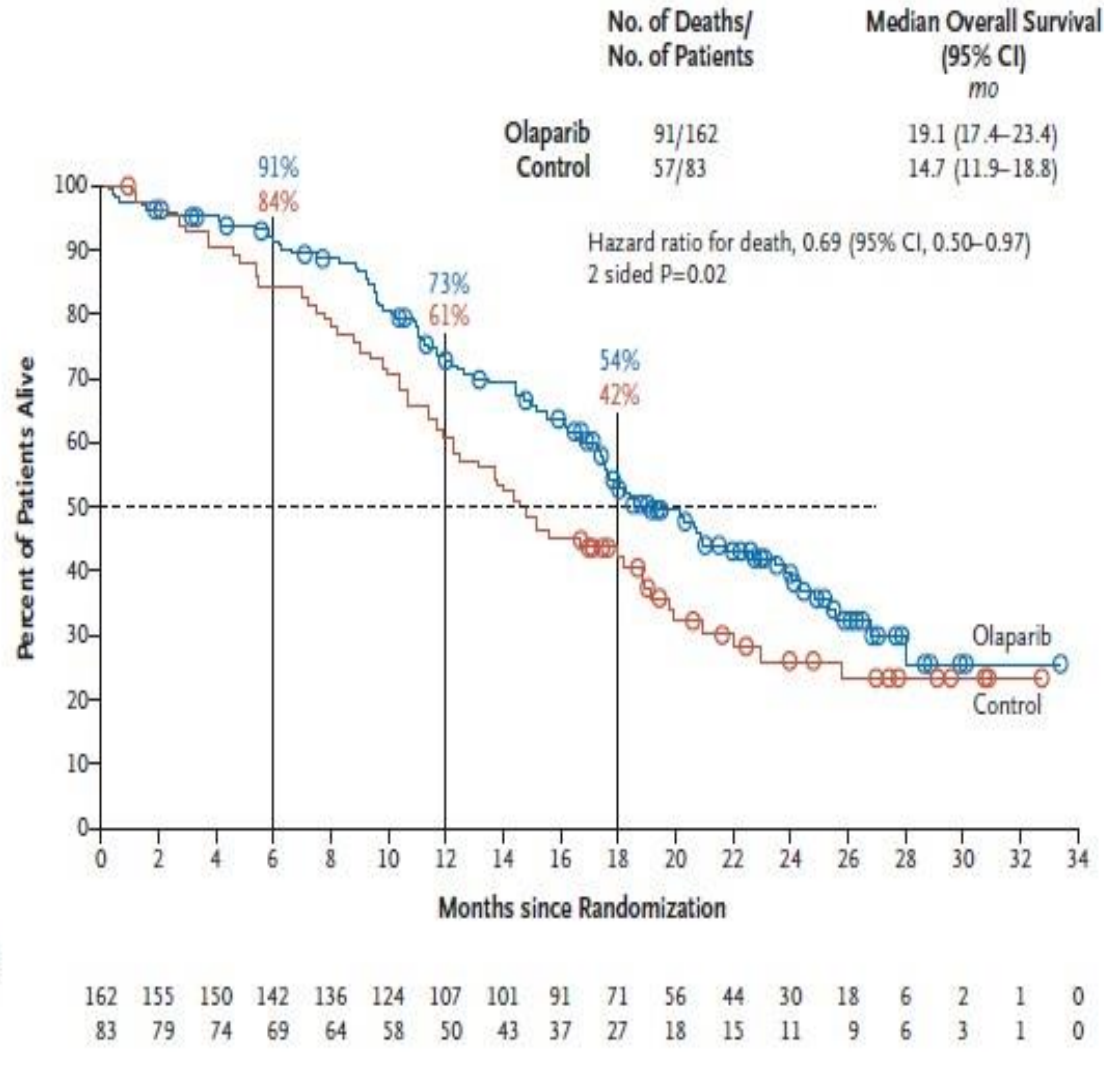


\* BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L

# PROfound Trial: Results

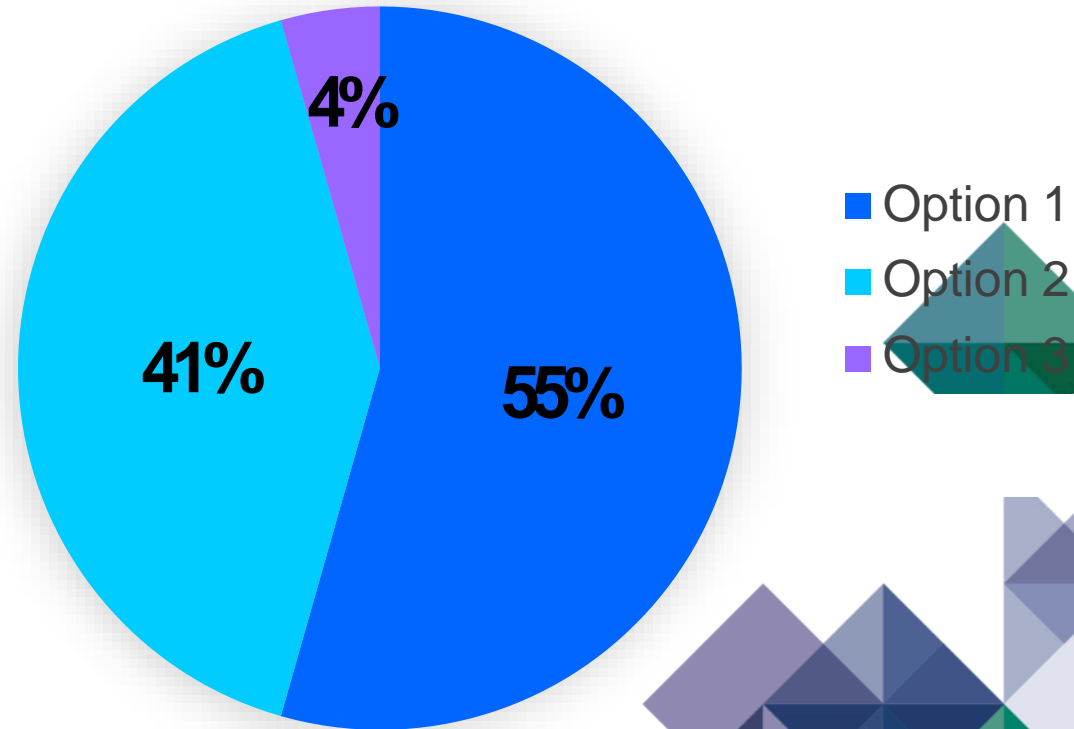


A Overall Survival in Cohort A



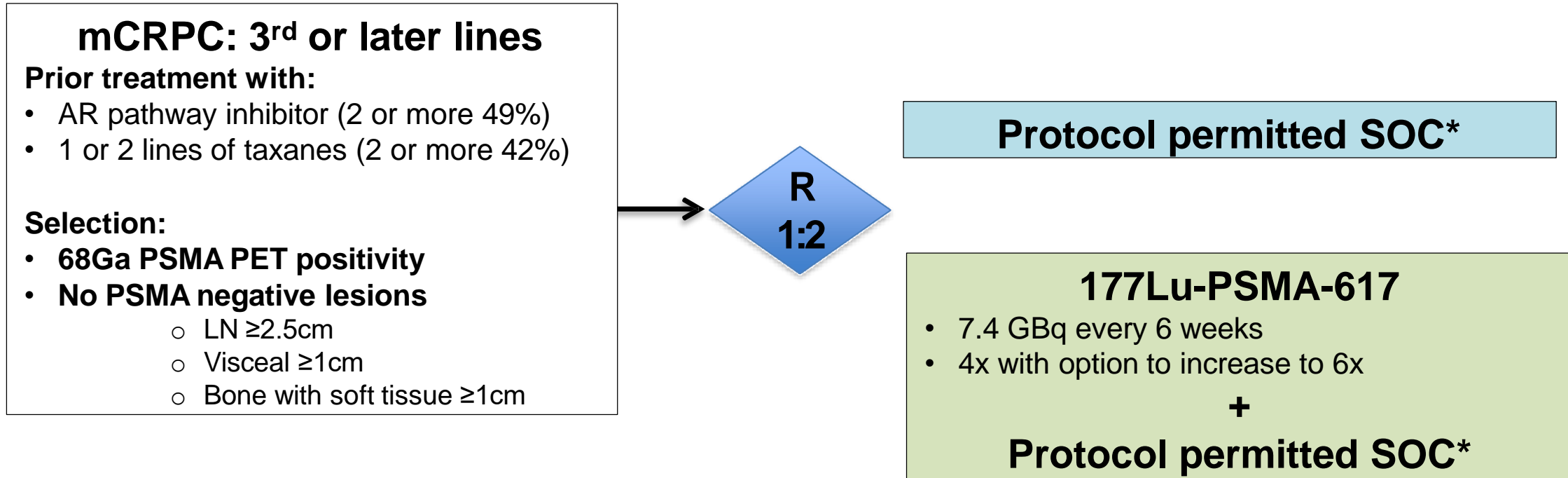
## Patients avec BRCA1/2 aberration Quand introduire un iPARP ?

1. Après une ligne AR
2. Après une ligne AR et une ligne de chimiothérapie
3. Après une ligne AR, une ligne de chimiothérapie et Lutetium- PSMA
4. iPARP non recommandé chez les patients avec altération BRCA1/2 si une autre option est accessible



Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2021

# VISION Trial: Design



VISION n=831

Accrual: 06/2018 – 10/2019

\*Protocol permitted SOC: AR pathway inhibitors e.g. abiraterone, enzalutamide, steroids, radiation therapy.

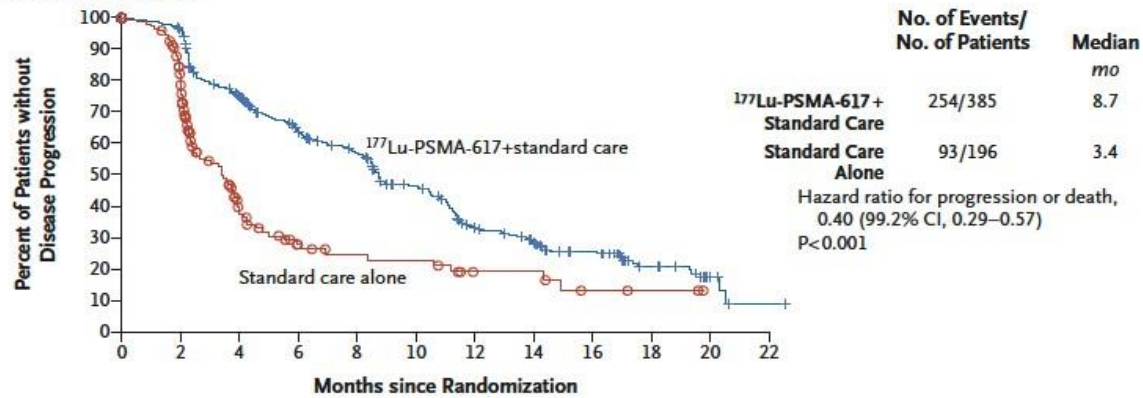
**NOT:** Chemotherapy or radium-223 or clinical trial

## Alternate Primary Endpoints

- **rPFS**
  - and/or
- **OS**

# VISION: Positive for primary endpoints

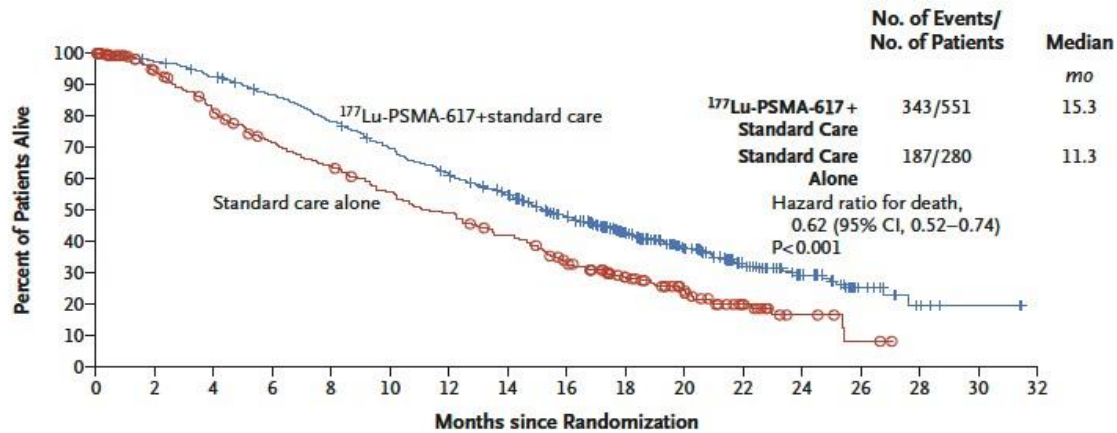
**A Imaging-Based Progression-free Survival**



**No. at Risk**

<sup>177</sup> Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

**B Overall Survival**



**No. at Risk**

<sup>177</sup> Lu-PSMA-617+standard care	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
Standard care alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

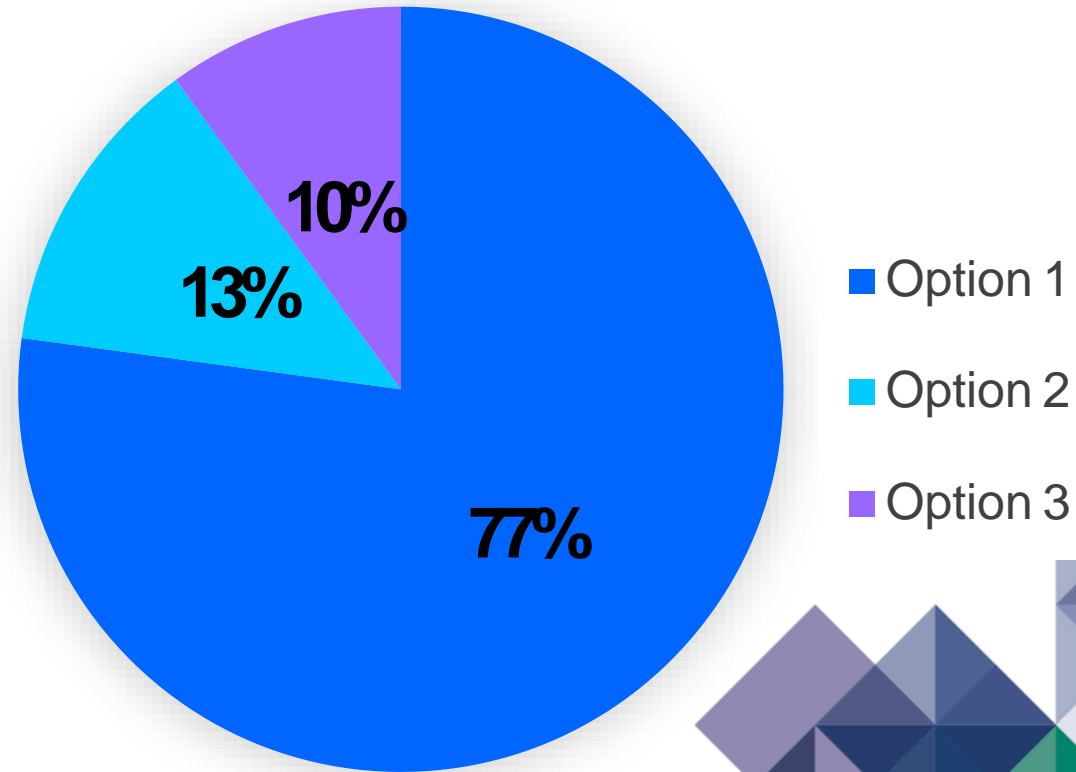
rPFS

OS

ORR: 9% CR and 42% PR  
PSA  $\geq$ 50%: 46%

**Patients fit pour la CT avec PET PSMA+ éligibles au Lutetium-PSMA,  
ayant reçu au moins une ligne AR et une CT type TAXANES**

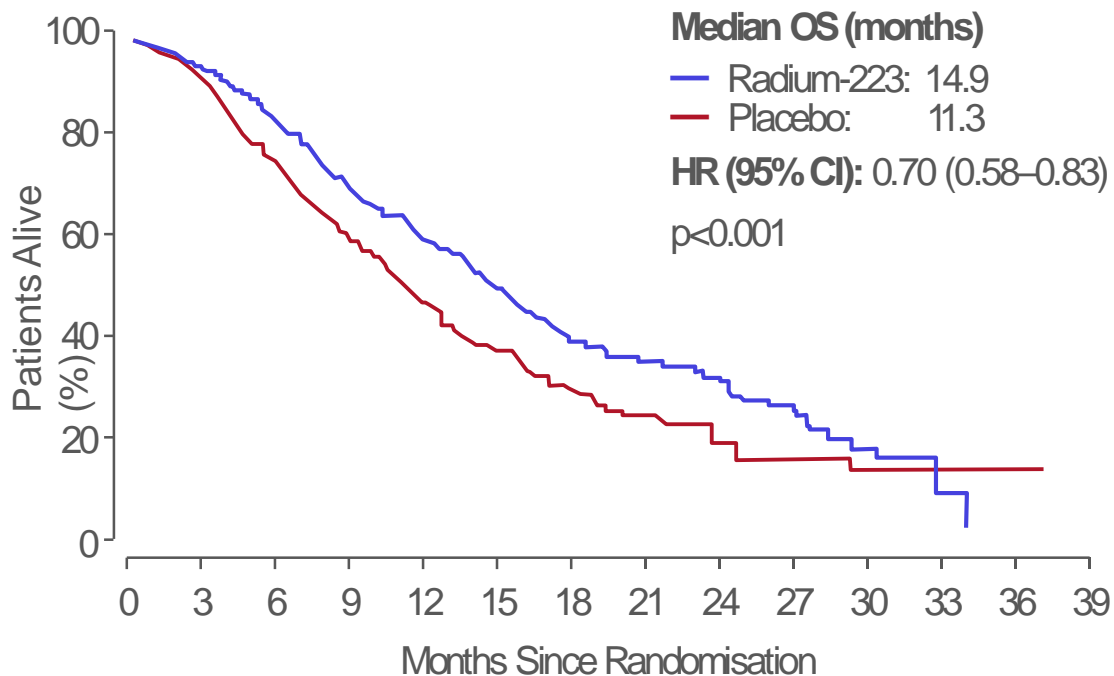
- 1. Lutetium-PSMA therapy**
- 2. Cabazitaxel**
- 3. Radium-223 si éligibles**



Preliminary results. For interpretation of results please refer to publication, which will follow shortly after APCCC 2021

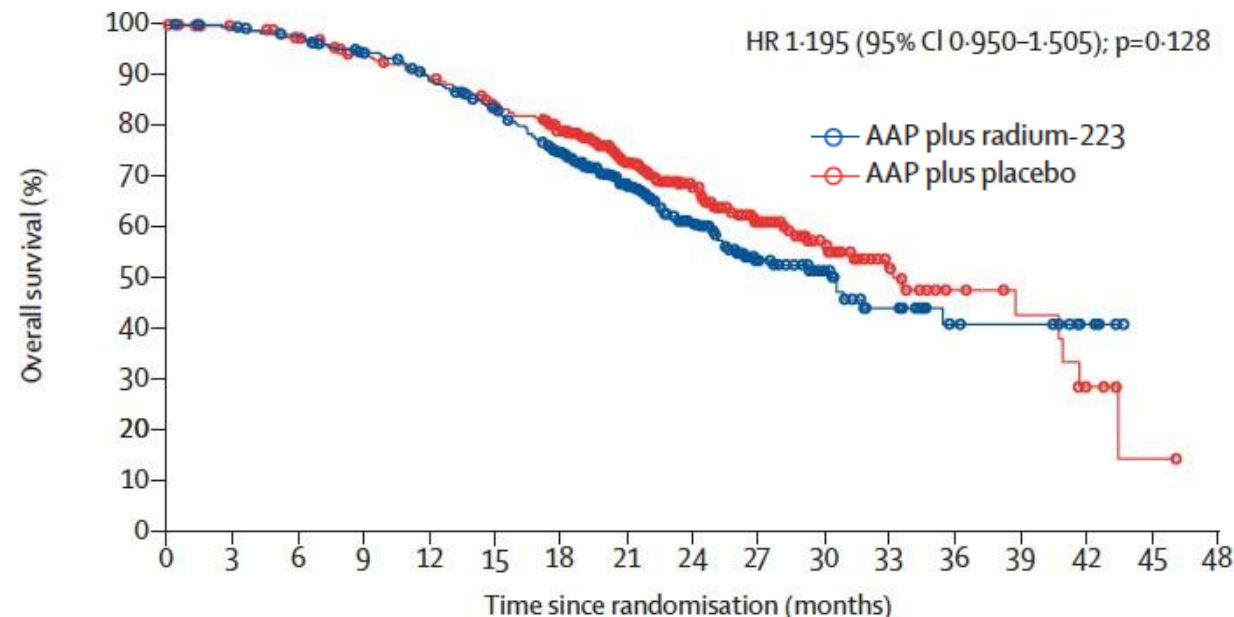
## ALSYMPCA: Phase 3 Study of Radium-223 vs Placebo in Men with mCRPC and Bone Metastases

### Overall Survival



Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

### Overall Survival



# Take Home Messages for mCRPC I

- Différents options thérapeutiques prolongeant la OS mais, séquence “optimale” non clairement établie
- Situation beaucoup plus complexe que celle des combinaisons thérapeutiques dans le mHSPC
- Les PSA seuls ne suffisent pas pour la prise de décisions dans le mCRPC: **Need Imaging!**
- Pas de changement de ligne devant l'élévation précoce des PSA en cas de M+ os seules.

# Take Home Messages for mCRPC II



- **La plupart des patients fit à la CT doivent recevoir des TAXANES**
- **Abi/P après Enza faible activité, Enza après Abi/P activité modeste chez des patients présélectionnés**
- **Le meilleur usage du Radium-223 n'est pas clairement élucidé, (uniquement pour les patients symptomatiques sans M+ viscérales ni adénomégalies)**

# Take Home Messages for mCRPC III

- La 3<sup>ème</sup> ligne chez les patients ayant reçu du docetaxel et une TNG: Cabazitaxel, Lutetium<sup>177</sup>-PSMA-617 ou Olaparib
- Nous disposons à présent d'un traitement pour un sous-groupe avec une présélection biomoléculaire: **Olaparib**, mais le timing optimal pour son usage est encore incertain.
- Le monitoring thérapeutique et la sélection minutieuse de la séquence thérapeutique demeurent importants

**Merci pour votre attention**

