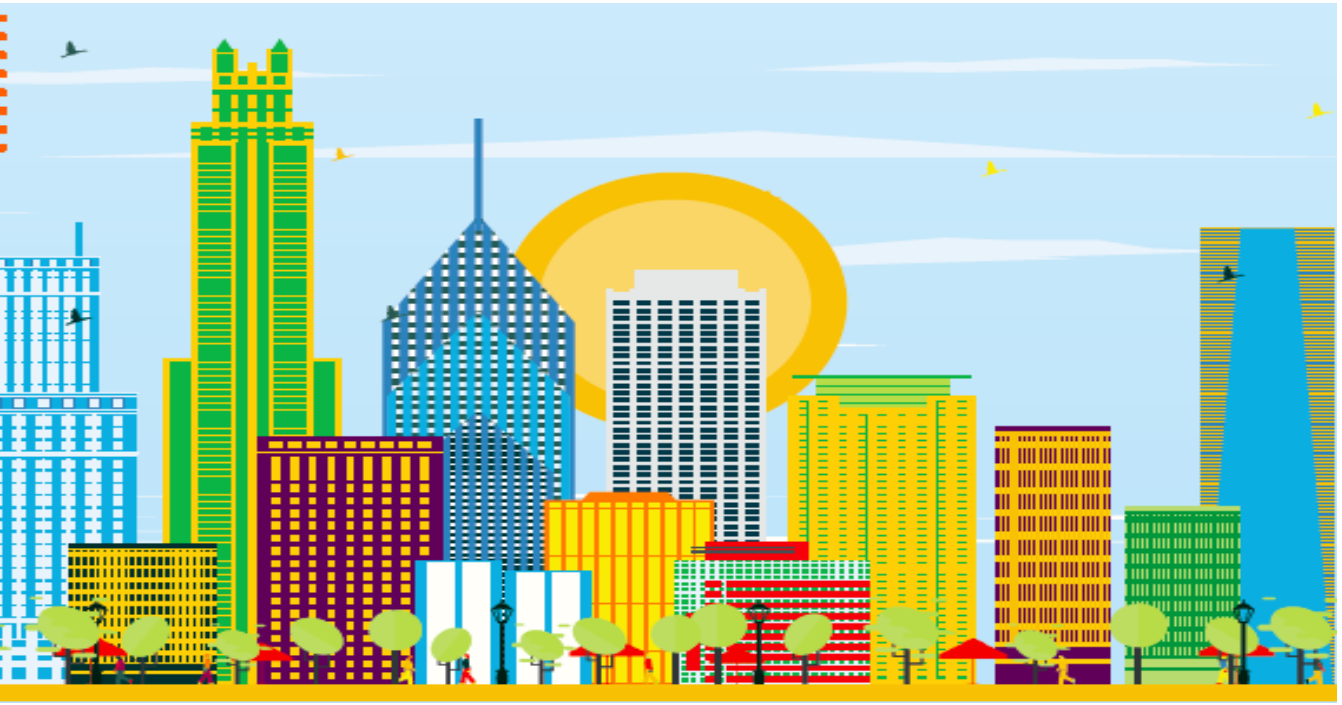
AIGOM
ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

19 GIUGNO
2023
ore 15.00 - 18.00

LE NOVITA'
DA CHICAGO 2023:
l'evoluzione delle conoscenze in oncologia...



Neoplasie Genito-Urinarie: Tumore della Prostata

Chiara Ciccarese, MD. PhD.
UOC Oncologia Medica
Fondazione Policlinico A. Gemelli IRCCS, Roma

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Comprehensive Cancer Center

Agenda

- **Il ruolo della RT nel trattamento del de-novo mCSPC – studio PEACE-1**
- ***Ruolo prognostico delle alterazioni di HRR (BRCA1/2) – studio CAPTURE***
- ***Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2***
- ***C'è spazio per nuove combinazioni? – studio LuPARP***

De-novo mCSPC - quale ruolo per la RT?

2023 ASCO ANNUAL MEETING

PEACE ProstatE cAncer Consortium in Europe

Prostate irradiation in men with *de novo*, low-volume, metastatic castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design

Alberto BOSSI,
Institut Gustave Roussy, Amethyst RT Group, France

Stéphanie Foulon, Xavier Maldonado, Paul Sargos, Ray McDermott, Paul Kelly, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Naji Salem, Fabio Calabro', Jean-François Berdah, Ali Hasbini, Marlon Silva, Jihane Boustani, Hélène Ribault, Karim Fizazi

La RT nel *de-novo* mCSPC - PEACE-1

Design of PEACE-1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease: ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)

Nov 2013 – Dec 2018

RANDOMIZATION 1:1:1:1

n = 1172

- **SOC (n = 296)**
- **SOC+Abiraterone (n = 292)**
- **SOC+Radiotherapy (n = 293)**
- **SOC+Abiraterone+ Radiotherapy (n = 291)**

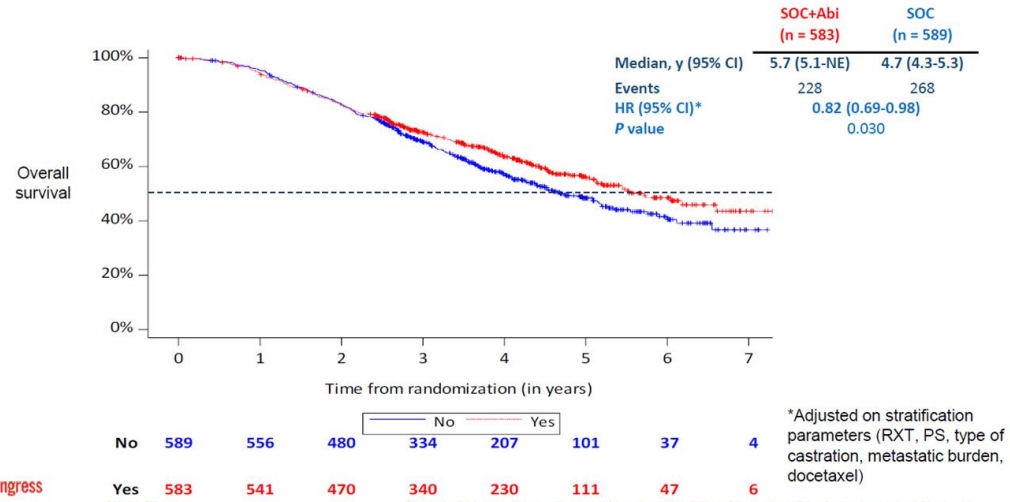
ECOG PS, Eastern Cooperative Oncology Group performance status

La tripletta nel *de-novo* mCSPC – *PEACE-1*

Patient characteristics (ADT+docetaxel population)

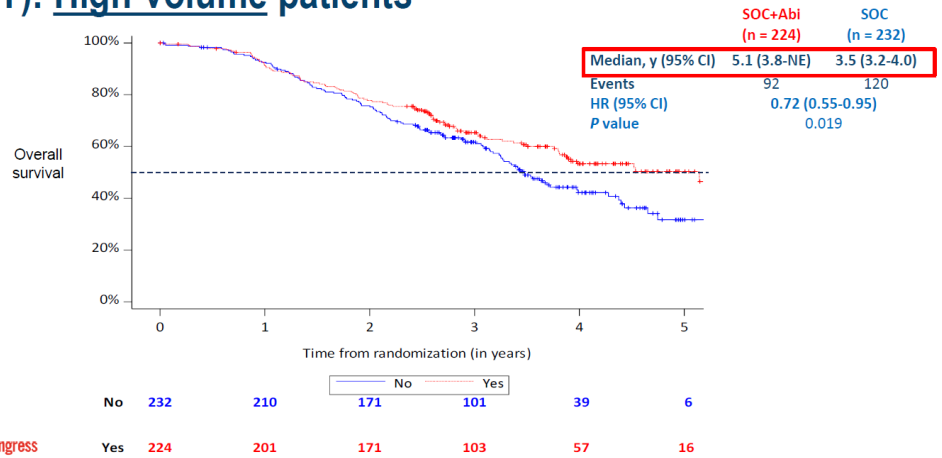
		SOC (+/- RXT) + Abiraterone (n = 355)	SOC (+/- RXT) (n = 355)
Median age, year (IQR)		66 (60–70)	66 (59–70)
ECOG PS score, n (%)	0 1-2	250 (70) 105 (30)	246 (69) 109 (31)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	79 (23) 270 (77)	71 (21) 276 (79)
Median time from diagnosis, month (IQR)		2.2 (1.6-3.0)	2.2 (1.4-2.9)
Metastatic sites, n (%)	Lymph nodes only Bone without visceral Visceral	27 (8) 287 (81) 41 (12)	29 (8) 279 (79) 47 (13)
Disease burden, n (%)	Low High	131 (37) 224 (63)	123 (35) 232 (65)
Median baseline PSA, ng/mL (IQR)		13.7 (2.4-58.9)	12.0 (3.0-59.9)
Docetaxel, n (%)	Yes No	355 (100) 0 (0)	355 (100) 0 (0)

OS in the Overall population

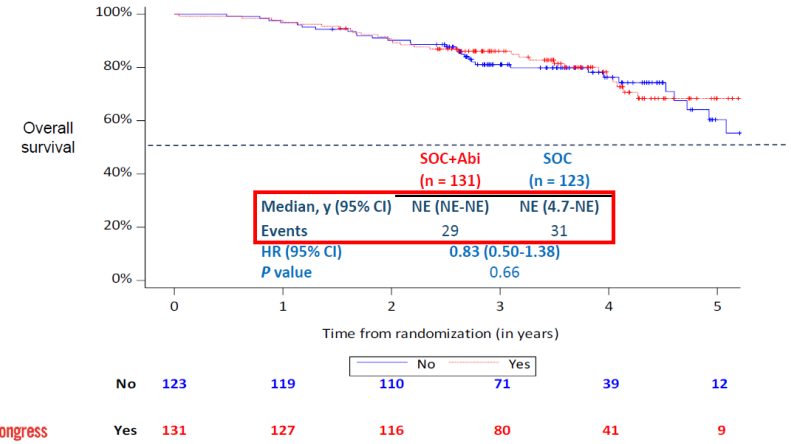


*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, docetaxel)

OS with Abiraterone in the ADT+docetaxel (+/-RXT): High-volume patients



OS with Abiraterone in the ADT+docetaxel (+/-RXT): Low-volume patients



La RT nel *de-novo* mCSPC – *PEACE-1*

Patients' characteristics (low volume population)

43%

11

		SOC (+/- Abi) (n = 253)	SOC (+/- Abi) + Radiotherapy (n = 252)
Median age, year (Min-Max)		67 (43–86)	66 (46–84)
ECOG PS score, n (%)	0 1-2	180 (71) 73 (29)	194 (77) 58 (23)
Gleason score at diagnosis, n (%)	≤ 7 ≥ 8 Missing	71 (27) 173 (70) 9 (3)	66 (26) 184 (73) 2 (1)
Median time from diagnosis, month (IQR)		2.5 (1.8-3.4)	2.6 (1.7-3.5)
Metastatic sites, n (%)	Lymph nodes only Bone only	47 (19) 206 (81)	41 (16) 211 (84)
Median baseline PSA, ng/mL (IQR)		10.3 (3.3-31)	9 (2.3-39.1)
Docetaxel, n (%)	Yes No	127 (50) 126 (50)	127 (50) 125 (50)

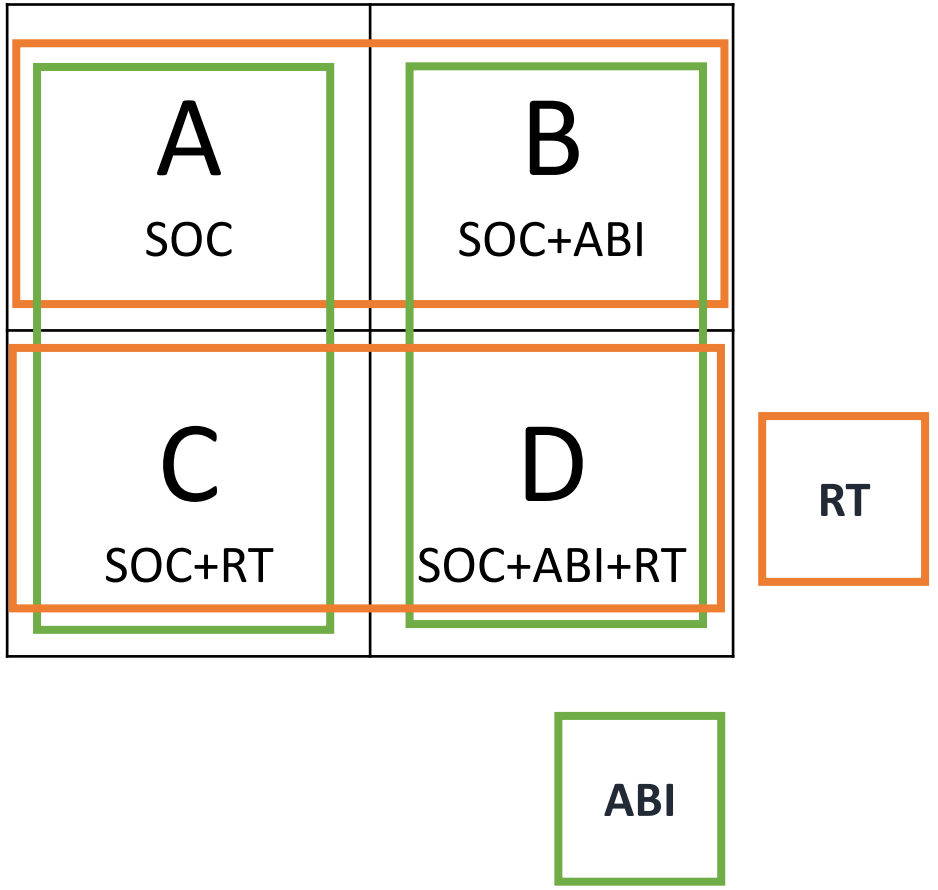
median follow-up : 73 months

La RT nel *de-novo* mCSPC – *PEACE-1*

Statistical Analysis

For rPFS, a qualitative interaction between RT and Abi was observed (p=0.026) and each experimental arm was assessed individually.

For OS, the predefined threshold for a statistical interaction was not reached (p=0.12) and the 2 RT arms were pooled for the analysis.



La RT nel *de-novo* mCSPC – *PEACE-1*

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A SOC	B SOC+ABI
C SOC+RT	D SOC+ABI+RT

La RT nel *de-novo* mCSPC – *PEACE-1*

Statistical Analysis

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A SOC	B SOC+ABI
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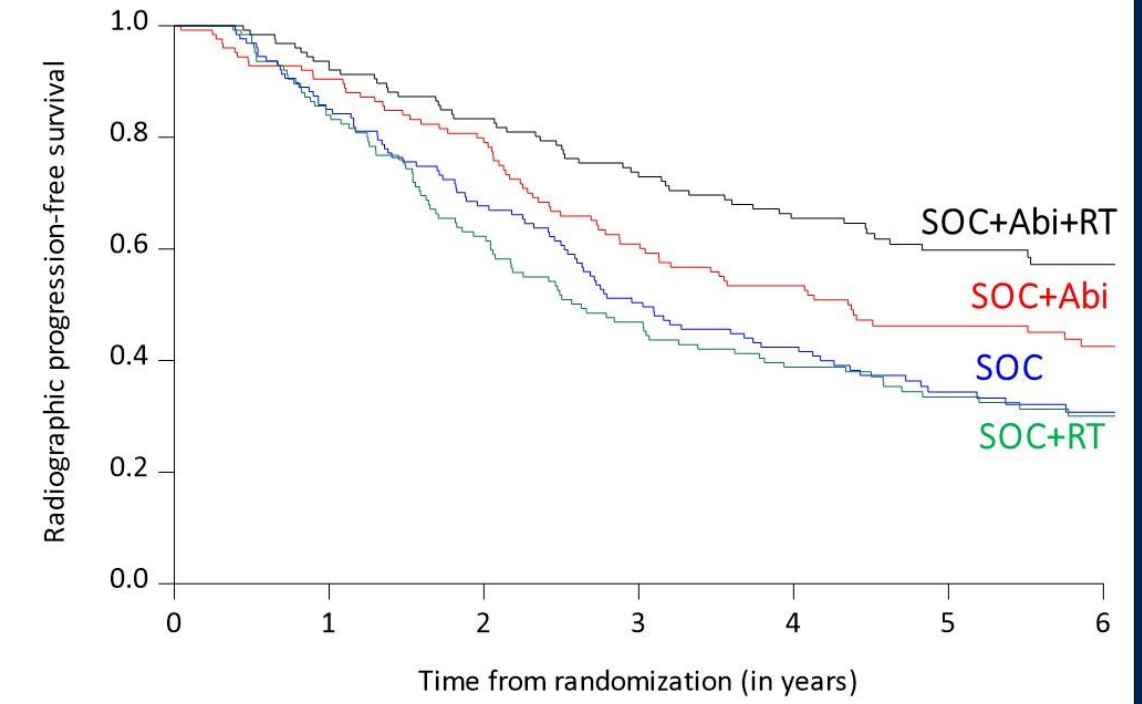
La RT nel *de-novo* mCSPC – *PEACE-1*

rPFS (low volume population)



Number at risk (censored)

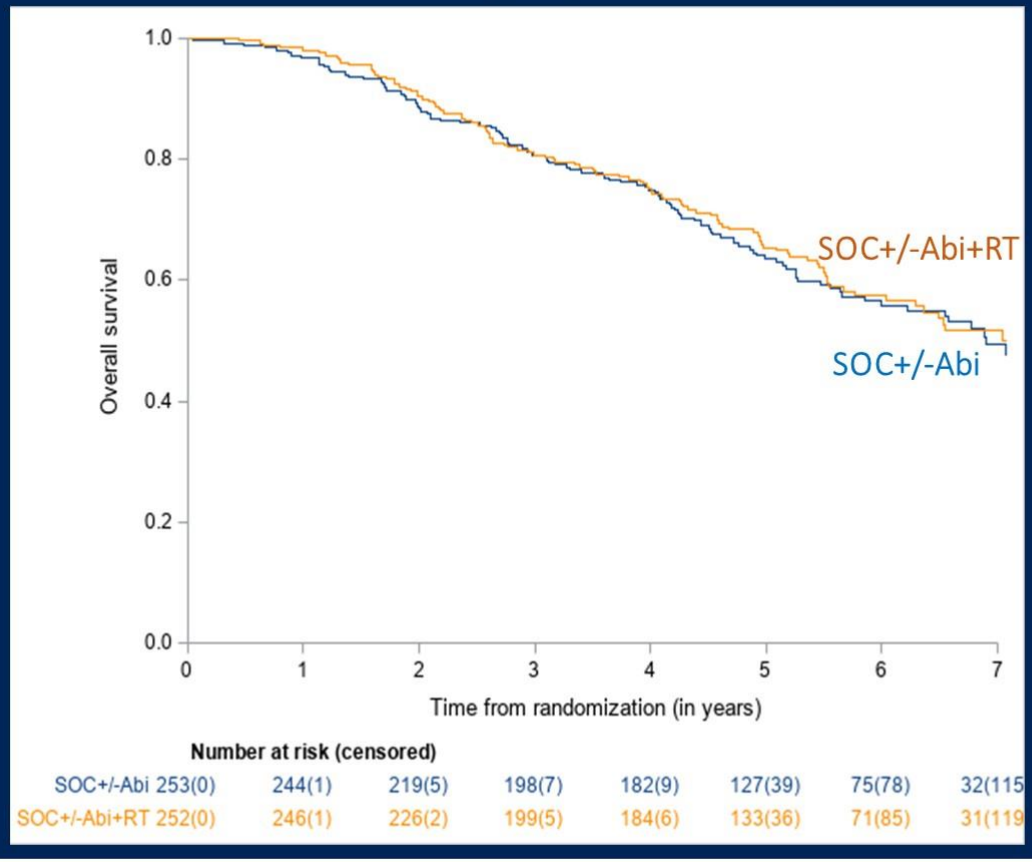
SOC	127(0)	108(0)	86(0)	64(0)	53(1)	34(11)	20(22)
SOC+Abi	126(0)	113(1)	96(4)	73(5)	64(5)	46(15)	31(27)
SOC+RT	126(0)	105(1)	77(2)	58(2)	48(2)	36(8)	23(18)
SOC+Abi+RT	126(0)	116(0)	105(0)	89(3)	79(4)	60(17)	34(41)

	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

*Adjusted on stratification factors (PS, type of castration, docetaxel)

La RT nel *de-novo* mCSPC – *PEACE-1*

OS (low volume population)



	SOC+/Abi (n=253)	SOC+/-Abi++RT (n=252)
Median, ys. (95.1% CI)	6.9 (5,9-7,5)	7.5 (6-NE)
Events, n	111	104
HR*	Ref	0.98 (0.74-1.28)
p-value	0.86	

*Adjusted on Abitraterone and stratification factors (PS, type of castration, docetaxel)

PRESENTED BY: Alberto Bossi

La RT nel *de-novo* mCSPC – *PEACE-1*

Time to serious genito-uninary events

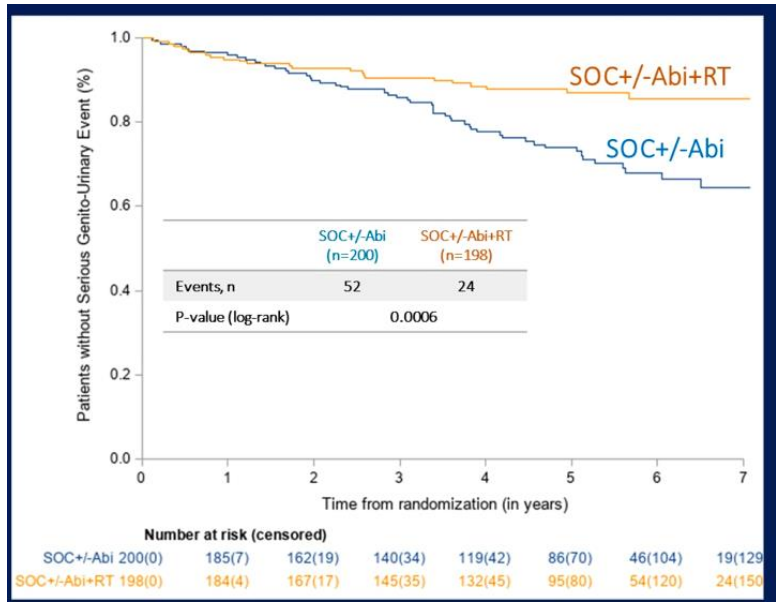
Low-volume

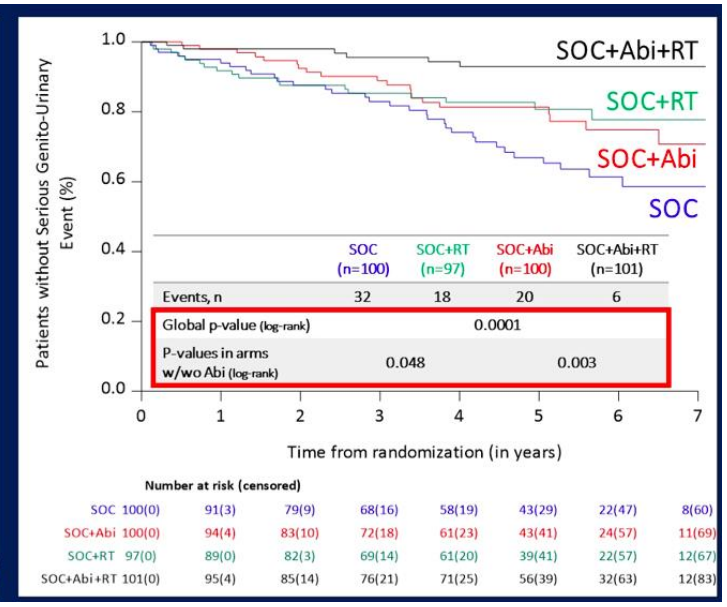
25%

Serious genito-urinary events

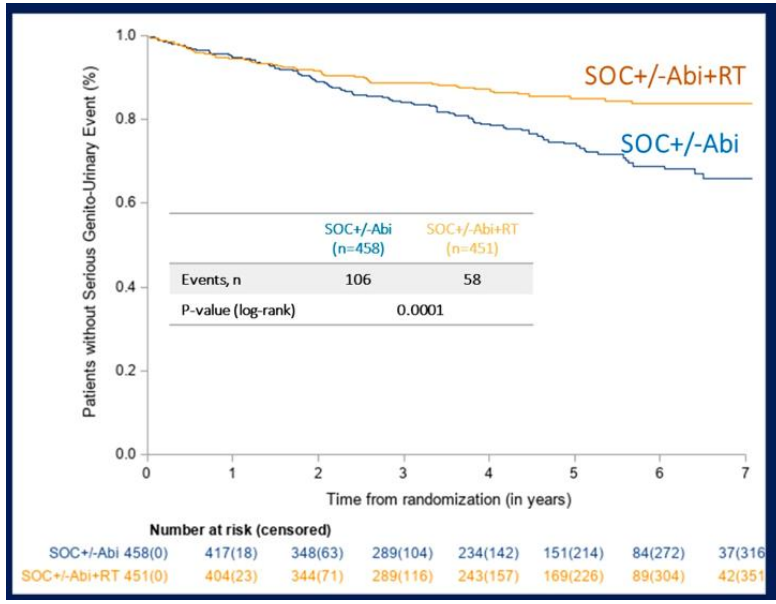
	No RT (n=200)	RT (n=198)
Urinary Catheter	9	6
Double J Stent	13	12
Nephrostomy	2	1
Prostate RT or TURP	27	4 TURP (all RT)
Radical Prostatectomy	1	1

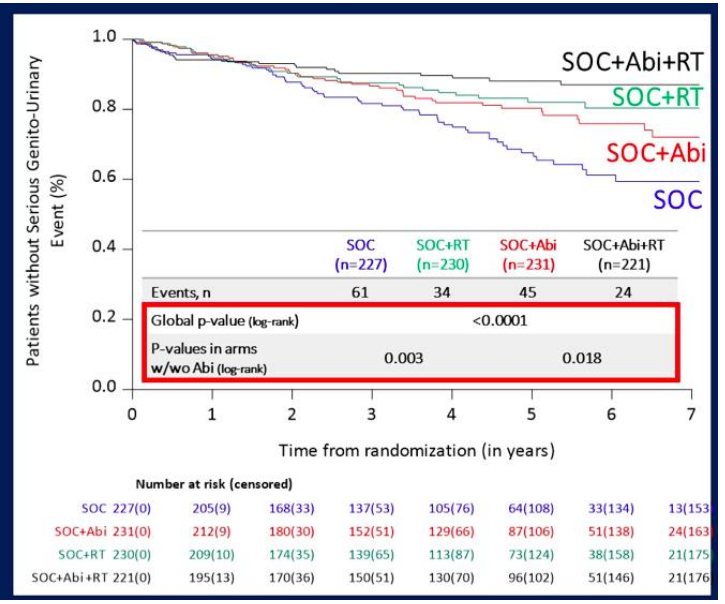
High radiation dose (74 Gy)



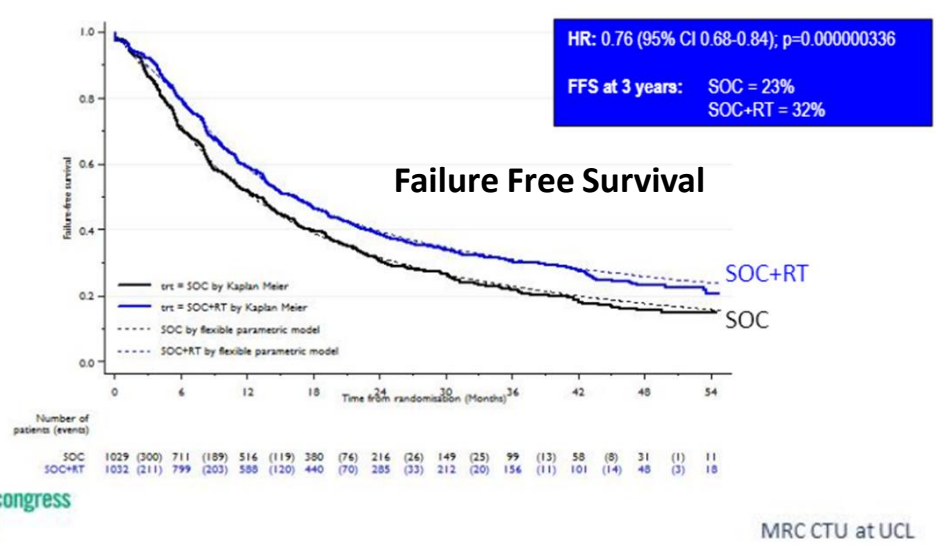


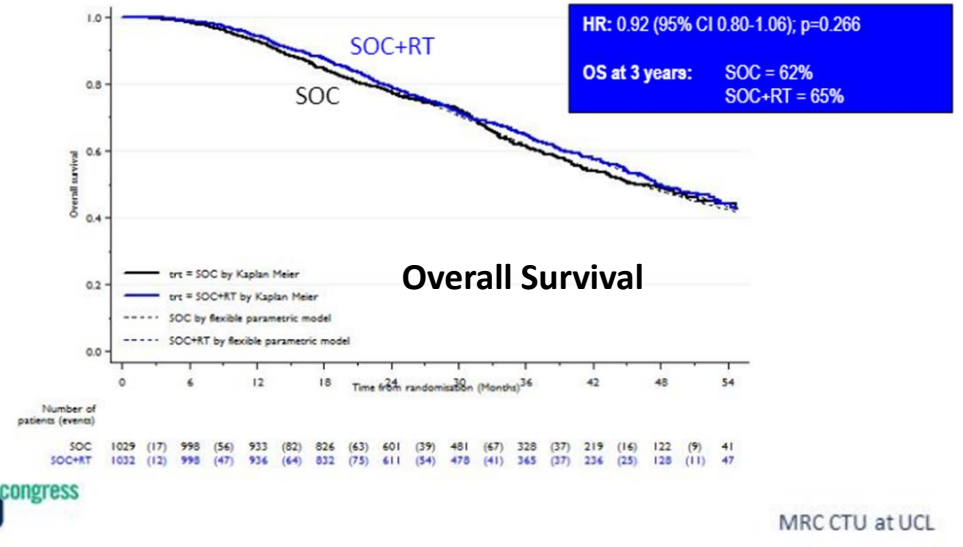
Overall population



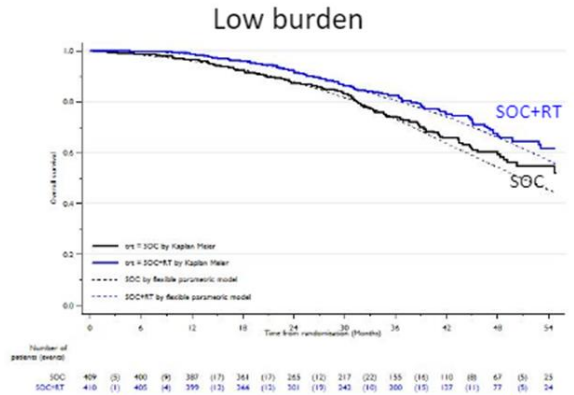


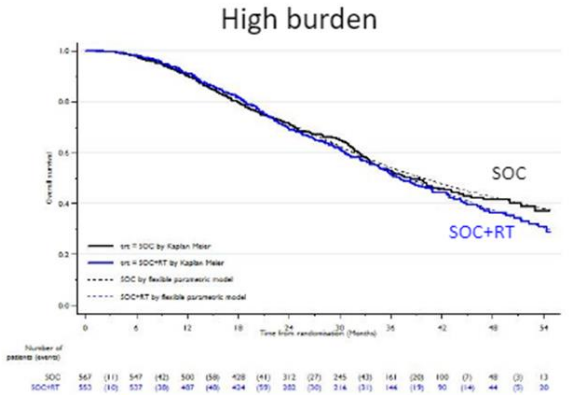
Studio STAMPEDE arm H e ruolo della RT sul tumore primario





La RT sul tumore primario sembra avere un ruolo nel prolungare la sopravvivenza solo nei pazienti a basso volume di malattia

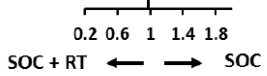


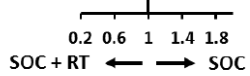


Studio STAMPEDE arm H e ruolo della RT sul tumore primario

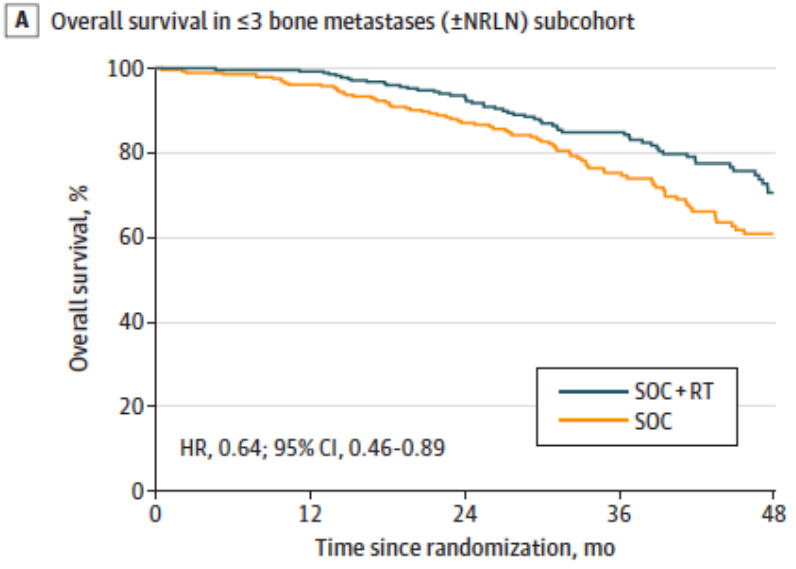
TREATMENT EFFECTS BY BONE METASTASIS COUNTS

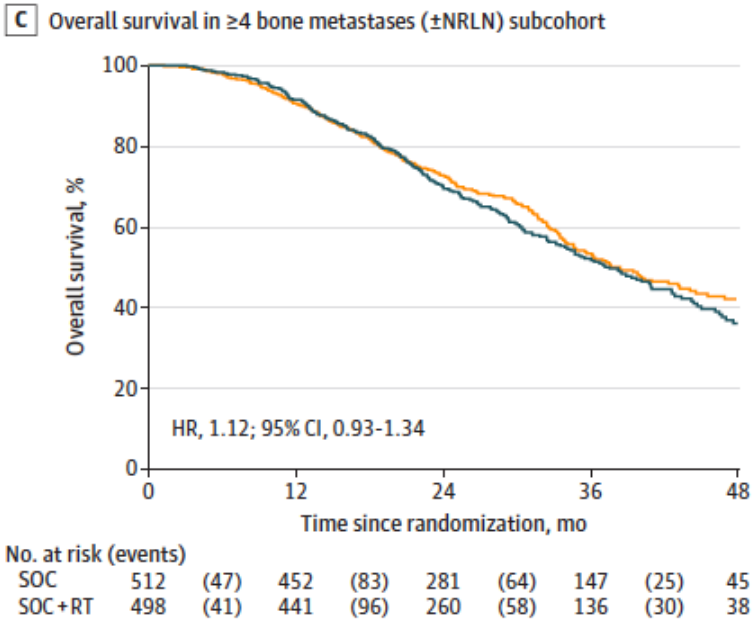
Number of bone metastasis	Overall survival SOC	Overall survival SOC + RT	Overall survival HR (95%CI)	Failure-free survival SOC	Failure-free survival SOC +RT	Failure-free survival HR (95%CI)
0	46/138	28/120	0.59 (0.37 – 0.95)	88/138	57/120	0.57 (0.41 – 0.81)
1	41/137	34/156	0.63 (0.40 – 0.99)	86/137	74/156	0.59 (0.43 – 0.81)
2	15/79	14/87	0.76 (0.37 – 1.58)	46/79	41/87	0.68 (0.44 – 1.04)
3	21/63	13/46	0.80 (0.40 – 1.60)	46/63	27/46	0.67 (0.41 – 1.08)
4	16/69	22/72	1.63 (0.85 – 3.12)	49/69	47/72	0.84 (0.55 – 1.26)
5	13/47	21/53	1.21 (0.60 – 2.44)	28/47	39/53	1.06 (0.64 – 1.75)
6	14/30	14/23	1.62 (0.75 – 3.47)	22/30	19/23	0.94 (0.51 – 1.76)
≥7	202/413	201/406	1.02 (0.84 – 1.24)	355/413	338/406	0.86 (0.74 – 1.00)





BARCELONA 2019 ESMO congress

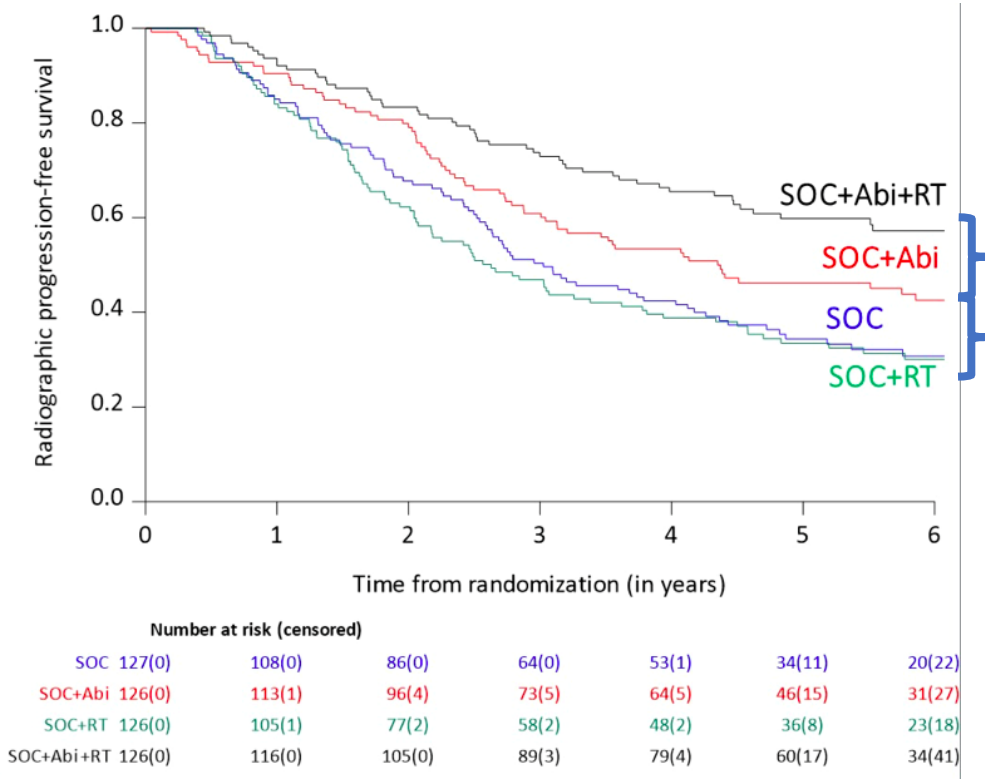




Amin A, et al. ESMO Abst #850PD
Amin A. JAMA Oncol 2021

La RT nel *de-novo* mCSPC

Il beneficio della RT dipende dall'efficacia delle terapie sistemiche?



Beneficio della RT
(HR 0.65)

Beneficio di Abi
(HR 0.76)

L'entità del beneficio di aggiungere la RT prostatica a SOC+Abi è simile al beneficio dato dall'aggiunta di Abi allo SOC

La RT nel *de-novo* mCSPC

Why No Benefit in Low Volume Population When RT Was Added to SOC Systemic Therapy?

Why do the results differ from Stampede Arm H?

- More effective initial SOC therapy (50% vs. 18% docetaxel)?
- More effective next line systemic therapies?
- Differences in patient population?

	Follow Up	Overall Survival	
		SOC	SOC + RT
STAMPEDE	5.1 yr	64 mo	86 mo
PEACE-1	6.1 yr	83 mo	90 mo

Bossi ASCO 2023;
Parker C PLOS Medicine 2022

La RT nel *de-novo* mCSPC

- Il trattamento RT sul tumore primitivo nel paziente con de-novo mCSPC a basso volume (ed in casi selezionati in pazienti ad alto volume) va valutato per prevenire i sintomi locali e migliorare il controllo di malattia, sebbene il suo impatto sulla sopravvivenza sia poco chiaro

- Resta da chiarire qual è il ruolo della metastasis-directed therapy e come questa possa influire sulla prostate-directed RT (anche considerando l'uso della PET-PSMA)

- Sono in corso studi per valutare se la chirurgia possa avere lo stesso ruolo della RT (IP2-ATLANTA, SWOG S1802)

Agenda

- Il ruolo della RT nel trattamento del de-novo mCSPC – studio PEACE-1
- ***Ruolo prognostico delle alterazioni germinali/somatiche di HRR (BRCA1/2) – studio CAPTURE***
- *Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2*
- *C'è spazio per nuove combinazioni? - studio LuPARP*

mCRPC e mutazioni di HRR – ruolo prognostico

2023 ASCO ANNUAL MEETING

CAPTURE

Hospital Universitario 12 de Octubre

Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients receiving first-line (1L) treatment stratified by BRCA status

David Olmos[1], David Lorente[2], Daniel Alameda[3], Carlo Cattrini[4], Nuria Romero-Laorden[5], Rebeca Lozano[6], Pedro P. Lopez-Casas[1], Camille Capone[7], Anne Marie Vanden Broecke[8], Marco Trevisan[9], Suzy Van Sanden[10], Alexandra Jürgens[11], Bernardo Herrera-Imbroda[3,12], Elena Castro[1,3]

1. Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain; 2. Hospital Provincial de Castellón, Castellón, Spain; 3. Instituto de Investigación Biomédica de Málaga, Málaga, Spain; 4. Maggiore della Carità University Hospital, Novara, Italy; 5. Hospital Universitario de la Princesa, Madrid, Spain; 6.Hospital Universitario de Salamanca, Salamanca, Spain; 7. Janssen Inc., Issy Les Moulineaux, France; 8. Janssen-Cilag B.V., Beerse, Belgium; 9. Janssen Pharmaceuticals, Zug, Switzerland; 10. Janssen Pharmaceutica NV, Beerse, Belgium; 11. Janssen, Neuss, Germany; 12. Hospital Universitario Virgen de la Victoria, Málaga, Spain

Ruolo della mutazione di BRCA nel CaP

In case of any BRCA1/2 mutation:

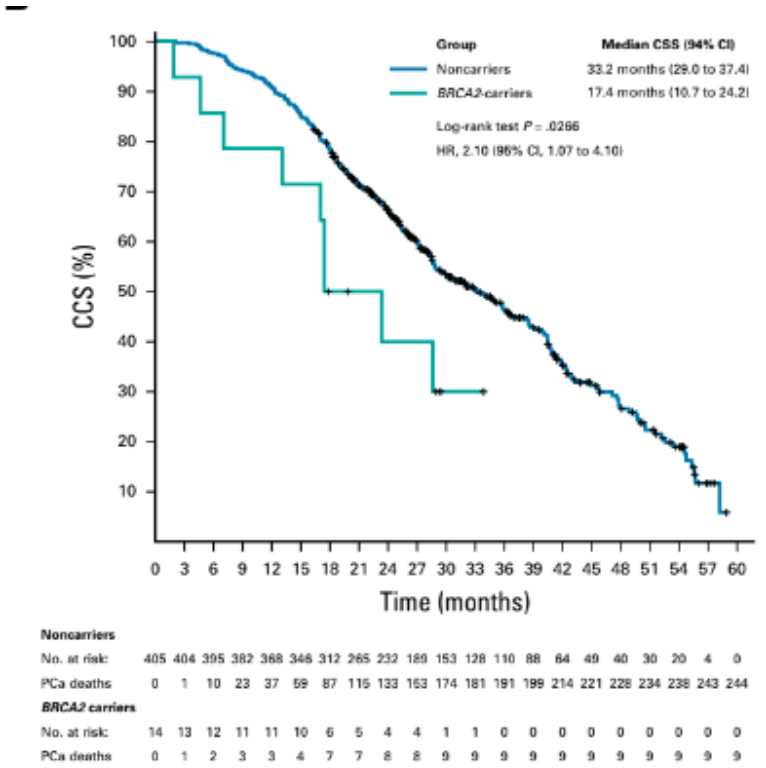
- About 2 times increased risk of PCa (OR = 1.90, 95% CI = 1.58-2.29) for BRCA1 and/or BRCA2 carriers;[1]
- Risk of PCa greater for BRCA2 (OR = 2.64, 95% CI = 2.03-3.47) than BRCA1 (OR = 1.35, 95% CI = 1.03-1.76)[1]

In case of mCRPC:

- The frequency of pathogenic alterations (LoF) in **DDR genes** is around 30%.[2]
- The frequency of pathogenic alterations in BRCA2 and BRCA1 in mCRPC is around 10%
- The incidence of germline mutations in HRR is lower than somatic ones.[3]

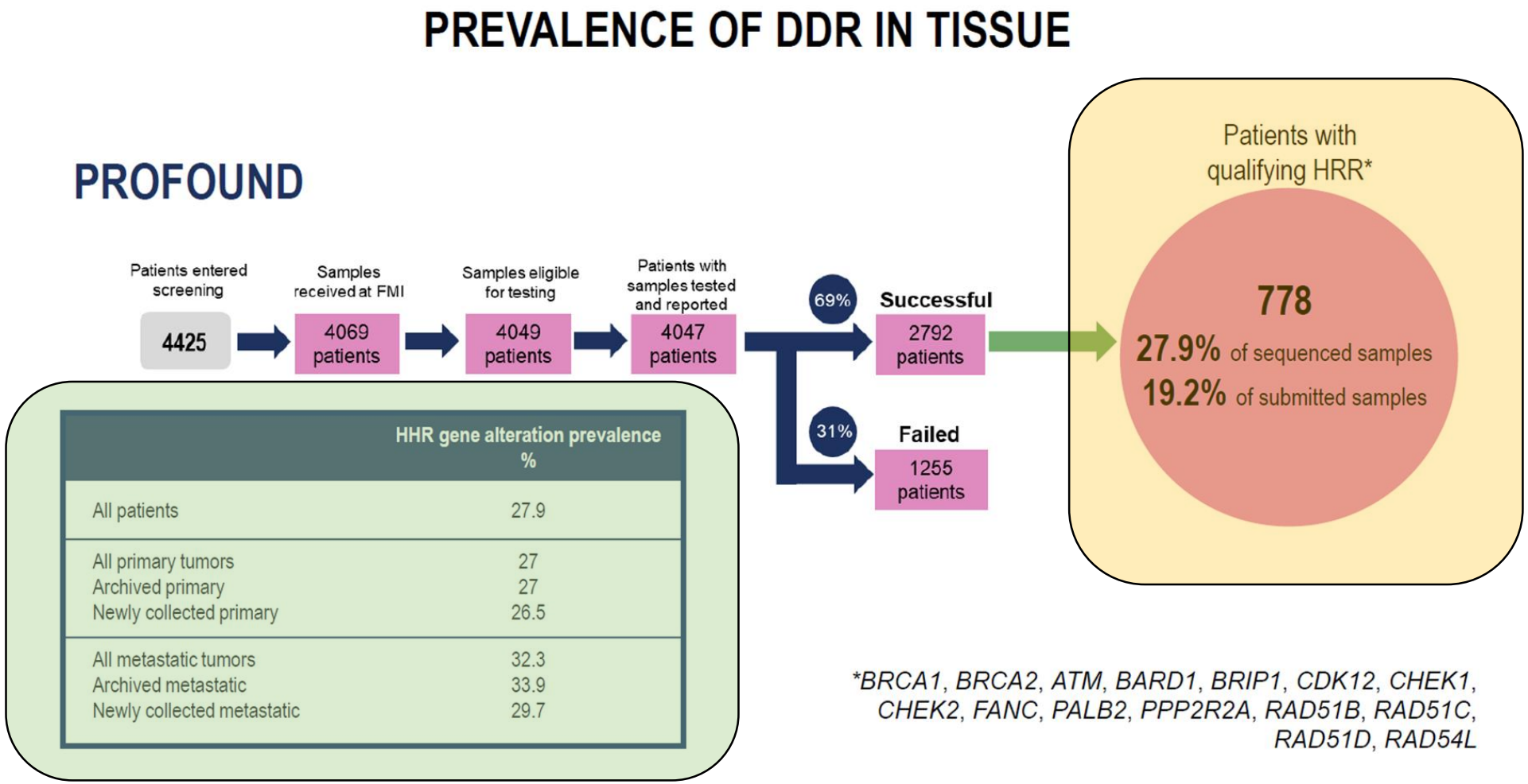
In case of PCa:

- **In BRCA2**, OS (HR = 2.21, 95% CI = 1.64-2.30) and CSS (HR = 2.63, 95% CI = 2.00-3.45) were significantly worse compared to noncarriers[4]
- **Germline mutations** LoF in **BRCA2** have been associated to **poor outcomes** in **mCRPC**[5]
- The poor prognostic role of somatic BRCA2 defects (and sDDR defects) has been suggested from indirect comparisons



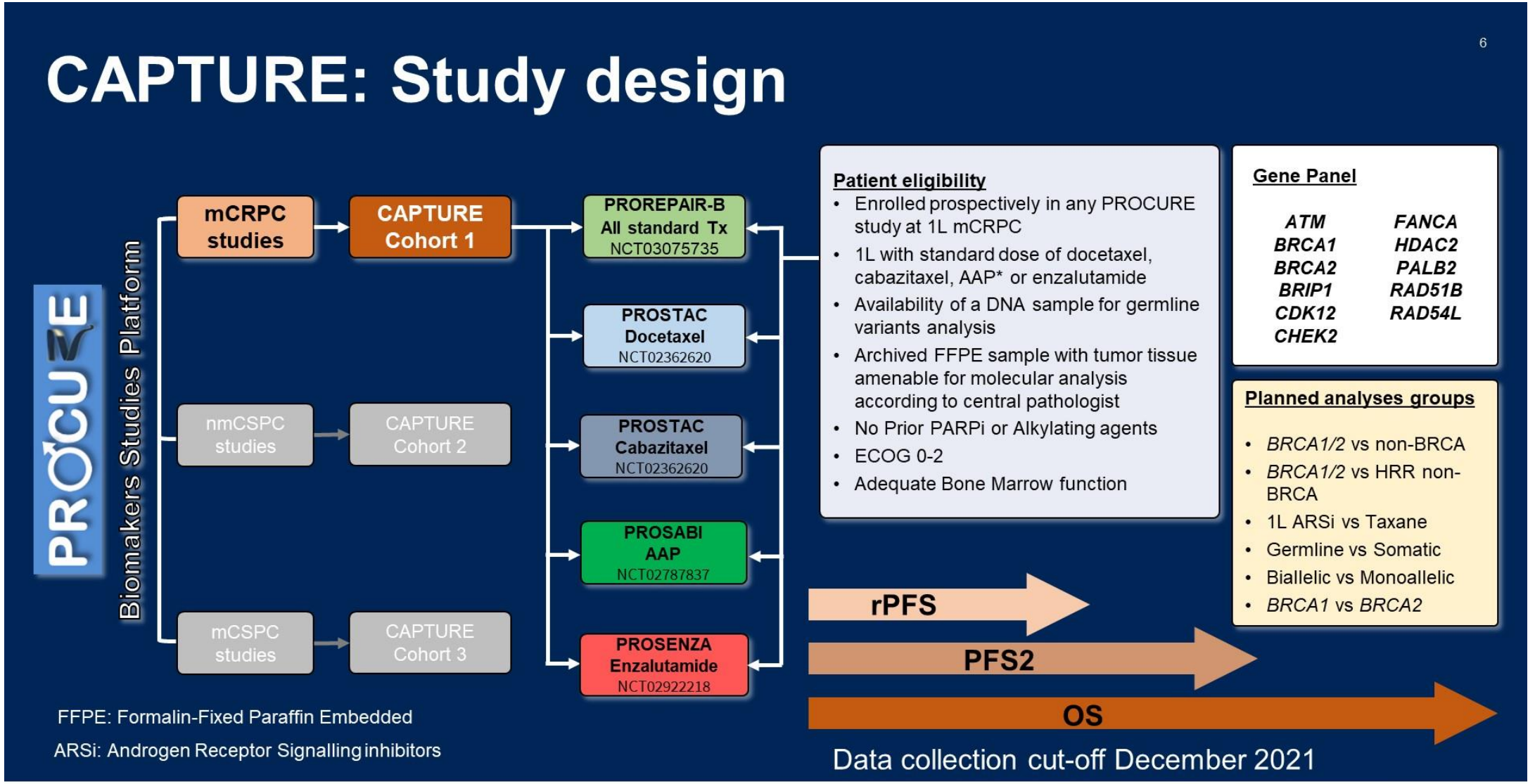
1.Oh M, et al. Prostate. 2019 Jun;79(8):880-895
2 Lozano et al Br J Cancer 2021
3. Mateo J et al. *New Engl J Med*. 2015;373:1697-708
4.Oh M, et al. Prostate. 2019 Jun;79(8):880-895
5. Castro E et al. J Clin Oncol 2019

Insegnamenti dal PROUND sul test



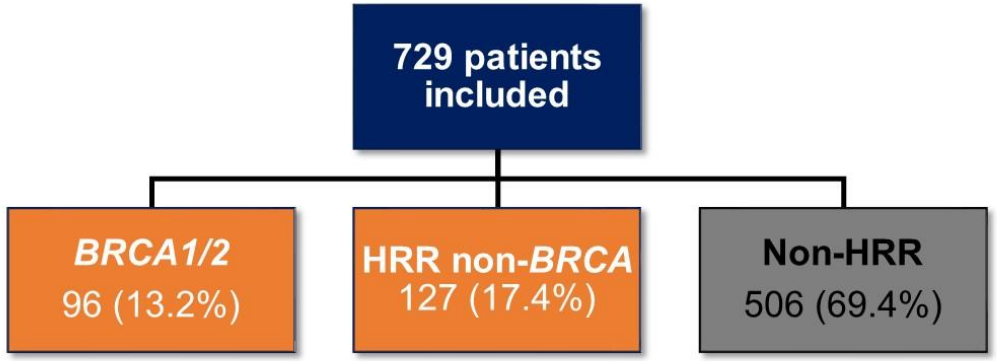
De Bono JS, et al. Annals of Oncology (2019) 30 (suppl_5): v325-v355.

mCRPC e mutazioni di HRR – ruolo prognostico

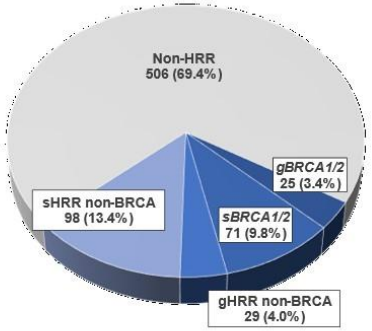


mCRPC e mutazioni di HRR – ruolo prognostico

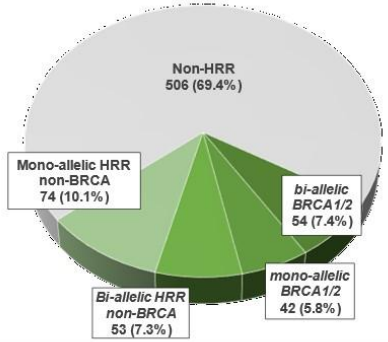
Prevalence and type of HRR alterations



Germline vs somatic



Bi-allelic vs Mono-allelic



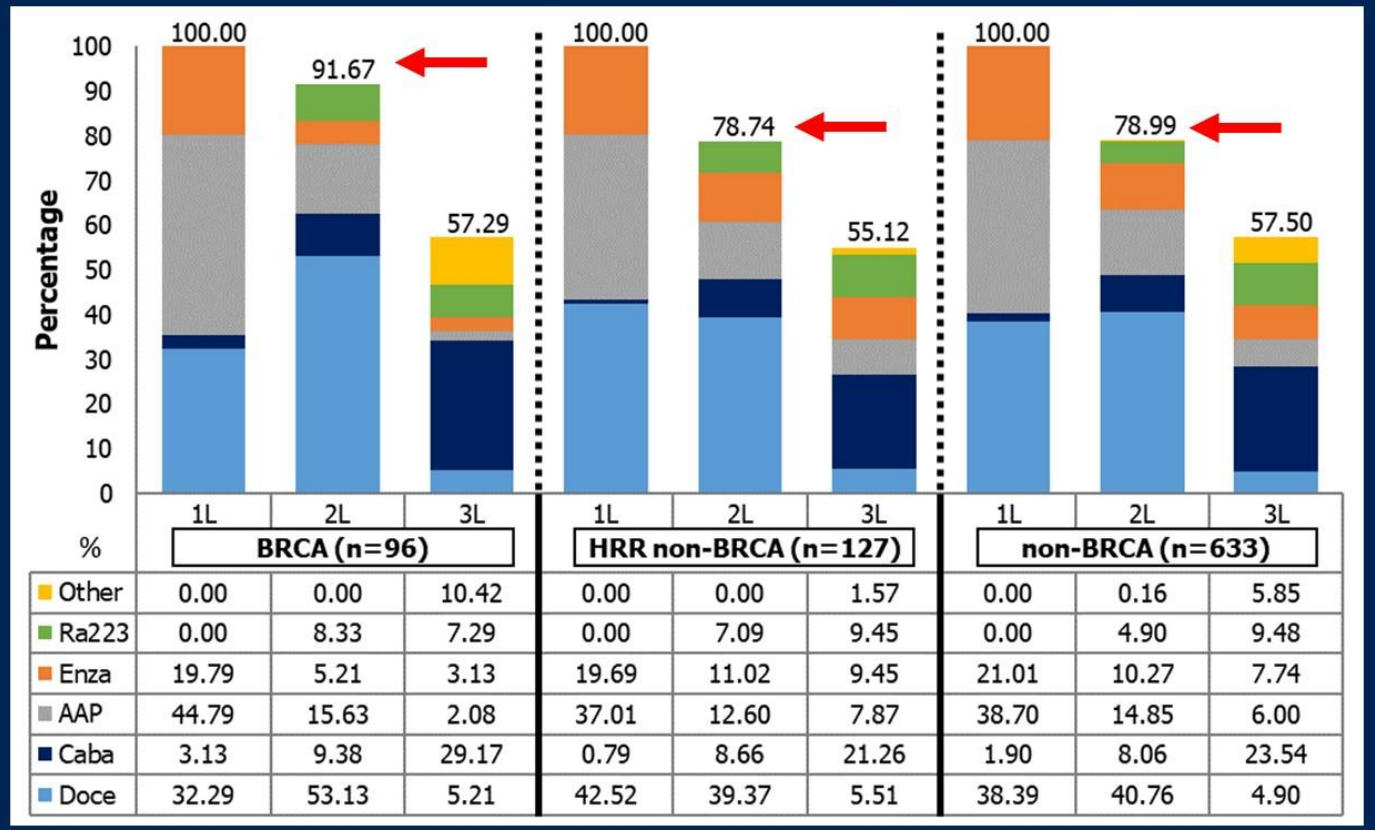
Gene by gene alterations*

Gene	n (%)
ATM	64 (8.8)
BRCA1	19 (2.6)
BRCA2	78 (10.7)
BRIP1	14 (1.9)
CDK12	15 (2.1)
CHEK2	11 (1.5)
FANCA	38 (5.2)
HDAC2	21 (2.9)
PALB2	4 (0.5)
RAD51B	3 (0.4)
RAD54L	5 (0.7)

*NOTE: 5.5% cases had alterations in >1 gene

mCRPC e mutazioni di HRR – ruolo prognostico

Treatment exposure by subgroup



%	1L	2L	3L	1L	2L	3L	1L	2L	3L
	BRCA (n=96)			HRR non-BRCA (n=127)			non-BRCA (n=633)		
Other	0.00	0.00	10.42	0.00	0.00	1.57	0.00	0.16	5.85
Ra223	0.00	8.33	7.29	0.00	7.09	9.45	0.00	4.90	9.48
Enza	19.79	5.21	3.13	19.69	11.02	9.45	21.01	10.27	7.74
AAP	44.79	15.63	2.08	37.01	12.60	7.87	38.70	14.85	6.00
Caba	3.13	9.38	29.17	0.79	8.66	21.26	1.90	8.06	23.54
Doce	32.29	53.13	5.21	42.52	39.37	5.51	38.39	40.76	4.90

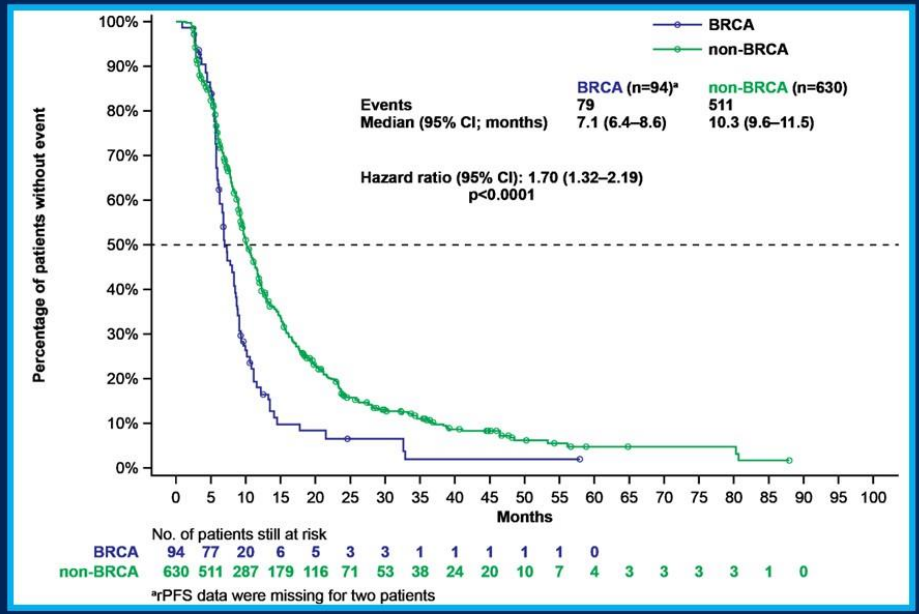
7pts BRCA1/2, 2 pts HRR non-BRC ,3 pts non-HRR non-BRCA received PARPi alone or incomabination as 3L, 4L or 5L for mCRPC

La scelta della prima linea di trattamento non differisce nei diversi gruppi molecolari, mentre i pazienti con mutazioni di BRCA1/2 hanno maggior probabilità di ricevere una II linea di terapia rispetto agli altri

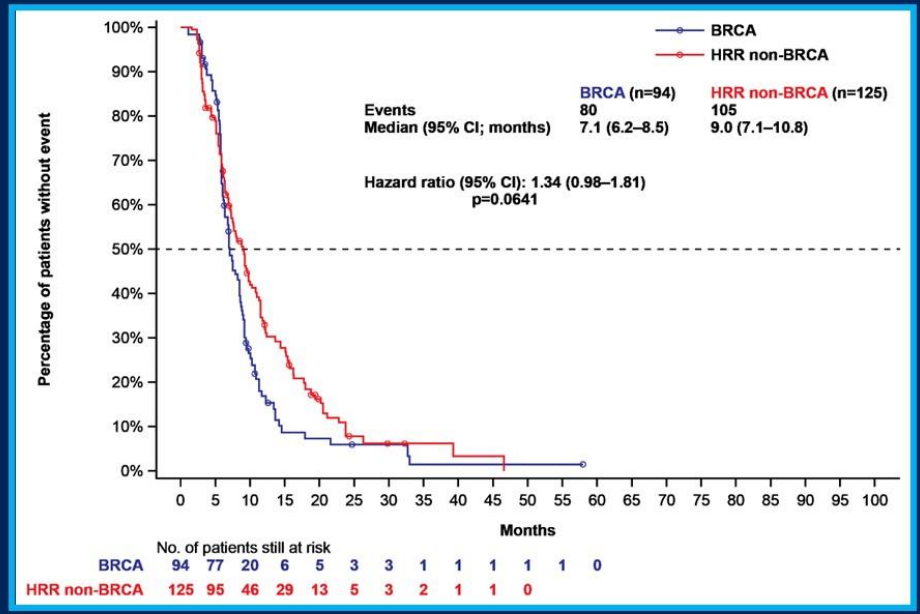
mCRPC e mutazioni di HRR – ruolo prognostico

Radiographic Progression Free-Survival

BRCA1/2 vs non-*BRCA*



BRCA1/2 vs HRR non-*BRCA*

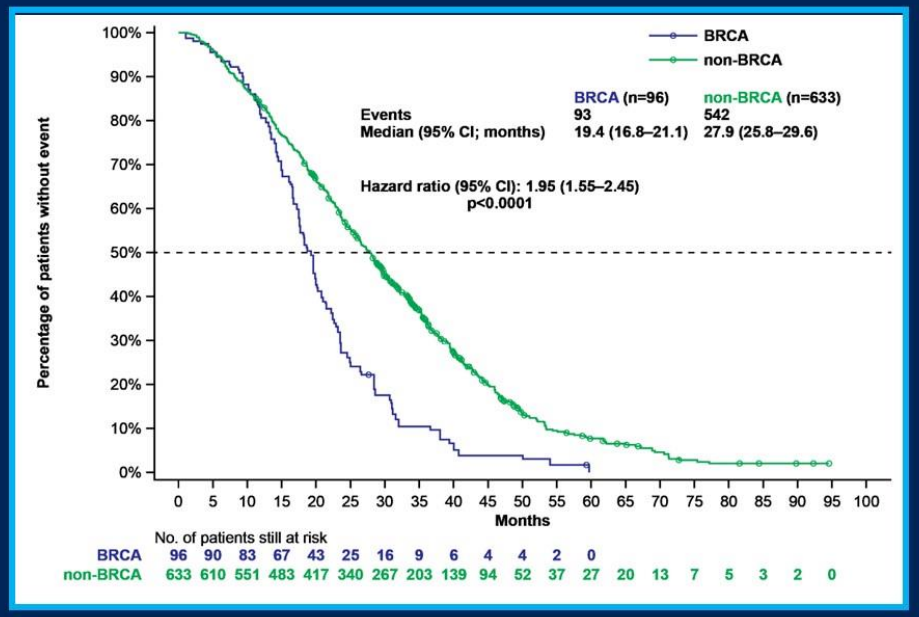


NOTE: propensity score weighted Kaplan Meier curves / Adjusted HR & p-values by Inverse probability weighted Cox models

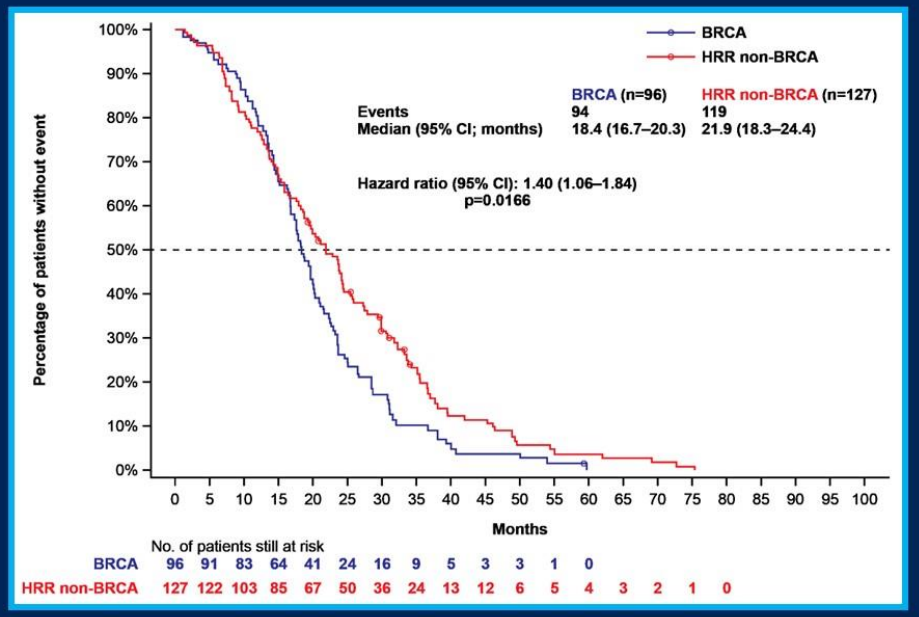
mCRPC e mutazioni di HRR – ruolo prognostico

Overall Survival

BRCA1/2 vs non-*BRCA*



BRCA1/2 vs HRR non-*BRCA*

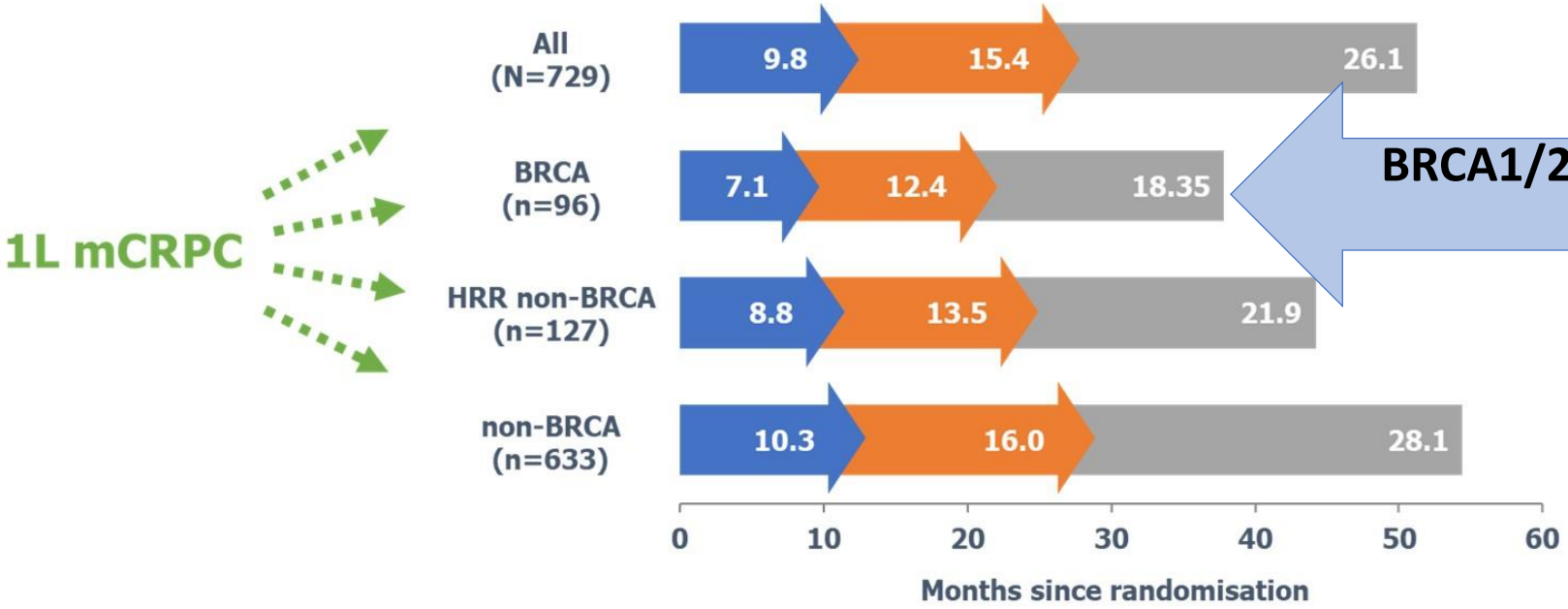


NOTE: propensity score weighted Kaplan Meier curves / Adjusted HR & p-values by Inverse probability weighted Cox models

mCRPC e mutazioni di HRR – ruolo prognostico

Summary of outcomes by subgroup

BRCA < HRR non-BRCA < All < non-BRCA



BRCA1/2 carriers have worse prognosis

NOTE: naïve, non-adjusted, median survival outcomes

mCRPC e mutazioni di HRR – ruolo prognostico

Exploratory analysis within BRCA1/2 subgroup

18

	rPFS		PFS2		OS	
	Median (95%CI)	HR (95%CI), p-value	Median (95%CI)	HR (95%CI), p-value	Median (95%CI)	HR (95%CI), p-value
Taxane 1L (n=34) vs ARSi 1L (n=62) *	7.0 m (3.0-9.5) vs 6.2 m (5.9-8.5)	1.03 (0.61-1.73), p = 0.918	12.7 m (9.5-16.6) vs 12.5 m (10.8-13.7)	1.06 (0.68-1.67), p = 0.796	18.7 m (14.1-19.7) vs 18.2 m (16.6-20.3)	1.21 (0.81-1.82), p = 0.346
Germline (n=25) vs Somatic (n=71) *	5.9 m (5.8-32.7) vs 8.2 m (6.4-8.9)	0.87 (0.38-.1.96), p = 0.729	13.9 m (9.0-19.0) vs 12.3 m (11.1-13.3)	0.67 (0.33-1.37), p = 0.270	22.5 m (16.7-31.2) vs 18.2 m (15.2-20.2)	0.56 (0.30-1.07), p = 0.078
Bi-allleic (n=54) vs Mono-allelic (n=42)	7.1 m (6.1-8.9) vs 7.0 m (5.9-9.4)	1.19 (0.75-1.88), p = 0.460	12.1 m (10.6-13.7) vs 12.6 m (10.9-15.8)	1.40 (0.92-2.15), p = 0.121	17.7 m (15.2-22.3) vs 19.4 m (13.4-20.9)	1.18 (0.76-1.85), p = 0.464
BRCA2 (n=78) vs BRCA1 (n=18) *	7.0 m (5.9-8.2) vs 8.6 m (5.9-10.9)	1.17 (0.76-1.81), p = 0.487	11.7 m (10.8-12.8) vs 14.4 m (8.1-19.3)	1.36 (0.81-2.30), p = 0.245	17.6 m (15.2-20.0) vs 20.3 m (11.3-31.0)	1.11 (0.68-1.83), p = 0.676

* Due to small sample size, the propensity score method was not able to fully balance the BL characteristics in the subgroup

- Nei pazienti con mutazioni di BRCA1/2 non vi è alcuna differenza fra la I linea con taxani o ARSI.
- Non si osserva inoltre nessuna differenza significativa fra mutazioni germinali o somatiche, alterazioni mono- o bi-alleliche, e mutazioni in BRCA 1 o 2.

mCRPC e mutazioni di HRR – ruolo prognostico

- Alterazioni germinali e somatiche di BRCA1 e 2 si associano a peggior outcomes (in termini di rPFS, PFS2 e OS) in pazienti con mCRPC trattati in I linea sia con ARSi che con taxani (quindi l'outcome peggiore è indipendente dal tipo di terapia in I linea)

- Alterazioni BRCA1/2 si associano a peggior prognosi rispetto alle alterazioni in altri geni HRR

- La prognosi peggiore di questi pazienti non è imputabile ad una minore esposizione a trattamenti efficaci nel sottogruppo di pazienti BRCA1/2 mutati

- Nel sottogruppo BRCA mutato non vi è alcuna differenza in PFS, PFS2 e OS per il tipo di mutazione (somatica vs germinale, mono-allelica vs bi-allelica, BRCA1 vs BRCA2)

BRCA1/2 are the key genes. Do molecular test!

Agenda

- Il ruolo della RT nel trattamento del de-novo mCSPC – studio PEACE-1
- *Ruolo prognostico delle alterazioni germinali/somatiche di HRR (BRCA1/2) – studio CAPTURE*
- ***Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2***
- *C'è spazio per nuove combinazioni? – studio LuPARP*

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

Presentation number 5004

2023 ASCO ANNUAL MEETING

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer harboring homologous recombination repair gene alterations (HRR-deficient population)

Karim Fizazi,[1] Arun A. Azad,[2] Nobuaki Matsubara,[3] Joan Carles,[4] Andre P. Fay,[5] Ugo De Giorgi,[6] Jae Young Joung,[7] Peter C. C. Fong,[8] Eric Voog,[9] Robert J. Jones,[10] Neal D. Shore,[11] Curtis Dunshee,[12] Stefanie Zschäbitz,[13] Jan Oldenburg,[14] Xun Lin,[15] Cynthia G. Healy,[16] Nicola Di Santo,[17] Fabian Zohren,[18] Neeraj Agarwal[19]

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ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

1L mCRPC: ARSI+PARPi

Trial	Therapy	rPFS HHRm	rPFS mBRCA1/2
MAGNITUDE	Abiraterone + Niraparib	0.73 (0.56 – 0.96)	0.53 (0.36 – 0.79)
PROpel	Abiraterone + Olaparib	0.50 (0.34 – 0.73)	0.23 (0.12 – 0.43)
TALAPRO-2	**Enzalutamide + Talazoparib**	**0.48 (0.31 – 0.74)**	**?**

Chi et al. JCO 2023
Clarke et al. NEJM Evidence 2022
Agarwal et al. ASCO GU 2023

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

Patient population
- First-line mCRPC
- ECOG performance status (PS) 0 or 1

Stratification factors
- Prior abiraterone[a] or docetaxel in castration-sensitive setting (yes vs no)
- HRR gene alteration status (deficient vs nondeficient or unknown)

All comers (Cohort 1), N=805

Nondeficient or unknown N=636 | HRRm N=169 | HRRm N=230

HRRm only (Cohort 2), N=399

1:1 (N=805)

Talazoparib 0.5 mg* + enzalutamide 160 mg, once daily
(N=402)
(*0.35 mg daily if moderate renal impairment)

Placebo + enzalutamide 160 mg, once daily
(N=403)

Primary endpoint
Radiographic progression-free survival (rPFS) by blinded independent central review (BICR)

Key secondary endpoint
- Overall survival (alpha protected)

Other secondary endpoints
- Time to cytotoxic chemotherapy
- PFS2 by investigator assessment[b]
- Objective response rate (ORR)
- Patient-reported outcomes
- Safety

(Data cutoff: August 16, 2022)

Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

We report results only from the all-comers cohort of men unselected for HRR gene alterations

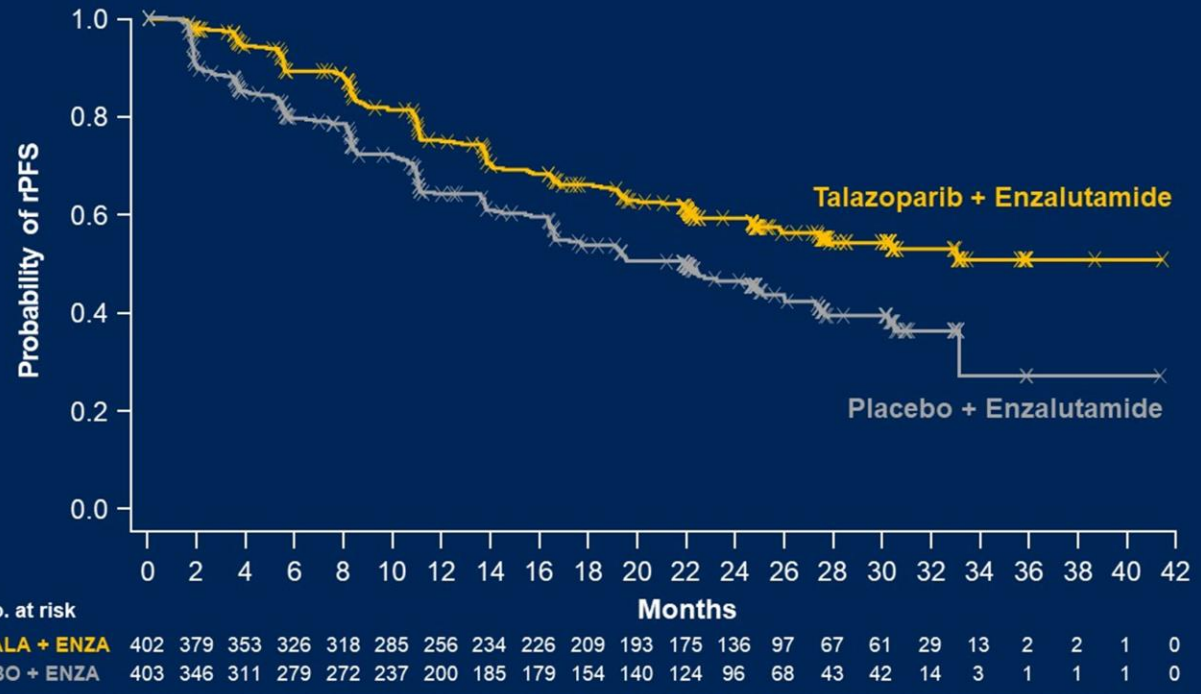
To maintain the overall type I error at or below 1-sided 0.025, alpha for rPFS by BICR was split equally between the all-comers and forthcoming molecularly selected cohort (1-sided alpha of 0.0125 for each). If the rPFS showed statistically significant improvement, overall survival was tested in a hierarchical stepwise procedure to preserve the overall type I error.

[a]Two patients in each treatment arm received prior orteronel. [b]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

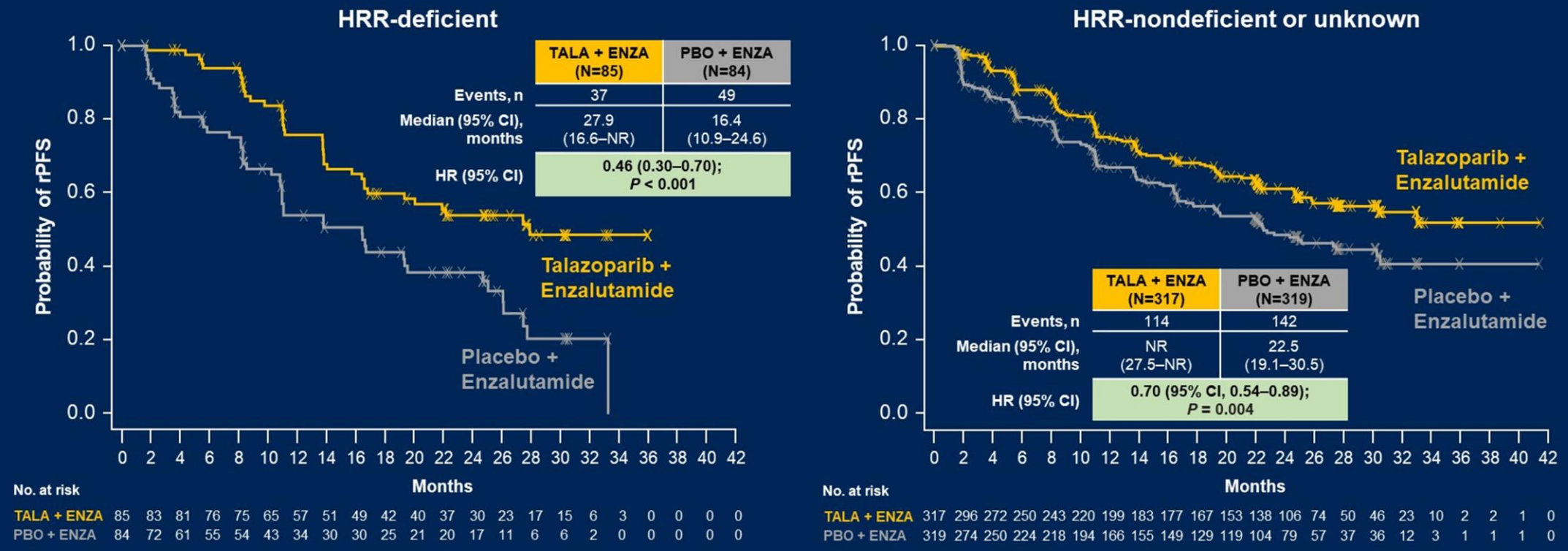
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

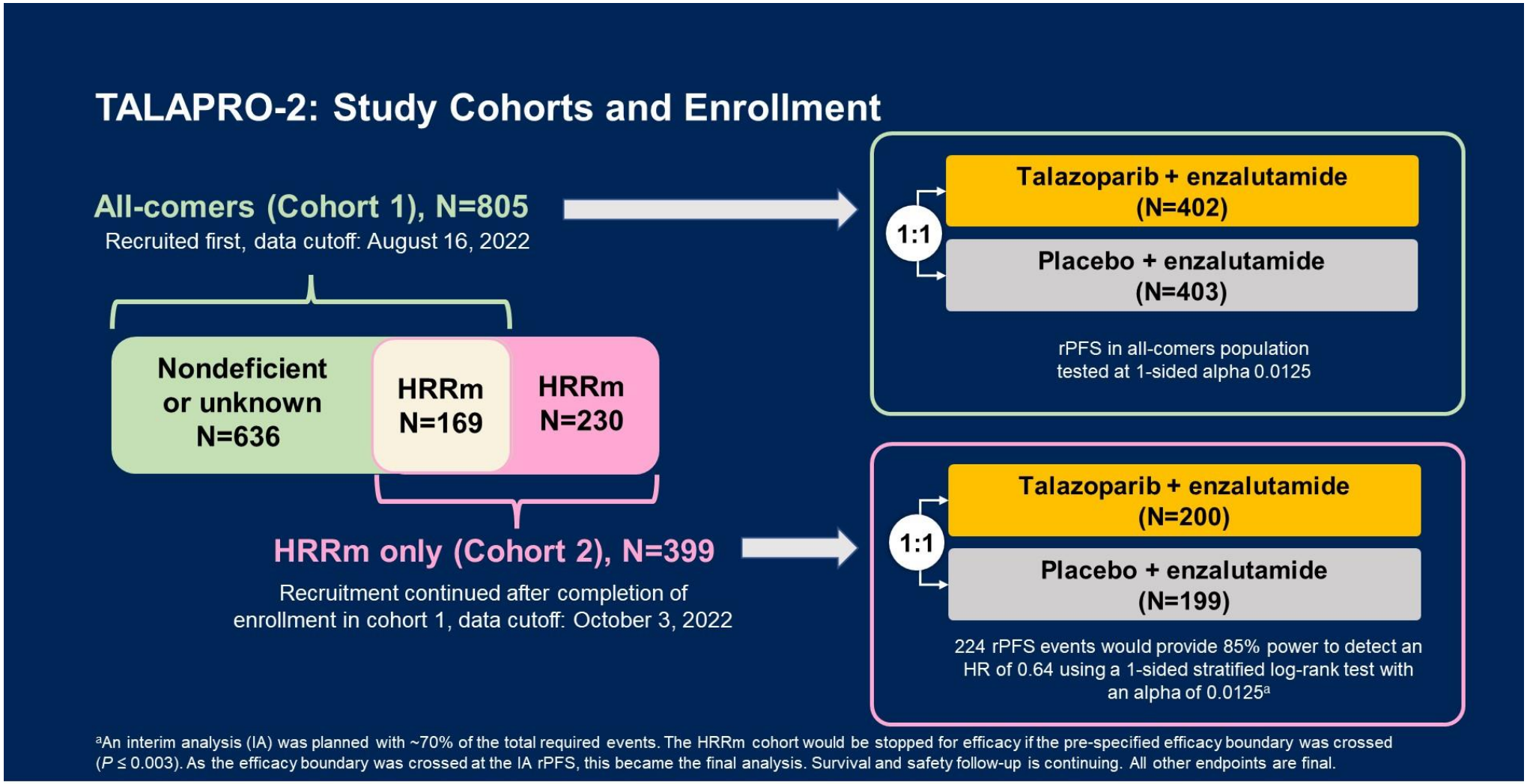
TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death was seen regardless of HRR status



HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor.

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2



Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2 HRR-Deficient: Baseline Demographics and Disease Characteristics

These were well-balanced between treatment arms

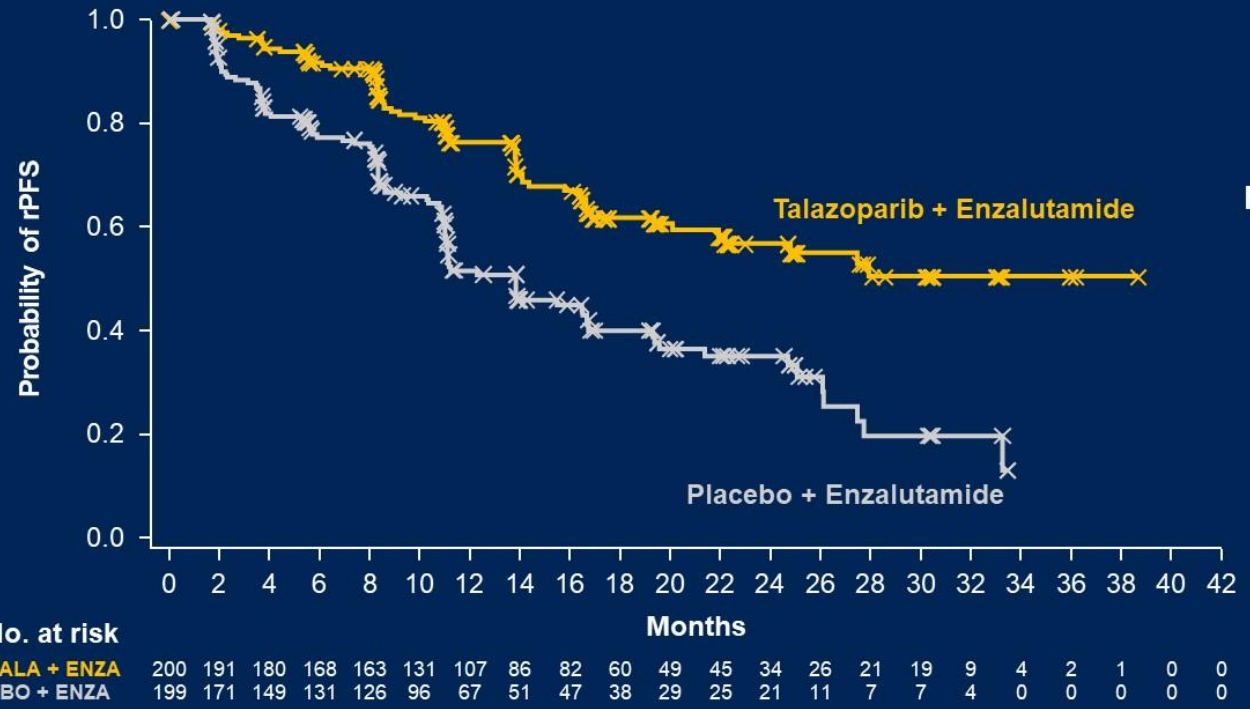
	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)
Age, median (range), years	70 (41–90)	71 (44–90)
Prostate-specific antigen (PSA), median (range), ng/mL	19.6 (0.2–3412.0)	18.0 (0.0–1055.0)
Disease site, n (%)		
Bone	175 (87.5)	158 (79.4)
Lymph node	82 (41.0)	94 (47.2)
Visceral (lung/liver)	23 (11.5)/9 (4.5)	26 (13.1)/6 (3.0)
ECOG PS 0/1, n (%)	128 (64.0)/72 (36.0)	118 (59.3)/81 (40.7)
Prior abiraterone[a] or docetaxel, n (%)	75 (37.5)	74 (37.2)
Abiraterone	16 (8.0)	16 (8.0)
Docetaxel	57 (28.5)	60 (30.2)
Tissue source for prospective HRR gene alteration testing, n (%)		
Tumor tissue only	76 (38.0)	80 (40.2)
Tumor tissue and blood (circulating tumor DNA)	121 (60.5)	115 (57.8)
Blood (circulating tumor DNA) only	3 (1.5)	4 (2.0)

[a]One patient in each treatment arm received prior orteronel.

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2 HRR-Deficient Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 55% reduced risk of progression or death



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	0.45 (0.33–0.61); *P* < 0.0001	

Median follow-up for rPFS was 17.5 and 16.8 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); *P* < 0.0001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

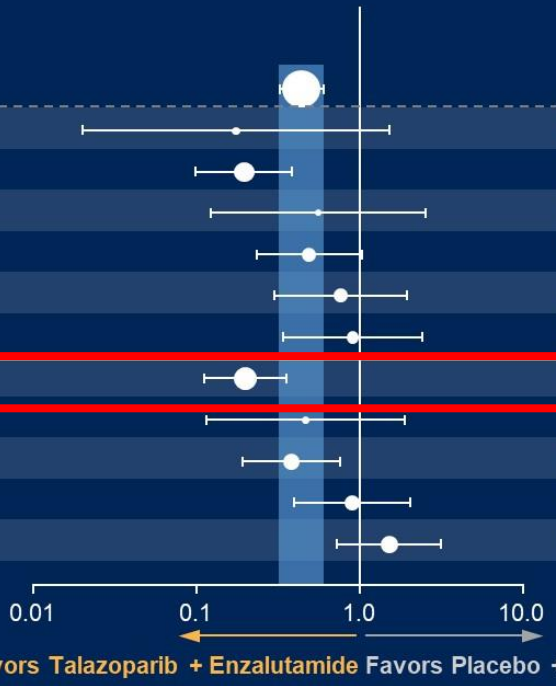
Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2 HRR-Deficient: rPFS by BICR by Selected Gene Subgroups

Broad treatment effect with talazoparib plus enzalutamide seen across gene subgroups

Subgroup	Talazoparib + Enzalutamide Events/N	Placebo + Enzalutamide Events/N	Median, mo	HR (95% CI)	2-Sided *P* Value
All HRR-deficient	65/198	104/197	NR/13.8	0.44 (0.32–0.60)	<0.0001
Only *BRCA1*	2/8	5/9	20.0/11.7	0.17 (0.02–1.51)	0.074
Only *BRCA2*	11/55	40/60	NR/11.0	0.19 (0.10–0.38)	<0.0001
Only *PALB2*	3/6	4/5	NR/8.6	0.56 (0.12–2.51)	0.44
Only *CDK12*	12/28	18/30	21.9/13.8	0.49 (0.23–1.02)	0.055
Only *ATM*	12/35	7/22	NR/27.7	0.76 (0.30–1.94)	0.58
Only *CHEK2*	8/24	8/24	22.1/NR	0.90 (0.34–2.39)	0.83
BRCA cluster	15/71	54/84	NR/11.0	0.20 (0.11–0.36)	<0.0001
PALB2 cluster	3/7	6/8	NR/8.3	0.46 (0.12–1.87)	0.27
CDK12 cluster	13/35	23/36	21.9/13.8	0.38 (0.19–0.76)	0.0045
ATM cluster	16/43	9/29	27.9/27.7	0.90 (0.39–2.04)	0.80
Other gene cluster	18/42	12/40	22.1/NR	1.51 (0.73–3.15)	0.26

Hierarchy



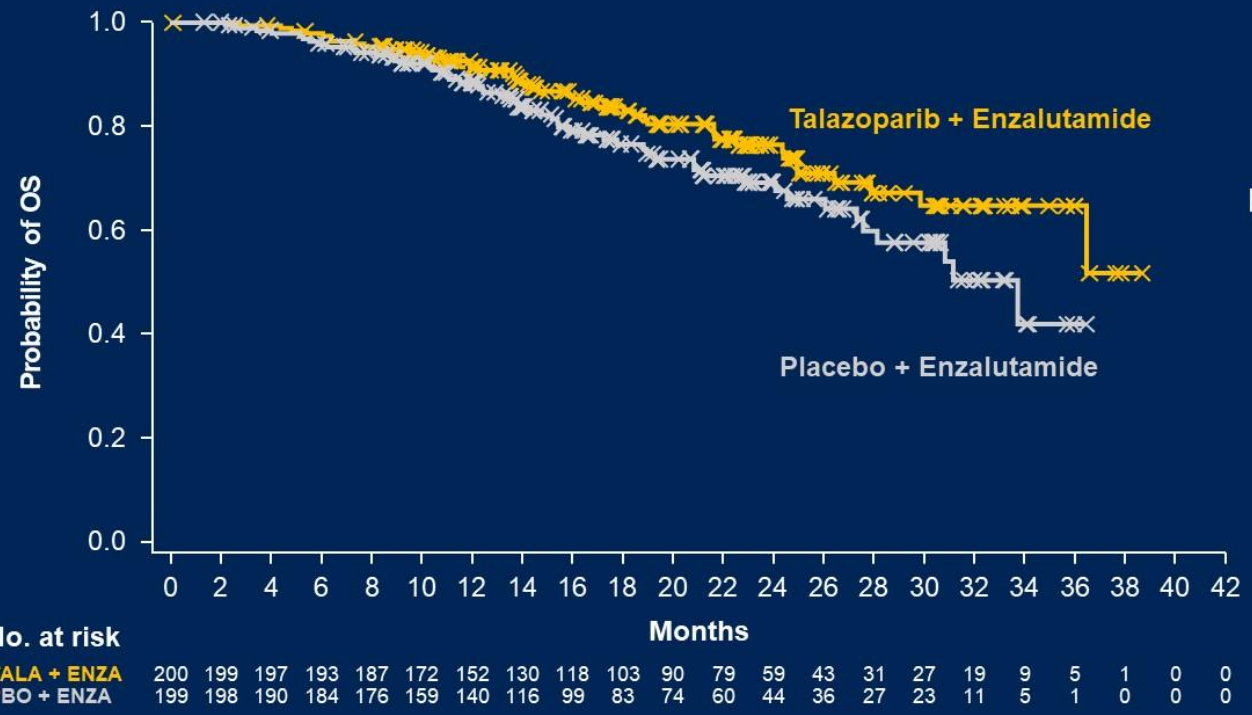
Gene clustering alteration dominance hierarchy is any *BRCA1/2* alteration (*BRCA cluster*), then any *PALB2* (*PALB2* cluster), then any *CDK12* (*CDK12* cluster), then any *ATM* (*ATM* cluster), then any of all other HRR12 genes (with each patient counted only once).

PRESENTED BY: Professor Karim Fizazi

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

TALAPRO-2 HRR-Deficient: Overall Survival (Interim Analysis)

Overall survival data are immature (24% maturity overall)



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	43	53
Median (95% CI), months	NR (36.4–NR)	33.7 (27.6–NR)
HR (95% CI)	HR 0.69 (95% CI, 0.46–1.03) *P* = 0.068	

***BRCA*m HR 0.61 (95% CI, 0.31–1.23; *P* = 0.16)**
non-*BRCA*m HR 0.71 (95% CI, 0.43–1.18; *P* = 0.18)

18 patients in the control arm and 3 patients in the talazoparib arm subsequently received olaparib

Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

Trial	Therapy	rPFS HHRm	rPFS mBRCA1/2
MAGNITUDE	Abiraterone + Niraparib	0.73 (0.56 – 0.96)	0.53 (0.36 – 0.79)
PROpel	Abiraterone + Olaparib	0.50 (0.34 – 0.73)	0.23 (0.12 – 0.43)
TALAPRO-2	**Enzalutamide + Talazoparib**	**0.48 (0.31 – 0.74)**	**0.20 (0.11 – 0.36)**

- **BRCA1/2 are great predictive biomarkers for PARP inhibitors**
- **Efficacy of Enzalutamide + Talazoparib is as good as other ARi + PARPi combinations**

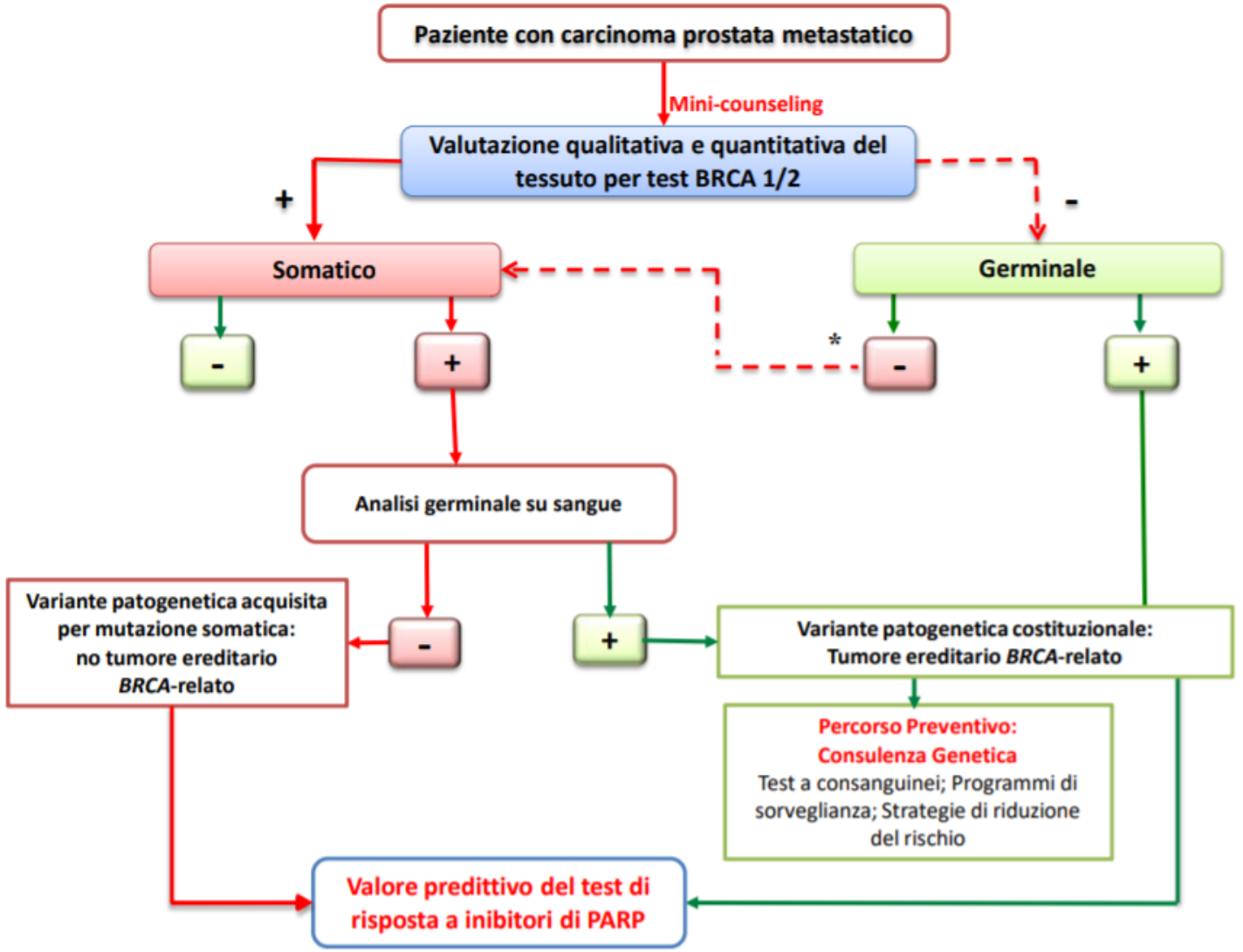
Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2

- Few patients previously received an AR pathway inhibitor
- Few patients who progressed on PBO received subsequent PARPi
- TALAPRO-2 studies the benefit of PARPi, not combination vs sequential ARi + PARPi

Trial	Therapies	rPFS HRRm (CI)	rPFS BRCA1/2 (CI)	Prior ARPI	Subsequent PARPi
TALAPRO-2[1]	**Enzalutamide + Talazoparib**	**0.45 (0.33-0.61)**	**0.20 (0.11-0.36)**	**8%**	**17%**
PROpel[2]	Abiraterone + Olaparib	0.50 (0.34-0.73)	0.23 (0.12-0.43)	0.15%	2%
MAGNITUDE[3]	Abiraterone + Niraparib	0.73 (0.56-0.96)	0.53 (0.36-0.79)	3.1%	?

Quanto l'ARSi aggiunge al PARPi (combo vs PARPi in monoterapia)?

Ruolo delle linee guida: AIOM



Raccomandazioni AIOM per l'implementazione dell'analisi mutazionale BRCA nei pazienti con carcinoma della prostata metastatico. 02/2021

Agenda

- Il ruolo della RT nel trattamento del de-novo mCSPC – studio PEACE-1
- *Ruolo prognostico delle alterazioni germinali/somatiche di HRR (BRCA1/2) – studio CAPTURE*
- *Ruolo predittivo delle alterazioni di HRR (BRCA1/2) – studio TALAPRO-2*
- ***C'è spazio per nuove combinazioni? – studio LuPARP***

C’è posto per nuove combinazioni? – studio LuPARP

2023 ASCO ANNUAL MEETING

LuPARP: Phase 1 trial of ^{177}Lu-PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer.

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C’è posto per nuove combinazioni? – studio LuPARP

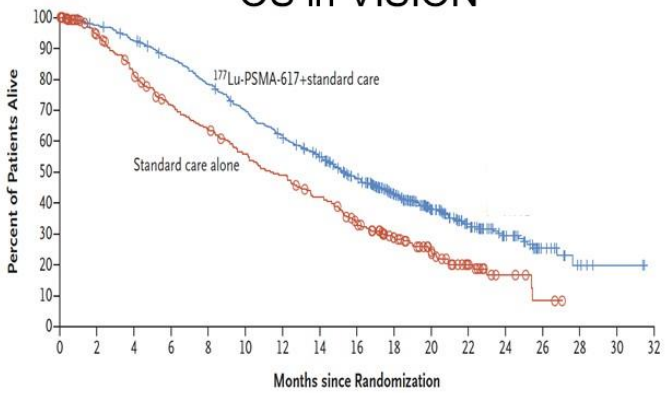
LuPARP: Background

Lu-PSMA radioligand therapy
- Similar OS outcomes vs cabazitaxel
- Better PSA responses, better safety profile

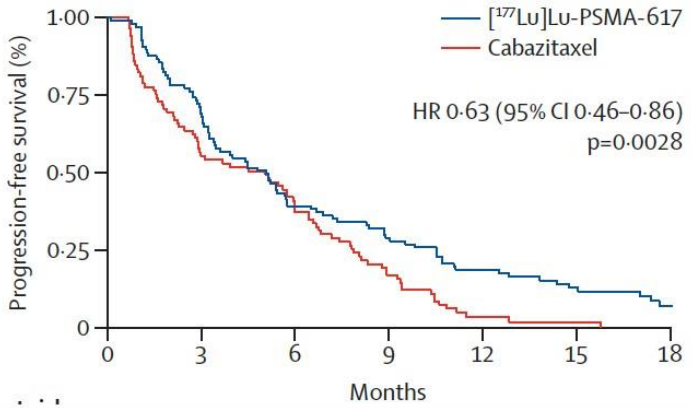
But…
- Not all patients have robust benefit
- No “tail on the curve”

Can addition of intermittent olaparib
- Increase the number of patients who benefit from Lu-PSMA therapy?
- Extend the benefit of Lu-PSMA therapy?

OS in VISION



PFS in TheraP



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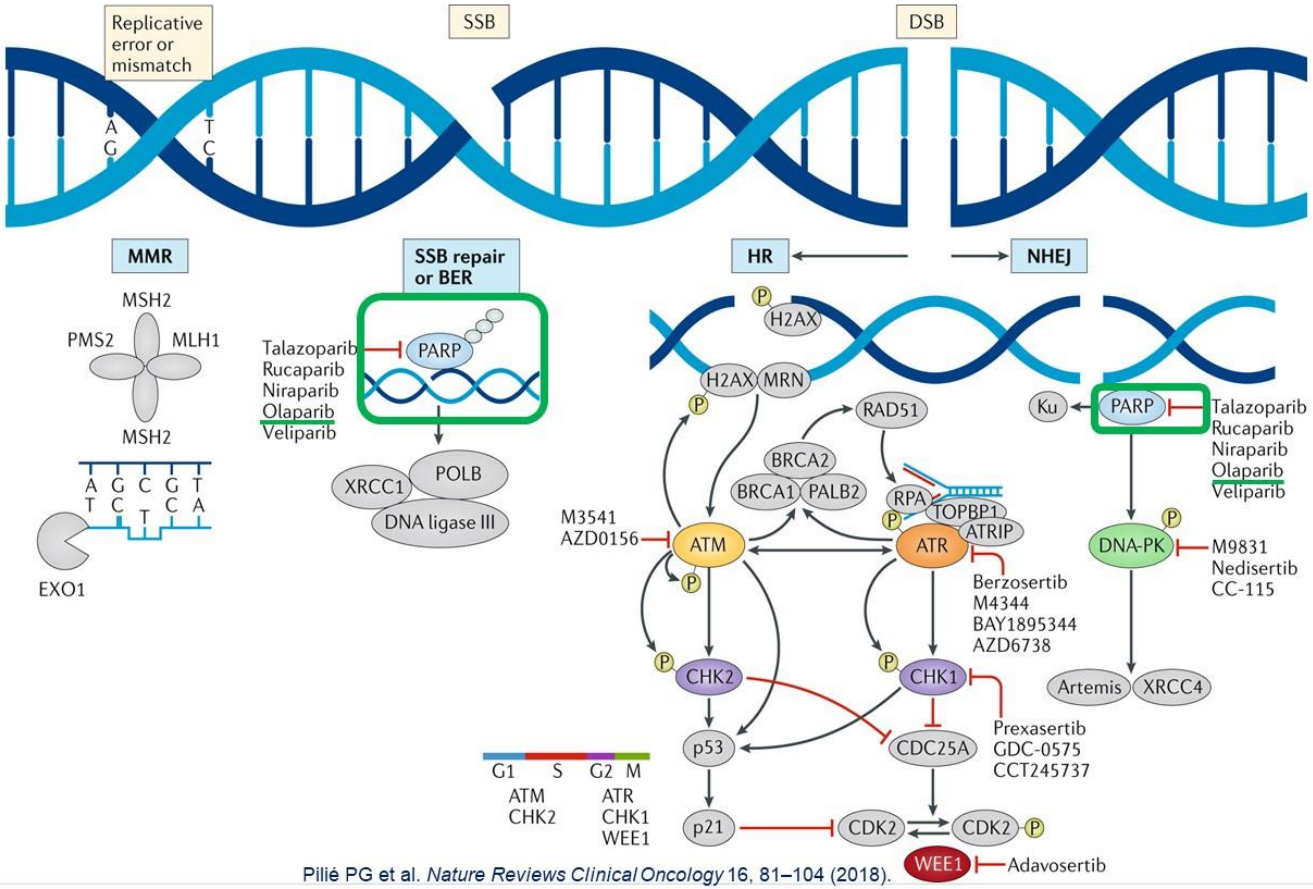
LuPARP: Leveraging Radiosensitization

- ^{177}Lu-PSMA-617 delivers a payload of β radiation to PSMA expressing tumors
- ^{177}Lu-PSMA-617 primarily causes SS-DNA breaks, repaired by PARP-dependent BER
- Blocking PARP could result in the conversion of DNA SSBs to lethal DSB via fork collapse
- ^{177}Lu-PSMA-617 in combination with olaparib leverages DNA-damaging and potential immune modulating effects of radioligand therapy
- Enhanced anti-tumor activity shown in combination of PARPi and radiotherapy including ^{177}Lu-DOTATATE[1,2]



Pilié PG et al. *Nature Reviews Clinical Oncology* 16, 81–104 (2018).

PRESENTED BY: Shahneen Sandhu

1. Nonnekens J et al. Theranostics. 2016;6(11):1821-32.
2. Cullinane C et al. Sci Rep. 2020;10(1):10196.

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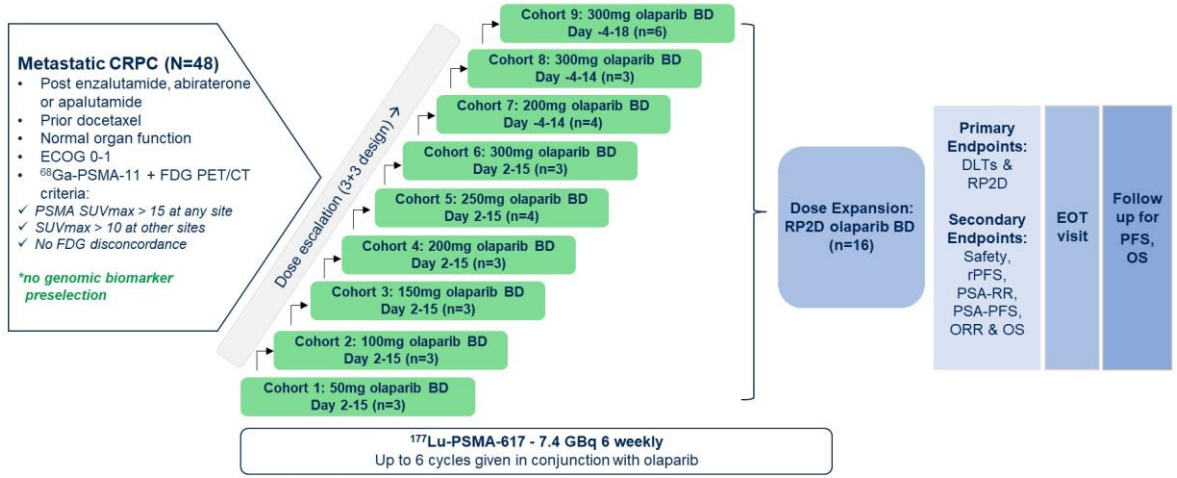
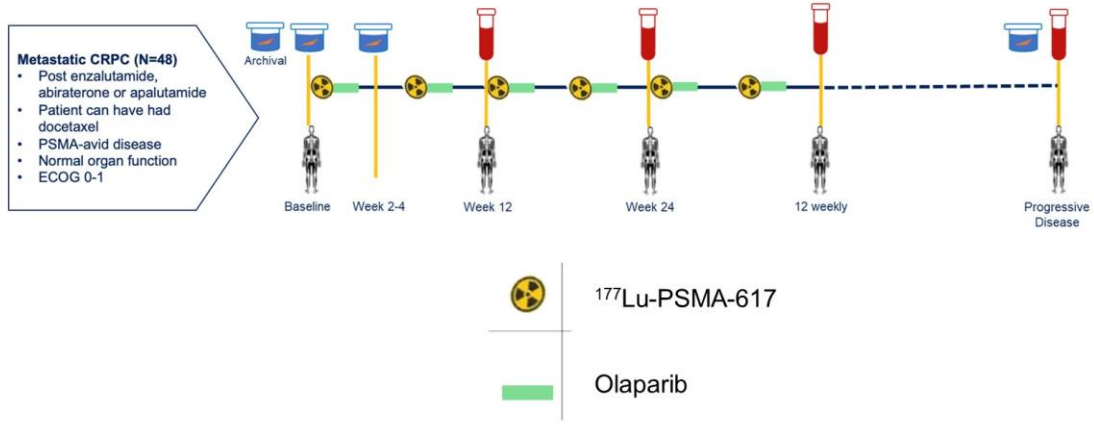
LuPARP: Phase 1 Trial Schema



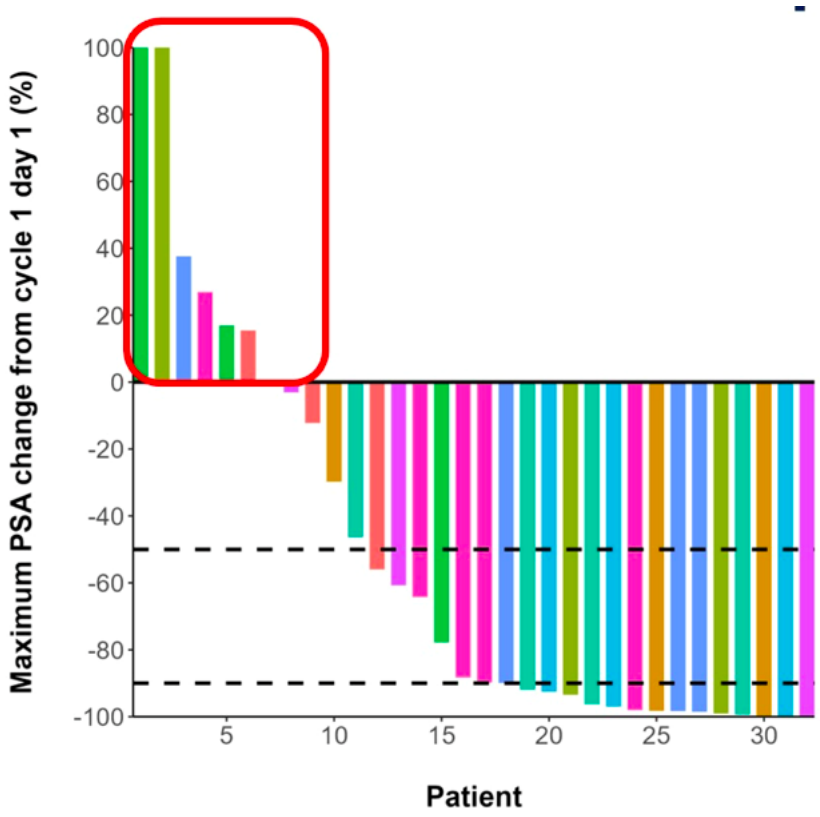
LuPARP

Lu-PSMA + 14-21 days olaparib starting around the time of Lu-PSMA infusion



Short-term Safety?	☑	32 patients • 0 DLTs • 3 Treatment Delays • 0 Treatment Discontinuation
Long-term Safety?	☐	
Responses and Duration?	☐	

C’è posto per nuove combinazioni? – studio LuPARP



Cohort 1: 50mg Day 2-15
Cohort 2: 100mg Day 2-15
Cohort 3: 150mg Day 2-15
Cohort 4: 200mg Day 2-15
Cohort 5: 250mg Day 2-15
Cohort 6: 300mg Day 2-15
Cohort 7: 200mg Day -4-14
Cohort 8: 300mg Day -4-14
Cohort 9: 300mg Day -4-18

PSA ≥ 50% response = 66% (21/32)
PSA ≥ 90% response = 44% (14/32)
ORR by RECIST 1.1 = 78% (7/9)

*Patients in cohorts 8 & 9 are early in treatment cycles

Study	Therapy	PSA 50	PSA 90 (80)
LuPARP	LuPSMA + olaparib	66%	44%
VISION[1]	LuPSMA	46%	(33%)
TheraP[2]	LuPSMA	66%	38%

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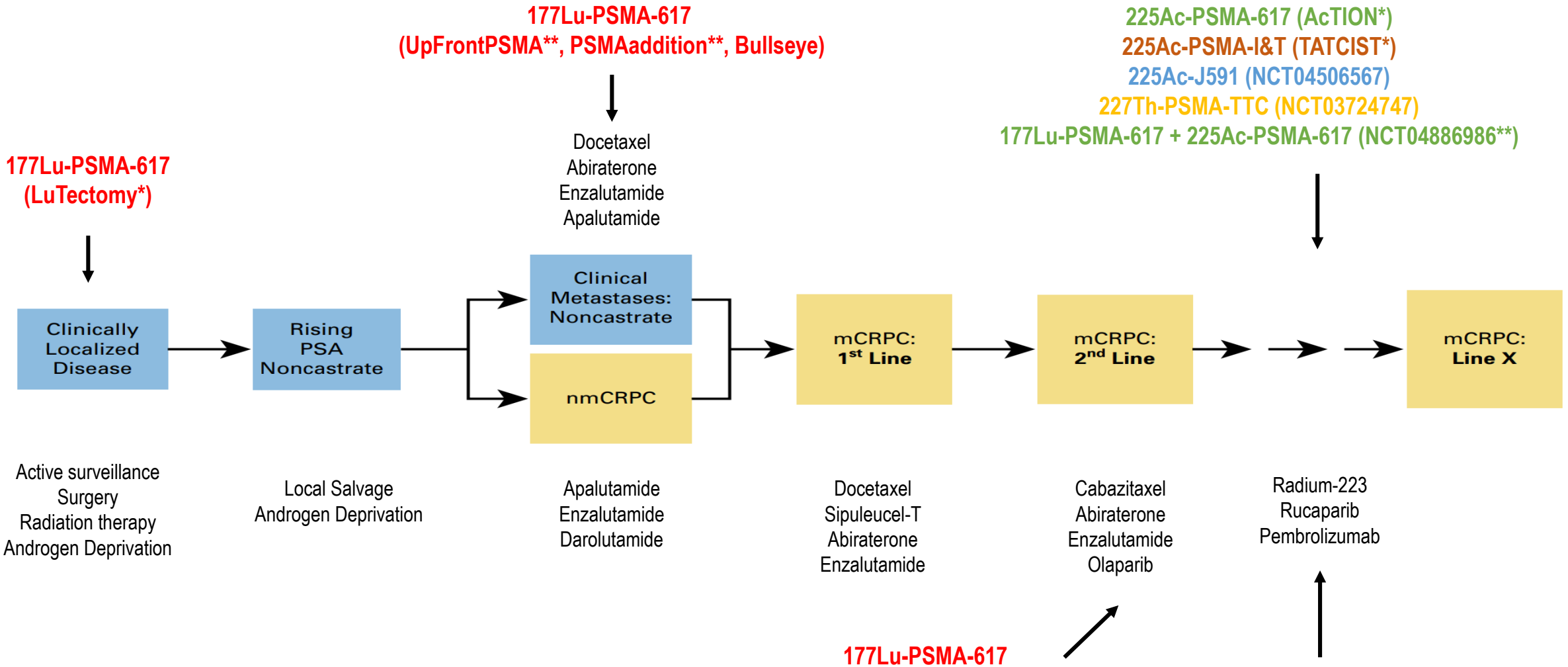

Different colours represent various PSMA-targeted radiopharmaceuticals
* = expected results in 2023
** = expected results in 2024

Courtesi of Dr. Bauckneht

Neoplasie Genito-Urinarie: Tumore della Prostata

Grazie!

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