Management of mHSPC progression: coffee for all?

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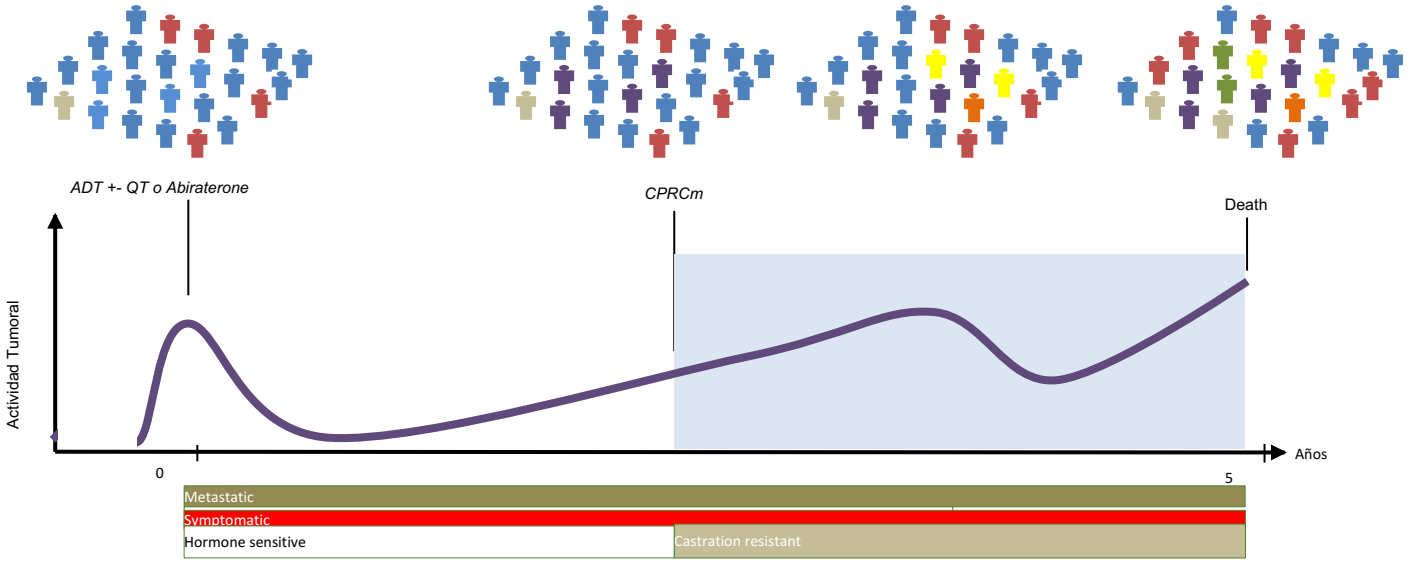
Aberrations can be at diagnosis or adquired while tumor progression

TP53; PTEN; DDR

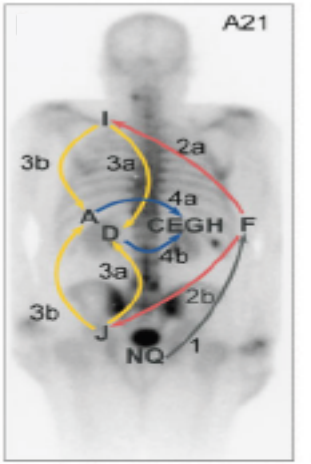
AR pathway aberrations (Mutations, Amplification,..)

Neuroendocrine dedifferentiation

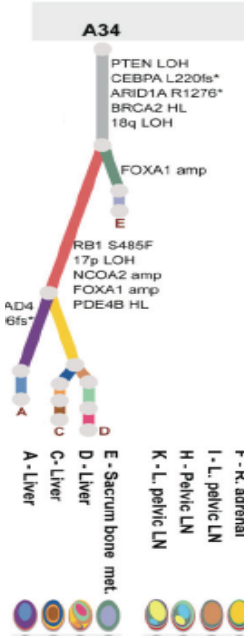
- P53 and PTEN loss
- DNA repair alteration (BRCA2/1; ATM; CDK12…)
- AR gain
- AR mutations
- AR-V*
- Neuroendocrine (Myc amp)



mCRPC is polyclonal and heterogeneous



A - L rib D - L adrenal
C - Liver F - R rib nod.
E - Liver I - L clavicle
G - Liver J - L iliac crest
H - Liver N - GL5 EPE
Q - GL3/5



Gundem, G. *et al. Nature* **520,** 353–357 (2015).

Patient selection in mCRPC

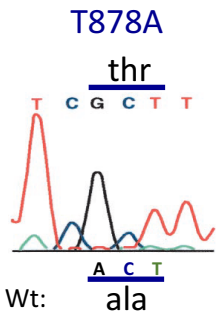
- AR dependent
- HRD (BRCA1/2; CDK12; PALB2; NGS)
- MMR (MSH2 def.. IHQ/NGS)
- Neuroendocrine o Aggressive variant

Patient selection in mCRPC

AR dependent mechanisms

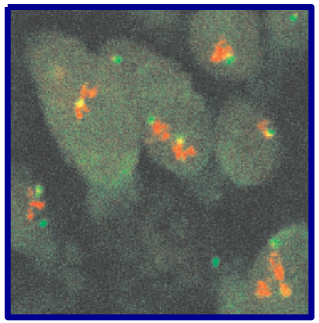
Up to 85% of lethal prostate cancers harbor Androgen Receptor Aberrations

AR mutations



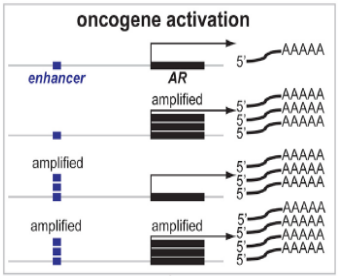
Taplin ME.
N Engl J Med 1995

AR gain



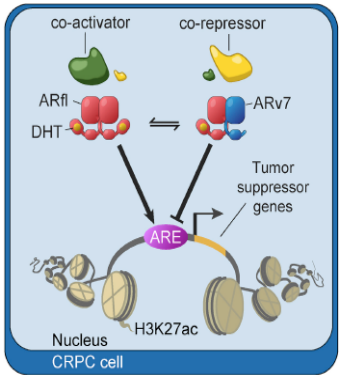
Holzbeierlein J.
Am J Path 2004

AR Enhancer Gain



Quigley DA.
Cancer Cell 2018

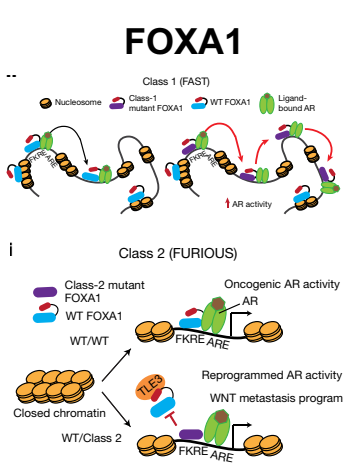
AR Splice Variants



Cato L.
Cancer Cell 2019

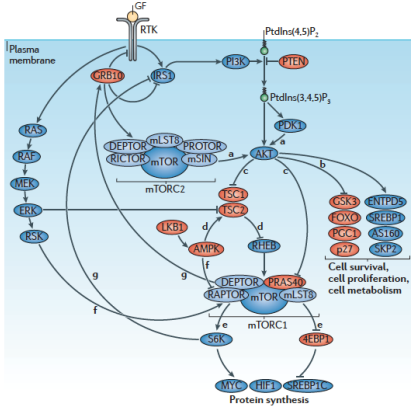
AR-Pathway regulators

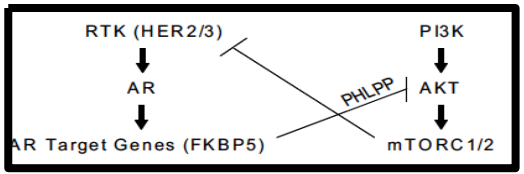
AR Co-Regulators



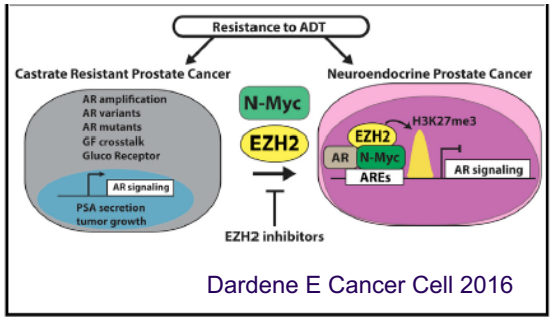
Parolia A.
Nature 2019

Pi3K-pathway Activation

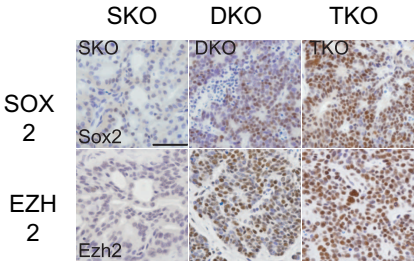




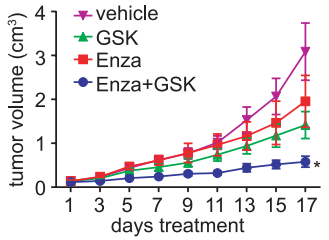
Epigenetic modifiers



Dardene E Cancer Cell 2016

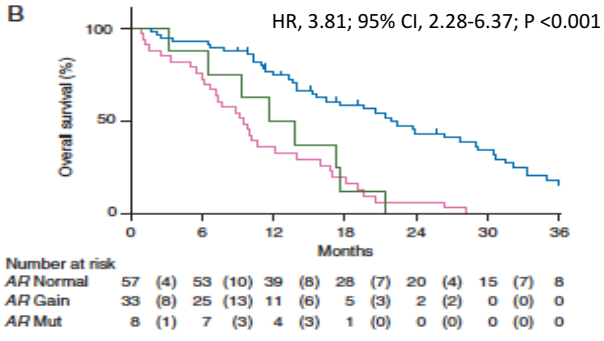


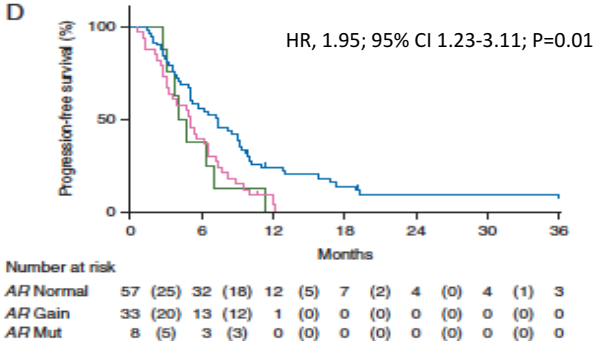
DKO CR

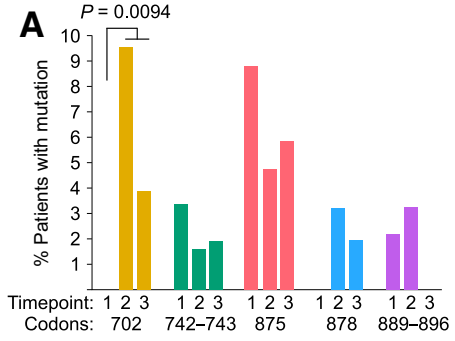


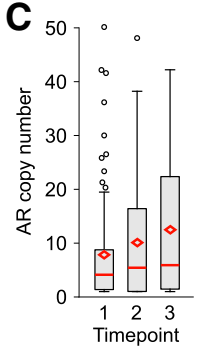
Ku, S.-Y. Science 2017

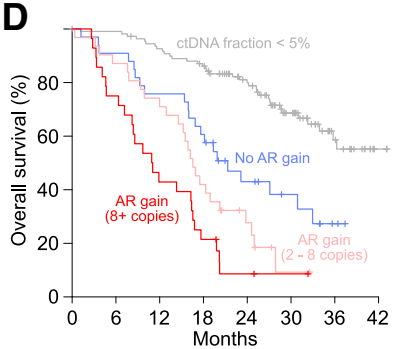
AR aberrations identify patients with worse outcome to new antiandrogens

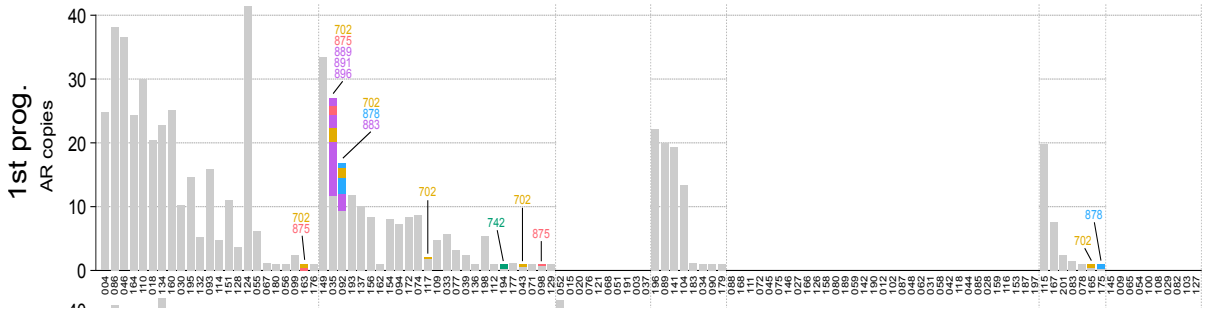










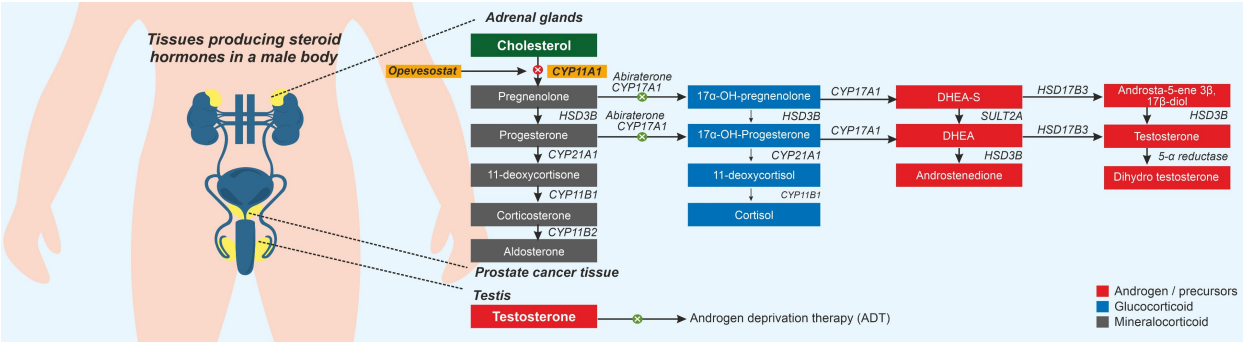


Conteduca V. Annals of Oncology 2017

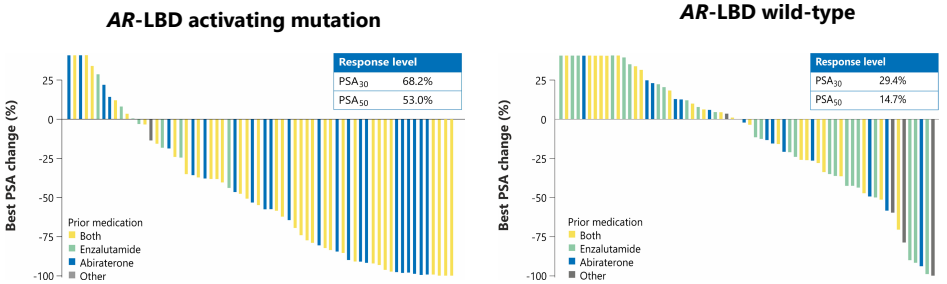
Annala M. Clin Cancer Res 2021

Opevesostat

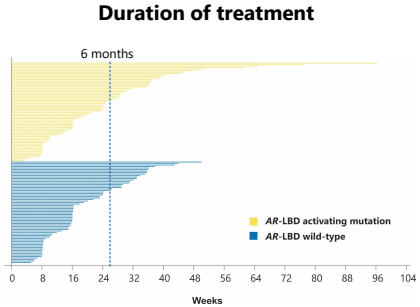
(ODM-208; CYP11A1i)



CYPIDES (ESMO 24)



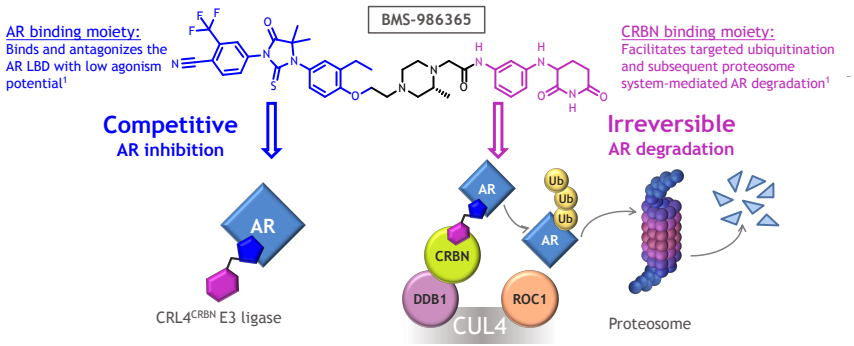
- At time of analysis, 2 *AR*-LBD mutated patients and 15 *AR*-LBDwt patients were ongoing on treatment.
- Durable responses have occurred in patients with and without *AR*-LBD mutation.

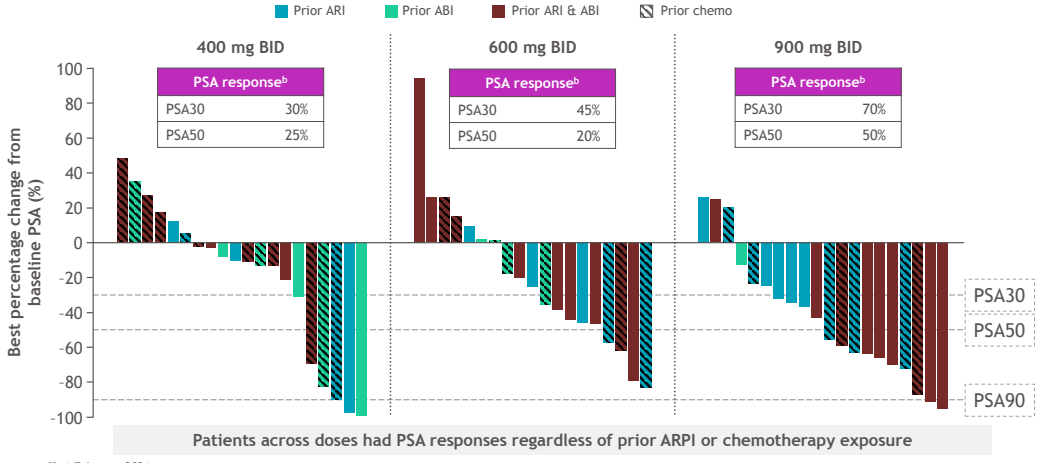


Fizazi K. ESMO 24

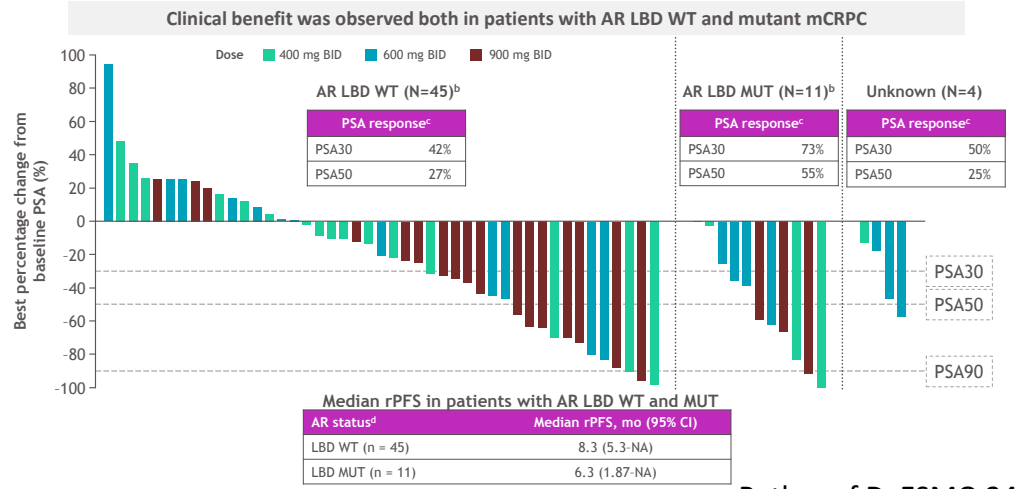
AR Degraders by LBD mutational status

AR degraders and inhibitors





PSA response and median rPFS in patients based on AR LBD mutational status[a]

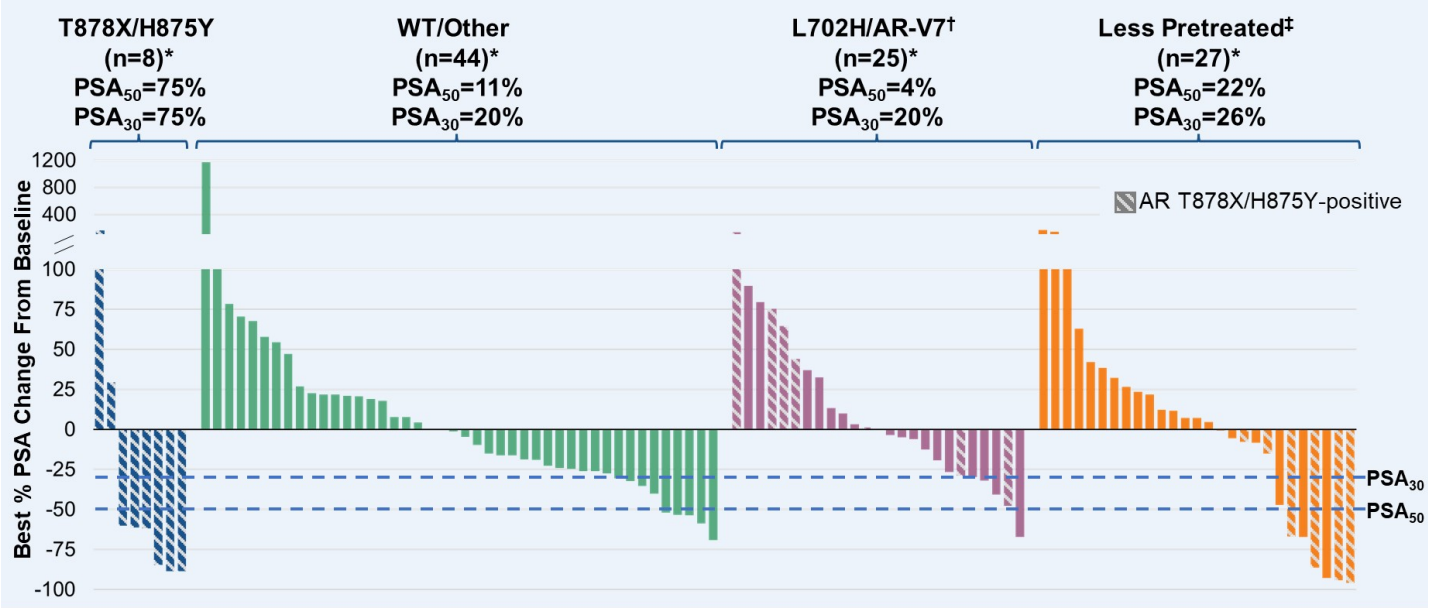


Median rPFS in patients with AR LBD WT and MUT

AR status[d]	Median rPFS, mo (95% CI)
LBD WT (n = 45)	8.3 (5.3-NA)
LBD MUT (n = 11)	6.3 (1.87-NA)

Rathpopf D. ESMO 24

ARV-110 (Bavdegalutamide)



Gao X. ASCO GU 2022

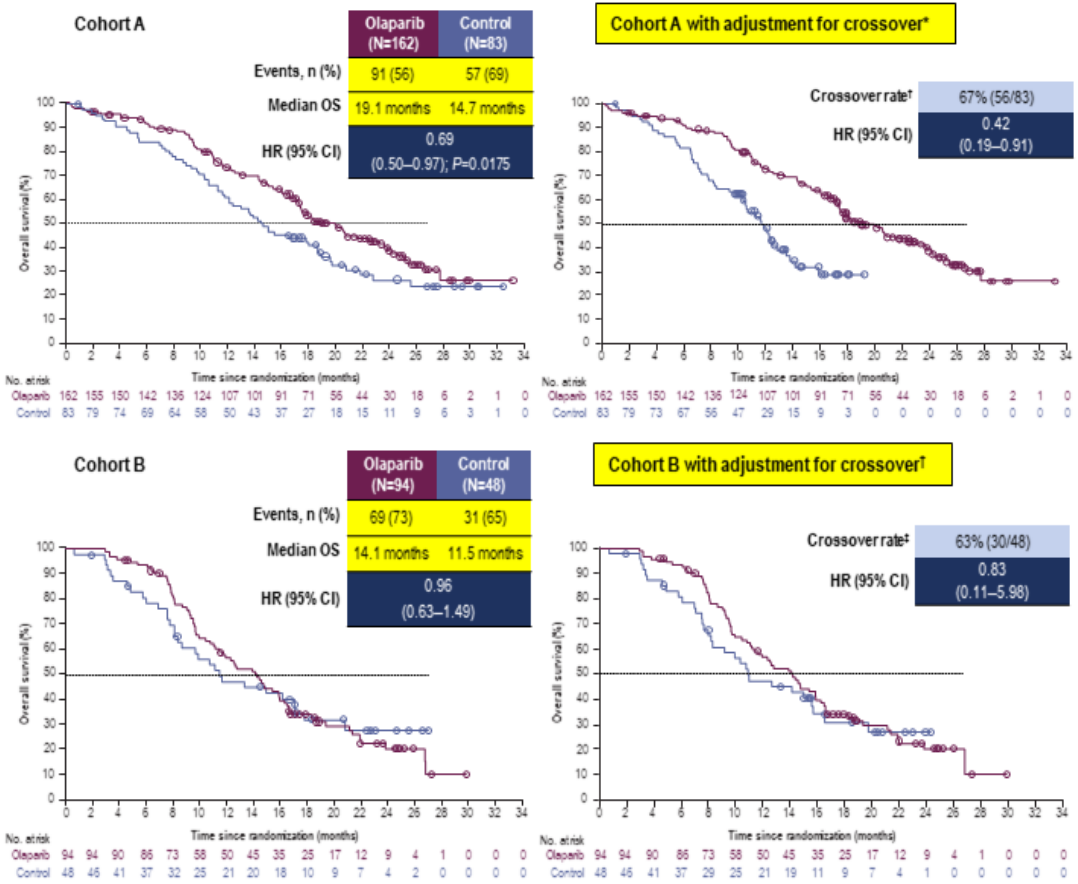
Resultados disponibles con Inh. de AKT

	IPATASERTIB	CAPIVASERTIB
Clinical trial	IPATential	ProCAID
Phase	III	II
Number of patients enrolled	1101	150
Primary endpoint	rPFS	cPFS
Stage of the disease	mCRPC	mCRPC
Association to AKTi	Abiraterone + Prednisolone	Docetaxel + Prednisolone
Control	Placebo	Placebo
Primary outcome's HR	0.77 (95% CI, 0.61–0.98); $p = 0.034$	0.92 (80% CI, 0.73–1.16); $p = 0.32$
Grade $\geq$ 3 adverse events	70%	62%
AEs leading to treatment discontinuation	21%	23%

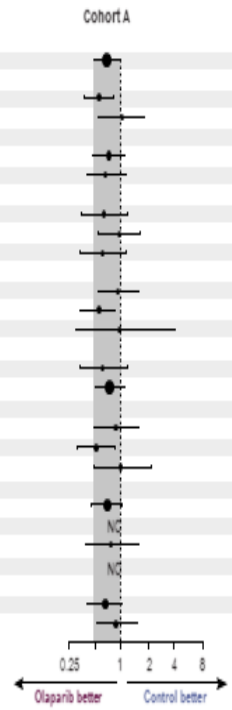
Selección de Pacientes en mCRPC

HRD (BRCA1/2; CDK12; PALB2; NGS)

Olaparib improves OS in HRR defective tumor BRCA1/2 derive the greatest benefit-



Subgroup	Olaparib n/N	Control n/N	Total N	HR (95% CI)
All patients	91/162	57/83	245	0.69 (0.50–0.97)
Previous taxane use				
Yes	60/106	41/52	158	0.56 (0.38–0.84)
No	31/56	16/31	87	1.03 (0.57–1.92)
Measurable disease at baseline				
Yes	55/95	33/46	141	0.73 (0.47–1.13)
No	36/67	24/37	104	0.67 (0.40–1.15)
Metastases at baseline				
Bone only	30/57	15/23	80	0.64 (0.35–1.22)
Visceral	29/46	22/32	78	0.99 (0.57–1.74)
Other	27/49	16/23	72	0.62 (0.34–1.18)
ECOG score at baseline				
0	46/84	18/34	118	0.94 (0.55–1.66)
1	35/67	36/46	113	0.55 (0.35–0.88)
2	10/11	3/3	14	0.98 (0.30–4.37)
Age at randomization				
<65 years	29/54	16/23	77	0.62 (0.34–1.17)
≥65 years	62/108	41/60	168	0.74 (0.50–1.10)
Region				
Asia	32/57	18/28	85	0.86 (0.49–1.55)
Europe	36/68	29/38	106	0.52 (0.32–0.85)
North & South America	23/37	10/17	54	0.99 (0.48–2.18)
Race				
White	61/109	38/55	164	0.69 (0.46–1.04)
Black/African American	1/2	1/1	3	NC
Asian	23/43	12/19	62	0.76 (0.39–1.59)
Other	1/1	1/1	2	NC
PSA at baseline				
≥Median	43/68	37/48	116	0.65 (0.42–1.01)
<Median	46/92	19/33	125	0.88 (0.52–1.53)

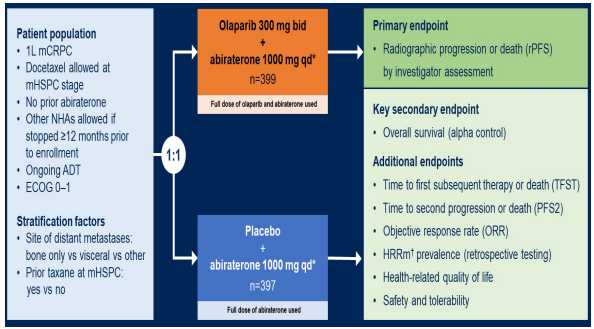


CI values were not calculated for subgroups in which fewer than five survival events occured.
s of the circles are proportional to the number of events. ECOG, Eastern Cooperative Oncology
NC, not calculated; n/N, number of events/number of patients; PSA, prostate-specific antigen.

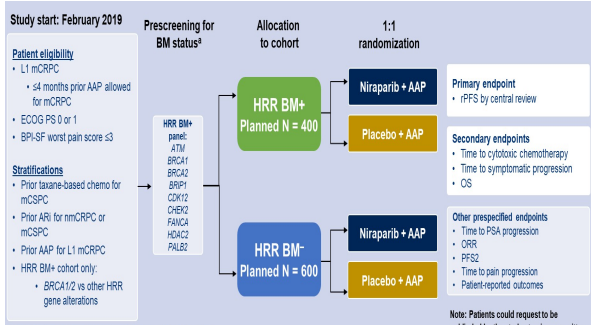
J. De Bono & J Mateo ESMO 2020
Hussain & J Mateo. M. NEJM 2020

	Olaparib			Niraparib	Talazoparib	
Trial	**N. Clarke et al**	**PROPEL**	**BRCAAWay**	**MAGNITUDE**	**TALAPRO-2**	**ZZ-First**
Phase	Phase 2 rand	Phase 3	Phase 2	Phase 3 randomized	Phase 3 randomized	Phase 2 (2:1)
Treatment	AAP +/- Olaparib	AAP +/- Olaparib	AAP, Olap or AAP-Olap	AAP +- Niraparib	Enza +- talazoparib	Enza +- Talazoparib
Scenario	CPRCm pre-treated (Taxane & ARSI)	CPRCm pre-treated (Taxane)	CPRCm BRCA mut	CPCRm 1L w/o DDR	CPRCm	CPHSm naive
N	142	796	70	765	1037	54
P. Endpoint	rPFS	rPFS	PFSr (BRCA/ATM)	rPFS	rPFS	PCS-CR
Population	All commers	All commers	DDR mut	Non-DDR & DDR	All Commers & DDR	All Commers
Molecular Testing	Central Lab	Central (Tissue & ctDNA)	Central Lab (tissue)	Central (Tissue & ctDNA)	Central Lab (Foundation Medicine)	Academic Lab
ID	NCT0197221	NCT01682772	NCT03012321	NCT03748641	NCT03395197	NCT04332744
Publication	Lancet Oncol 2018	NEJM Evid 2022 Lancet Oncol 2023	ASCO 2022	JCO 2023	ASCO-GU 2023 Lancet-2023	NR

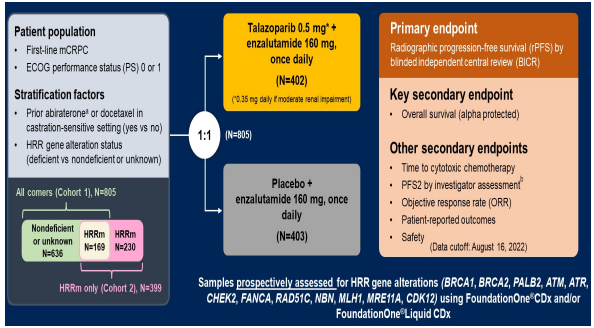
PROPEL



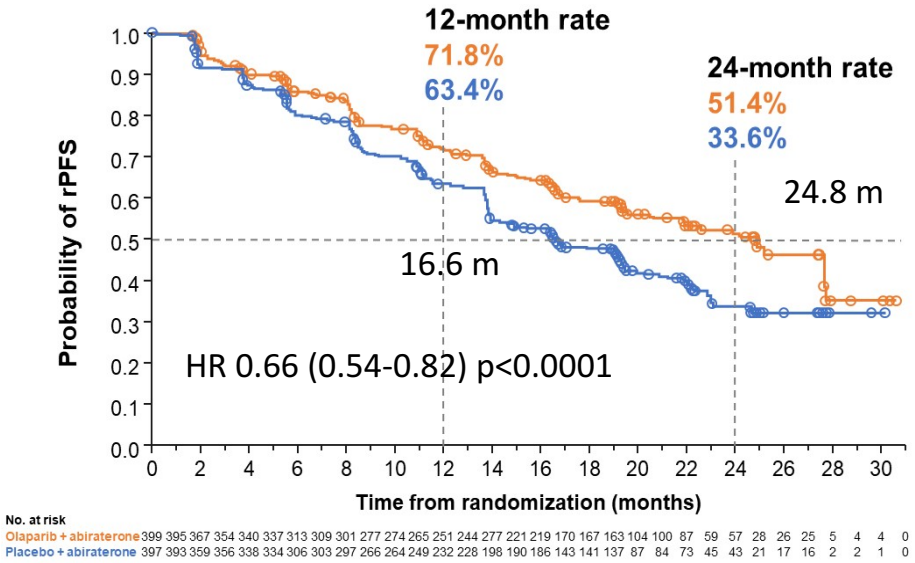
MAGNITUDE

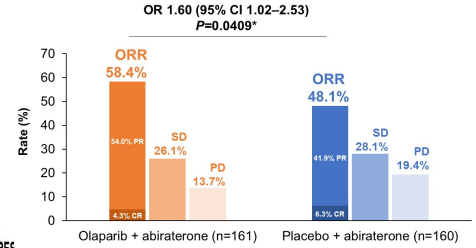


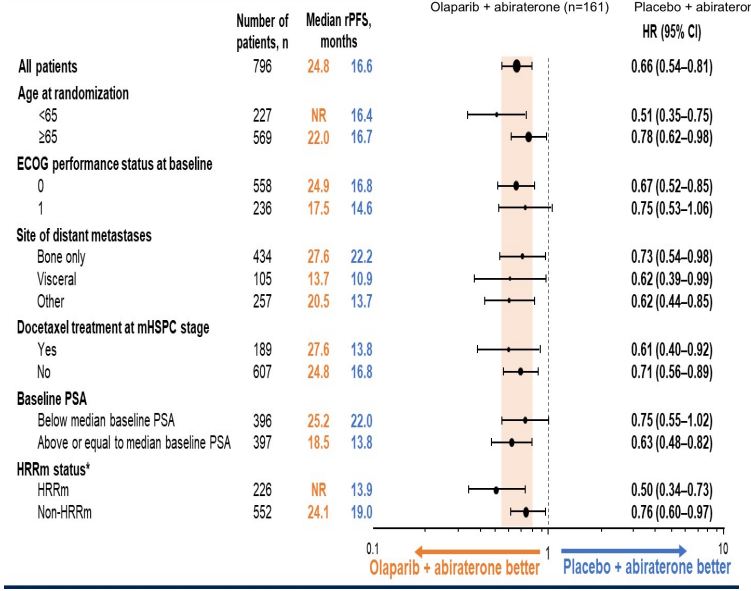
TALAPRO-2



PROpel : Primary Endpoint rPFS



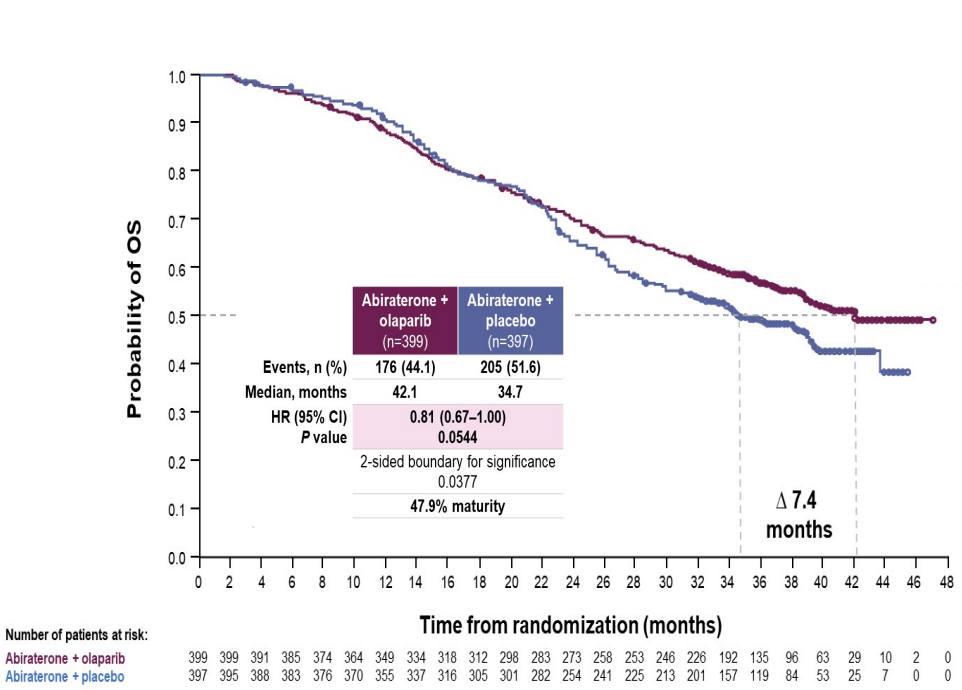


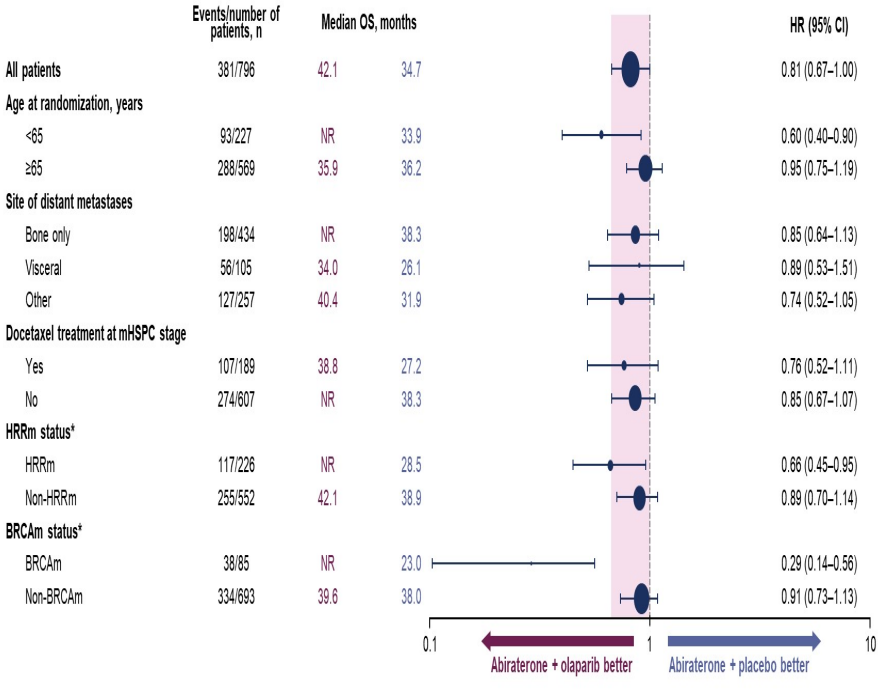


Retrospective NGS solid and Liquid Foundation One. HRR Genes (14 genes):
ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L

N. Clarke. NEJM Evid 2022

PROpel: OS analysis

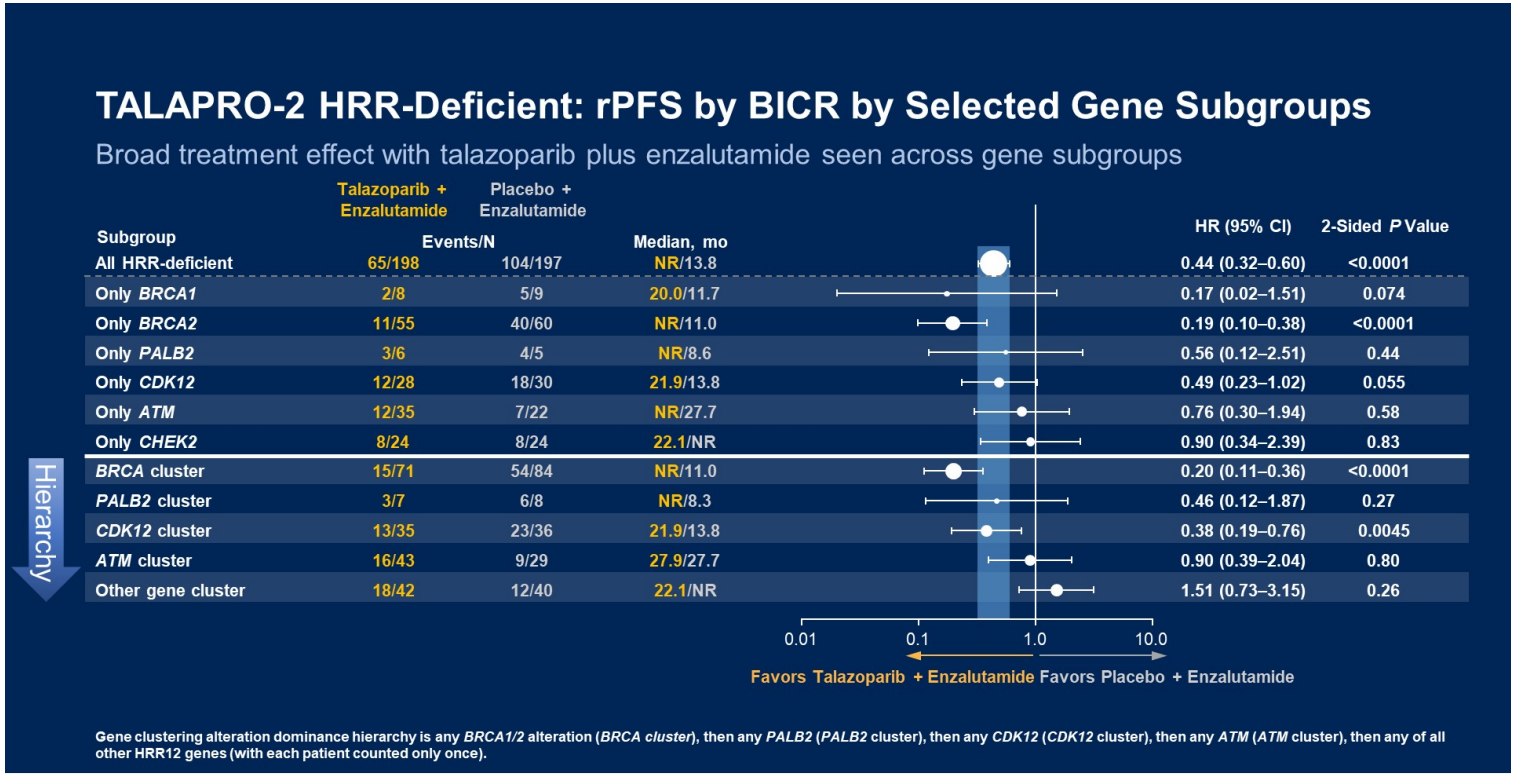




OS maturity not reached

N. Clarke. ASCO-GU 2023

TALAPRO-2 HRR-Deficient Expanded Cohort

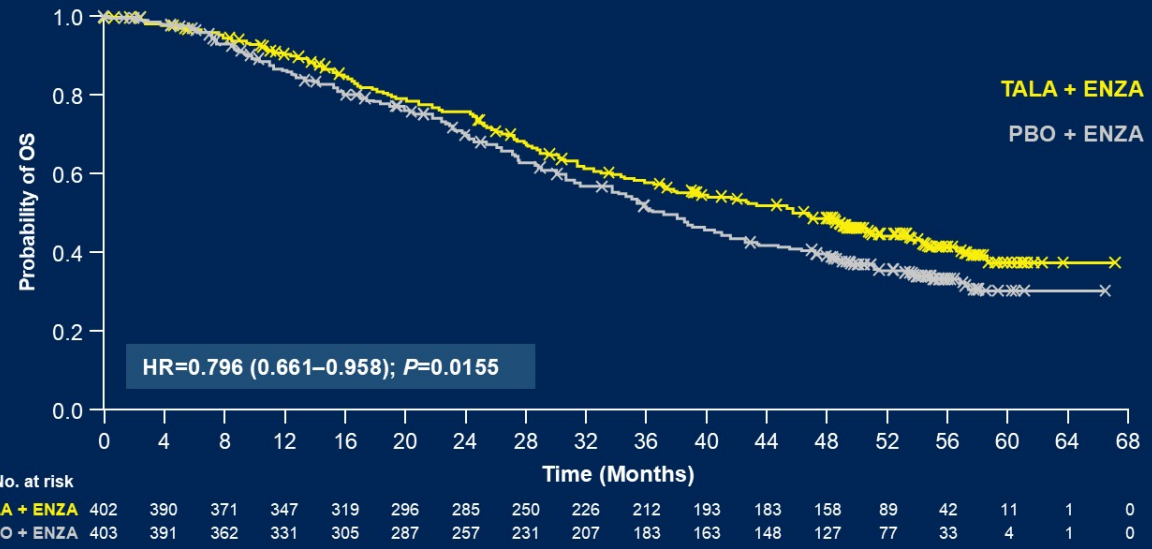


Fizazi K. ASCO 2023

TALAPRO-2 Unselected

Overall Survival (Final Analysis)

20.4% reduction in risk of death, >8 months improvement in median OS



	Events/patients	Median OS (95% CI), mo
TALA + ENZA	211/402	45.8 (39.4–50.8)
PBO + ENZA	243/403	37.0 (34.1–40.4)

8.8 months improvement

Median follow-up for OS was 52.5 months

For statistical significance at the final overall survival analysis, the stratified log-rank 2-sided *P* value needed to be ≤0.022 based on a group sequential design with O'Brien-Fleming spending function.

Data cutoff: September 3, 2024.

FDA Pooled Analysis of Six randomized phase 3 clinical trials

Benefit from PARPi is not the same across DNA damage repair genes

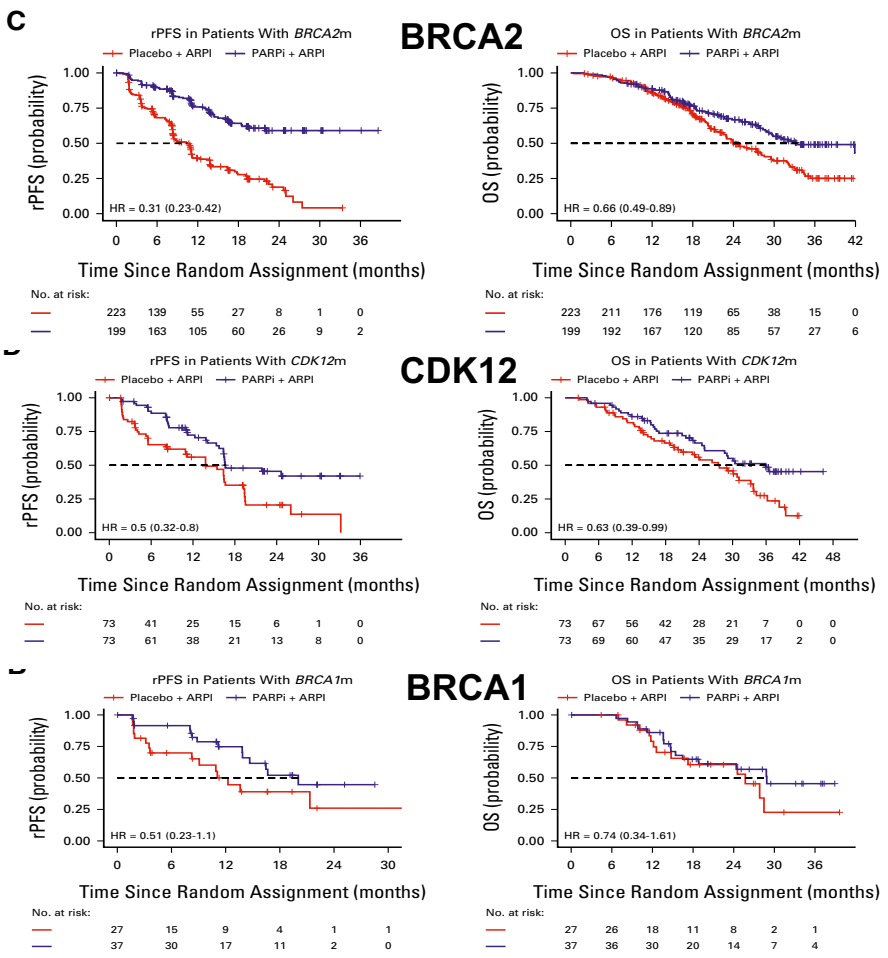
PROFOUND | PROPEL

TRITON-2 | MAGNITUDE

TALAPRO-1 | TALAPRO-2

N=1113 Freq Mut

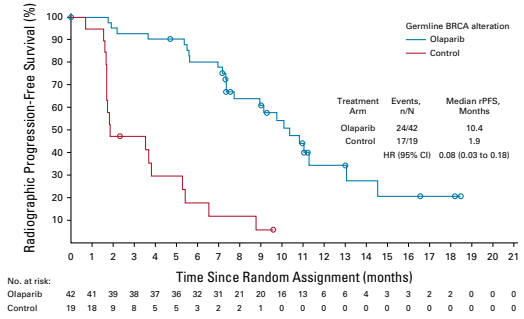
- **BRCA2 (N=422).√**
- ATM (N=268) †
- BRCA1 (N= 64)
- **CDK12 (N= 146) √**
- CHEK2 (N=172) †
- PALB2 (N= 41)



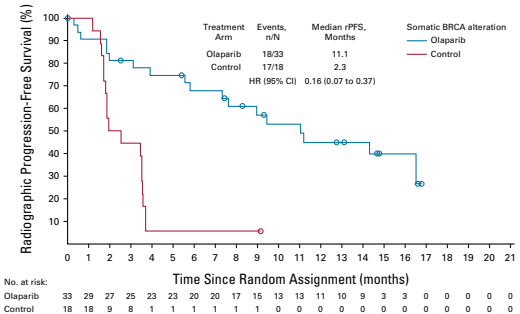
Fallah J et al. J Clin Oncol 2024

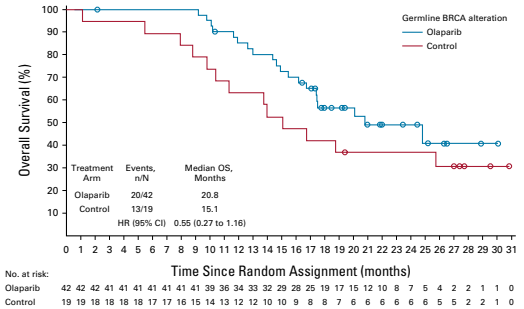
BRCA2 altered mCRPC, either of germline or somatic, Benefit from Olaparib

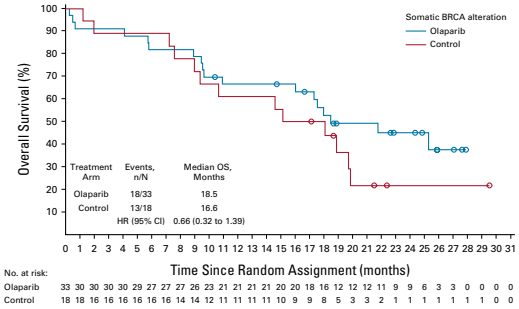
Germline



Somatic



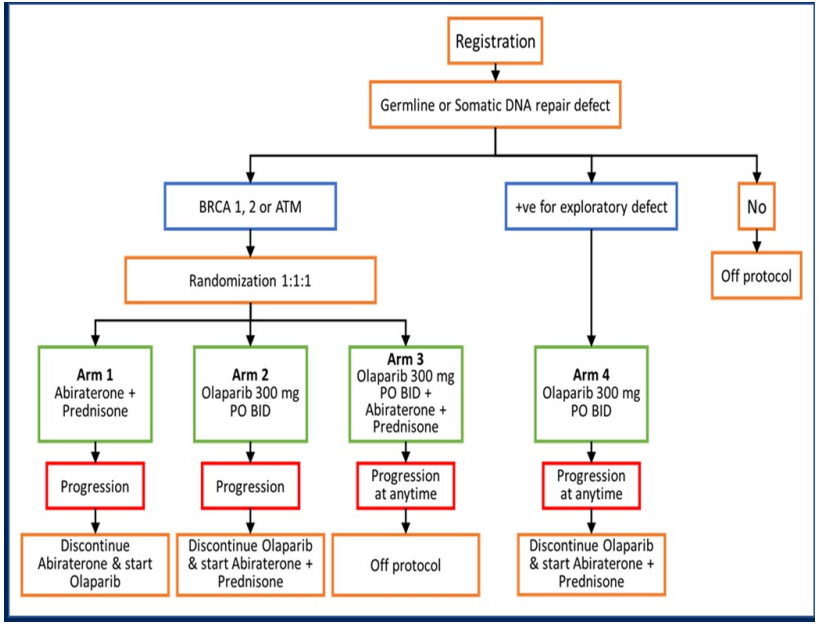




Mateo J et al. J Clin Oncol 2024

BRCAAway: A Randomized Phase 2 Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) bearing Homologous Recombination-Repair Mutations (HRRm)

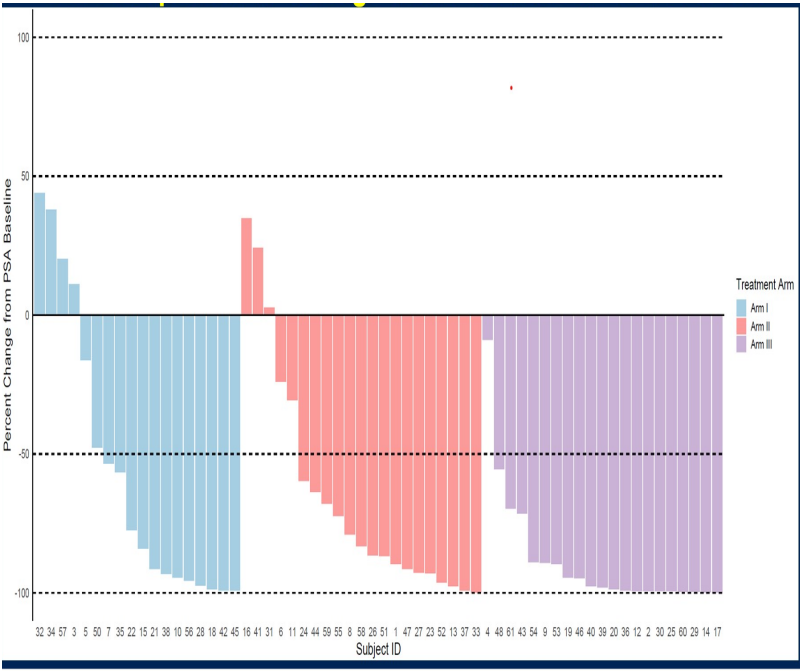
- **Eligibility:** mCRPC, no prior exposure to PARP-I, AR-I, or chemotherapy for mCRPC, washout of antiandrogen (for mHSPC), radiation, and other investigational agents.
- Eligible pts underwent tumor next-generation sequencing (NGS) & germline testing; pts with inactivating BRCA1/2 and/or ATM alterations were randomized 1:1:1 to:
  - Arm I: abiraterone (1000 mg qd) + prednisone (5mg bid),
  - Arm II: olaparib (300 mg bid)
  - Arm III: olaparib + abiraterone/prednisone
- Arm I and II pts could cross over at progression.



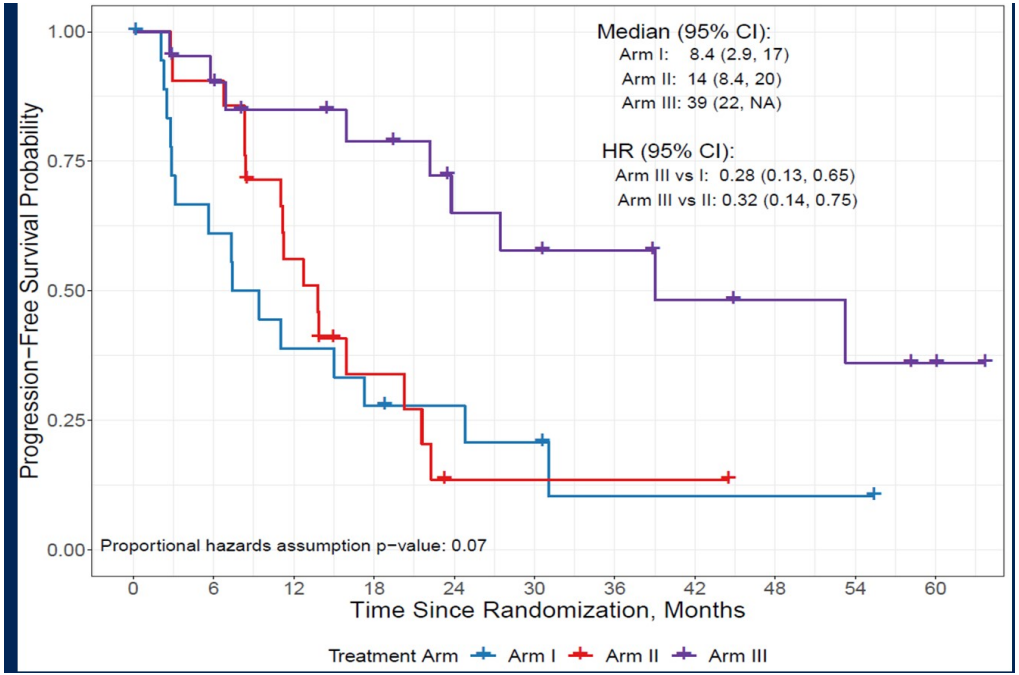
Hussain M. ASCO GU 2024

Olaparib plus AAP derives the greater Benefit in BRCA mut mCRPC

PSA response (%)

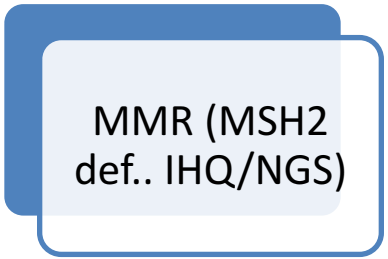


Progression Free Survival



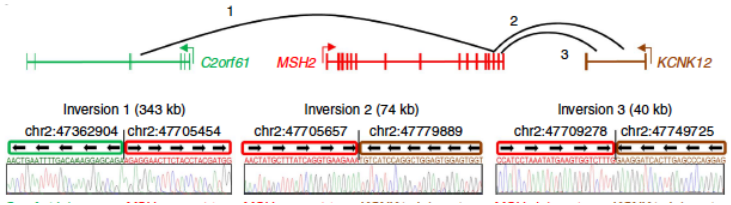
Hussain M. ASCO GU 2024

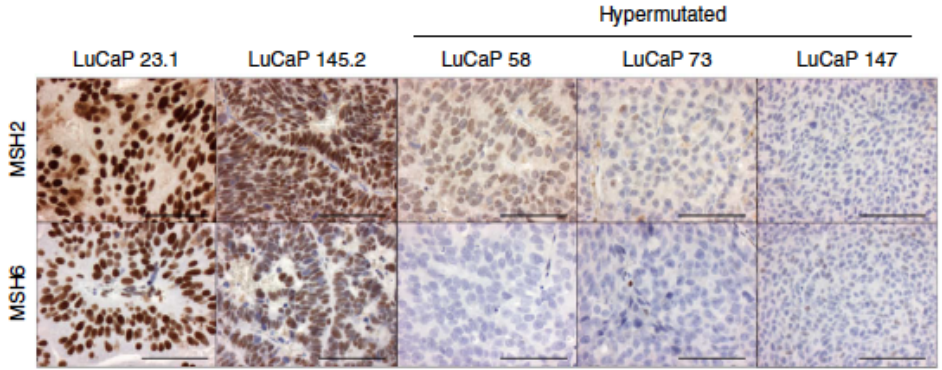
Selección de Pacientes en mCRPC



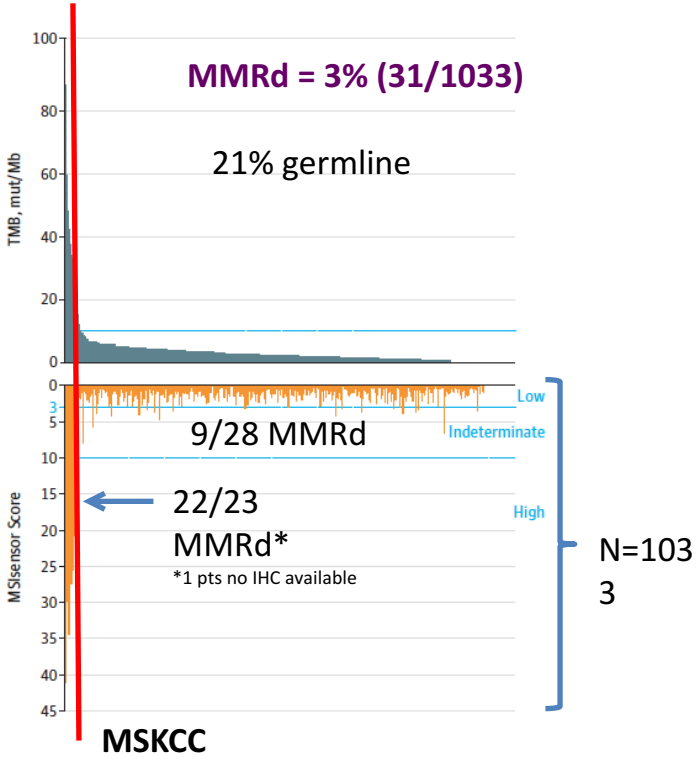
Advanced Pca is associated with Complex Rearrangementts in MMR, most frequently MSH2 and MSH6

IHC can be usefull and easily accesible





Pritchard CC. Nat Comm 2014

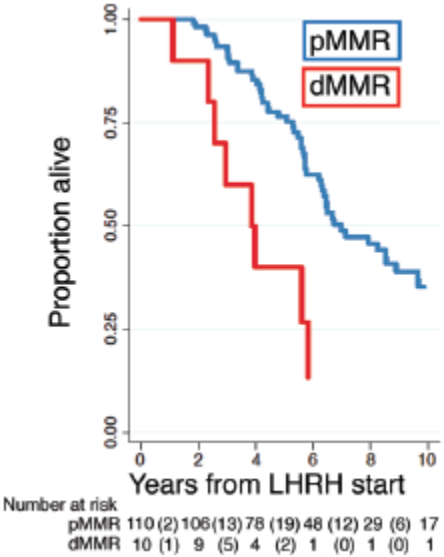


Abida W. JAMA Oncol 2018

MMRd is associated with more aggresive disease

	Ritch and colleagues (this study)	Abida and colleagues, 2018 (3)	Rodrigues and colleagues, 2018 (4)	Antonarakis and colleagues, 2019 (6)
Material analyzed	ctDNA	Tissue	Tissue	Tissue
Prevalence of MMRd/MSI-H	3.7% (16/434)	3.1% (32/1,033; all patients; 4.5% of 356 patients with CRPC)	8% (10/124)	10% (13/127)
Clinically evaluable MMRd patients	11	32	10	13
Median age at diagnosis (range)	74 (61–80)	64.5 (39–85)	62.9	64
GGG ≥ 4 at diagnosis	73% (8/11)	53% (17/32)	78% (7/9)	77% (10/13)
T stage ≥ 3 at diagnosis	89% (8/9)	—	80% (4/5)	77% (10/13)
Metastatic disease at diagnosis	45% (5/11)	44%	63% (5/8)	46% (6/13)
Definitive local therapy	36% (4/11)	—	40% (4/10)	—
Median PSA at diagnosis (Q1–3)	26.1 (11.6–90.5)	38.5 (range 0.9–701.3)	76 (45–155)	10 (5.4–43)
Median PSA at 1L CRPC therapy (range)	23 (7.8–188)	—	—	—
ECOG PS < 2 at 1L CRPC	70% (7/10)	—	—	—
Median TMB (mut/Mb) from targeted sequencing	31.1(20.3 in WES)	—	—	18–21
Germline MMR gene mutation	0.2% (1/433)	0.7% (7/1,033)	0.8% (1/124)	2.4% (3/127)
Time from ADT to CRPC, median (range, months)	9.1 (5.7–12.6)	8.6 (1.2–54.2)	—	—
Time on 1L ABI/ENZ for mCRPC, median (range, months)	3.9 (0.9–13.9)	9.9 (3–34.5)	—	24 (5–NR)
PSA50 to 1L ABI/ENZ	50% (5/10)	—	—	83% (5/6)

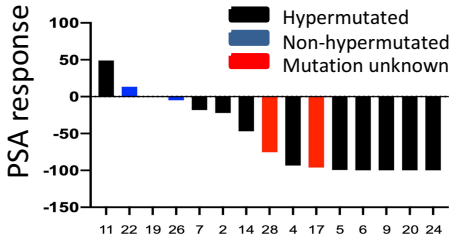
Note: Only 11 of 16 MMRd patients identified in this study had complete clinical data available for analysis.
Abbreviations: 1L, first-line; ABI, abiraterone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENZ, enzalutamide; PSA50, PSA decline ≥50% from baseline.

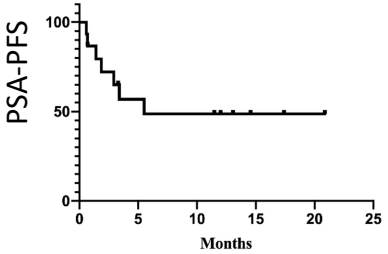


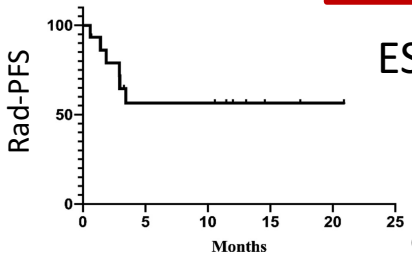
Ritch. Clin Cancer Res 2020
Abida W. JAMA Oncol 2018
Rodrigues. J Clin Invest 2018
Antonarakis E. Eur Urol 2019

Immunotherapy is effective in MMRd PCa

	Abida et al.	Antonarakis et al.	Ritch et al.	Graham et al.	Van Wilpe et al.
	N = 32	N = 13	N = 11	N = 27	N= 71
GS 8–10, no. (%)	17 (53)	10 (77)	8 (73)	19 (70)	NR
Metastatic Disease at Diagnosis, no. (%)	14 (44)	6 (46)	5 (45)	13 (48)	40 (59%)
Presence of Ductal/Intraductal Histology, no. (%)	1 (3)	3 (23)	Not Reported	8 (30)	2 (3%)
Presence of Pure Neuroendocrine Histology, no. (%)	3 (9)	1 (8)	Not Reported	0 (0)	0(0%)
Median Time to CRPC, mos.	8.6 (range 1.2–54.2)	55 (95% CI: 50–73)	9.1 (range 5.7–12.6)	14.2 (95% CI: 8.0–32.6)	NR
PSA50 response to 1st line abi/enza for mCRPC, no. (%)	Not Reported	5 (83)	Not Reported	10 (62.5)	NR
Median PFS on 1st line abi/enza for mCRPC, mos.	9.9 (range 3–34.5)	26 (95% CI: 6-NR)	3.9 (0.9–13.0)	8.56 (95% CI: 3.73–9.51)	NR
Received PD-1 blockade, no. (%)	11 (34)	4 (31)	Not Reported	17 (61)	100 % (Pembro 76%; Nivo 18%; Atezo 6%)
PSA50 response to PD-1 blockade, no. (%)	6 (54.5)	2 (50)	Not Reported	8 (53)	52 (60%)
Median PFS on PD-1 blockade, mos.	Not Reported	9 (95% CI: 4–11)	Not Reported	Not Reached (1.87-NR)	8.3 m (5.5 – 17.4)



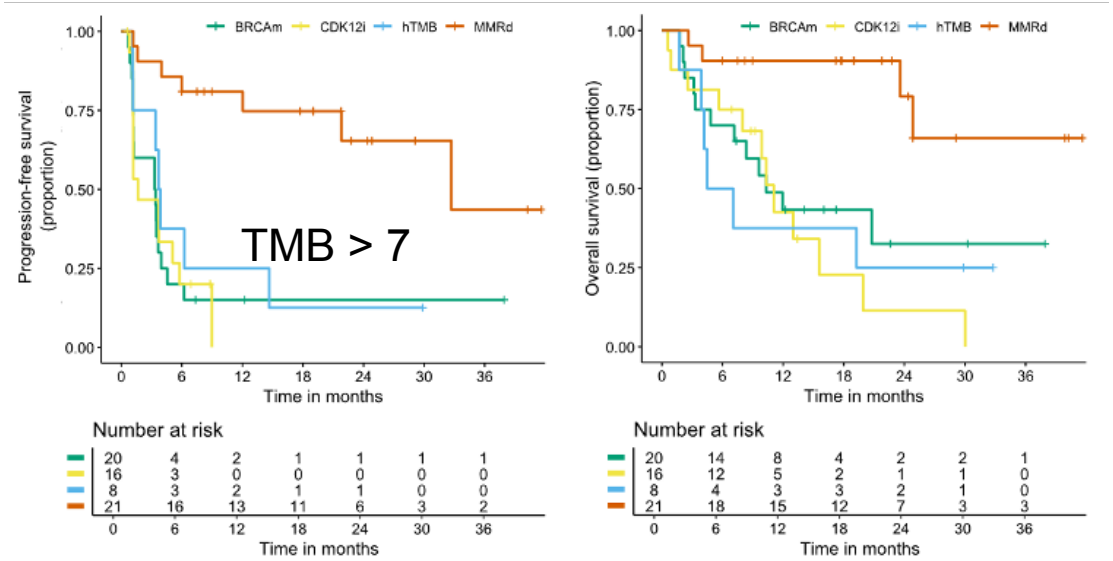




ESMO 24

Graham. Plos One 2020

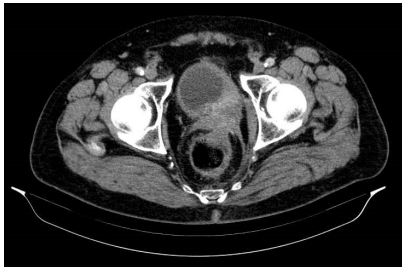
MMRd Benefit from Ipilimumab /Nivolumab

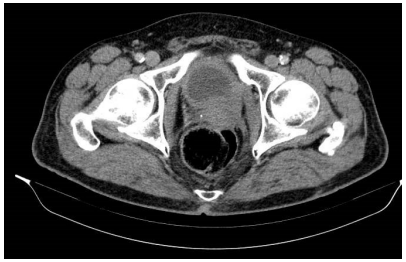


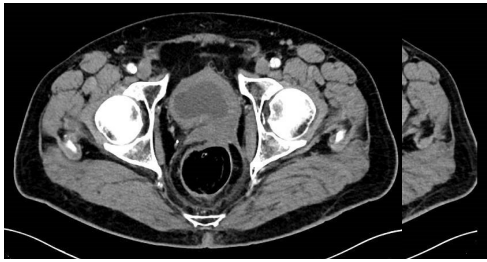
MMRd consistent benefit

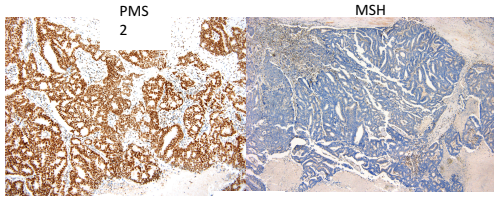
- 3% (17/460)
- PSA 50 response: 86% en MMR
- Most-responses are durable

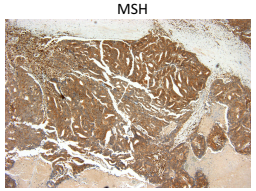
N. Mehra. ESMO 2024







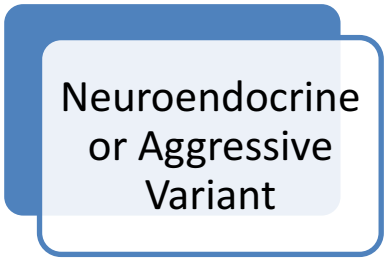




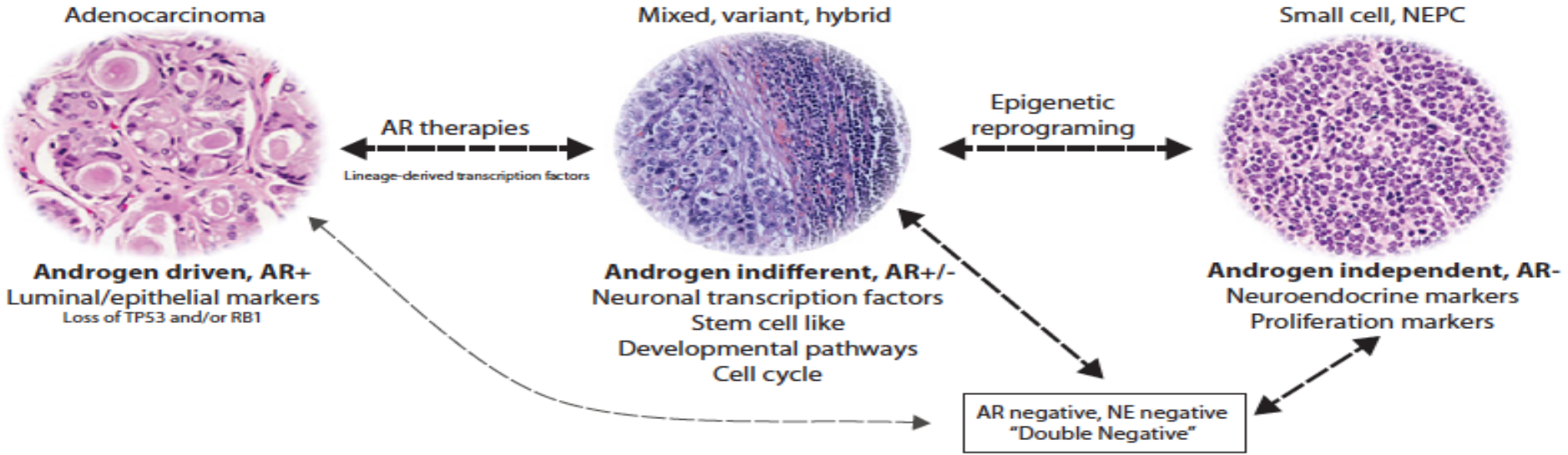
Pembrolizumab (35 ciclos)

Pembrolizumab rechallenge

Selección de Pacientes en mCRPC

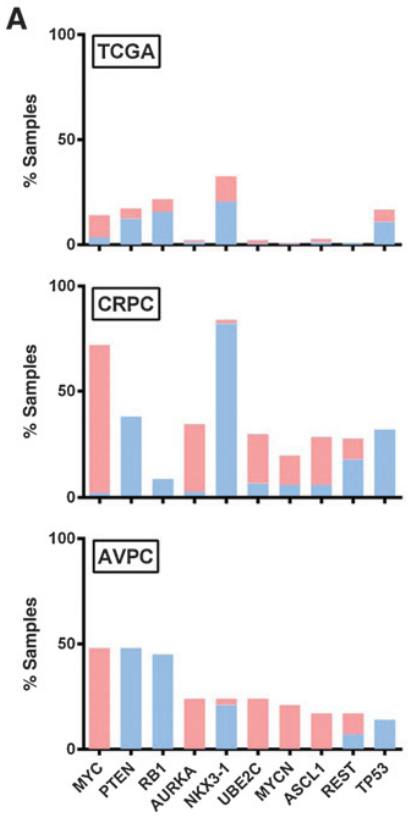


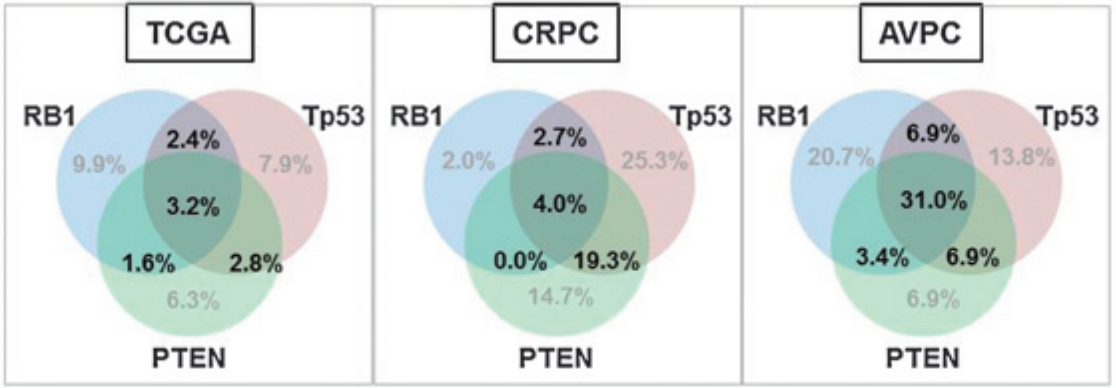
Neuroendocrine Dedifferenciation



H. Beltran. Clin Cancer Res 2019

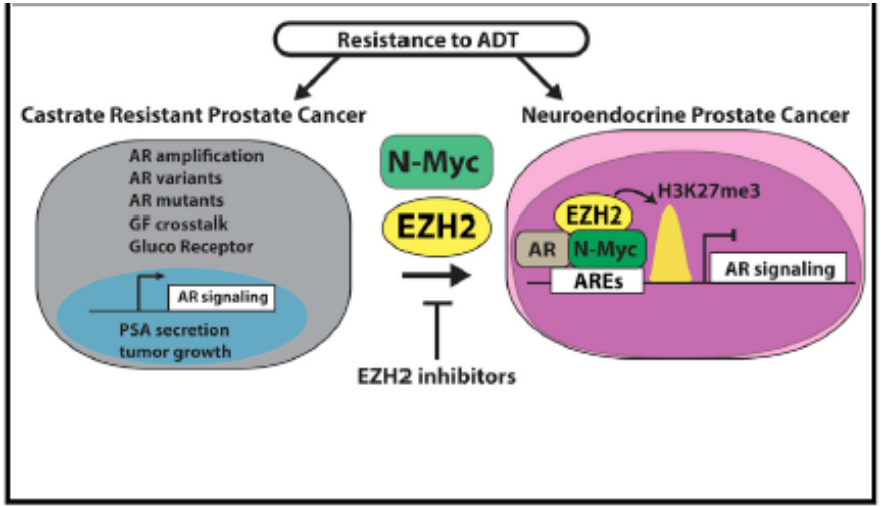
Agressive Variant are associated with AR independence and loss of TSG: RB1, PTEN & TP53

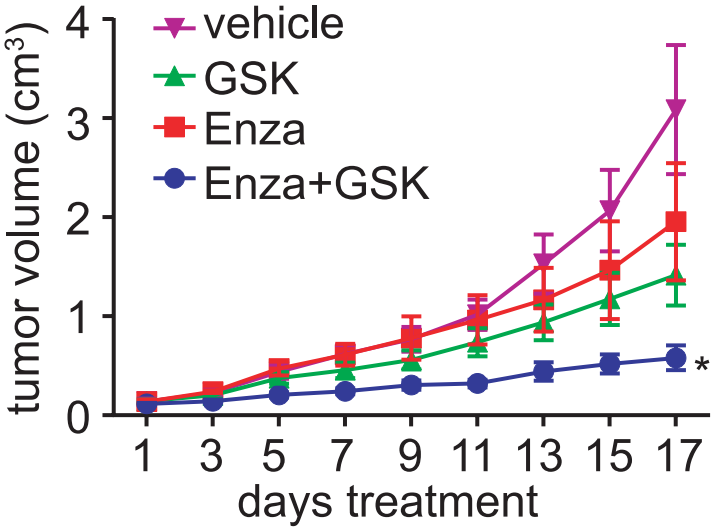




Aparicio, A. M. *et al. Clin Cancer Res* 2016.

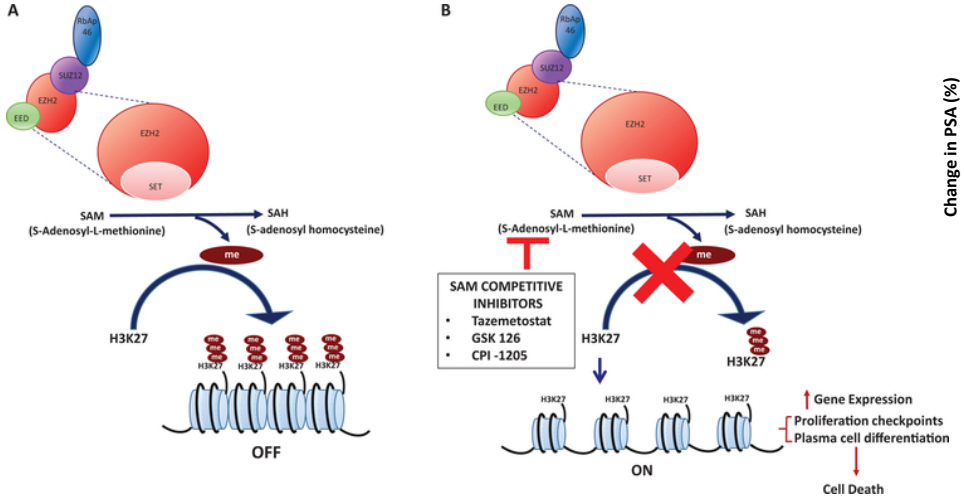
In prostate Cancer EZH2 mediates AR independence



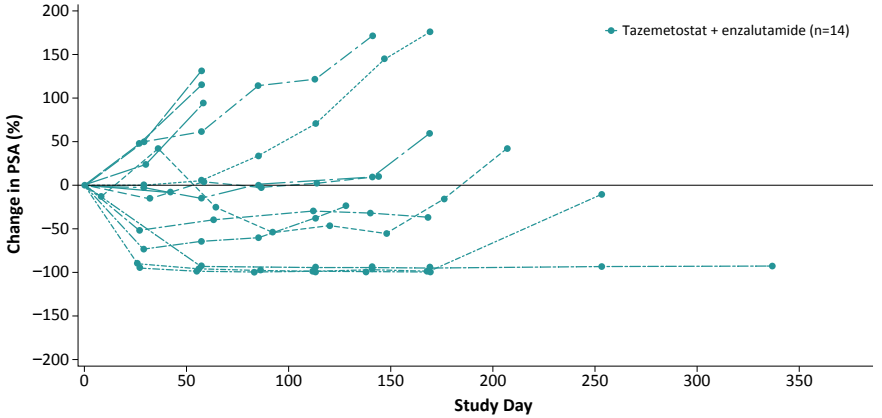


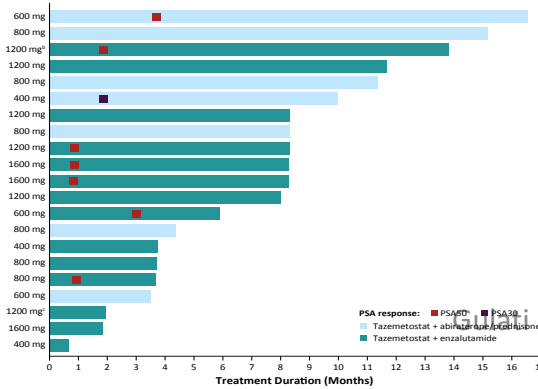
Ku, S.-Y. Science 2017

EZH2 mediates H3K27 methylation.



Tazemetostat (EZHi) demonstrates promising activity





Gounder M. Leukemia and Lymphoma. 2021; Abida W. ESMO 2021

EZH2 inhibition is to be explored in phase 3 trials

Chemotherapy-naïve adult patients with progressive mCRPC who have progressed on abiraterone acetate, with ECOG PS 0 to 1, and adequate organ function

Dosing schedule and endpoints

R
- TAZ 1200 mg BID + ENZ 160 mg QD
- ENZ 160 mg QD

28-day cycles

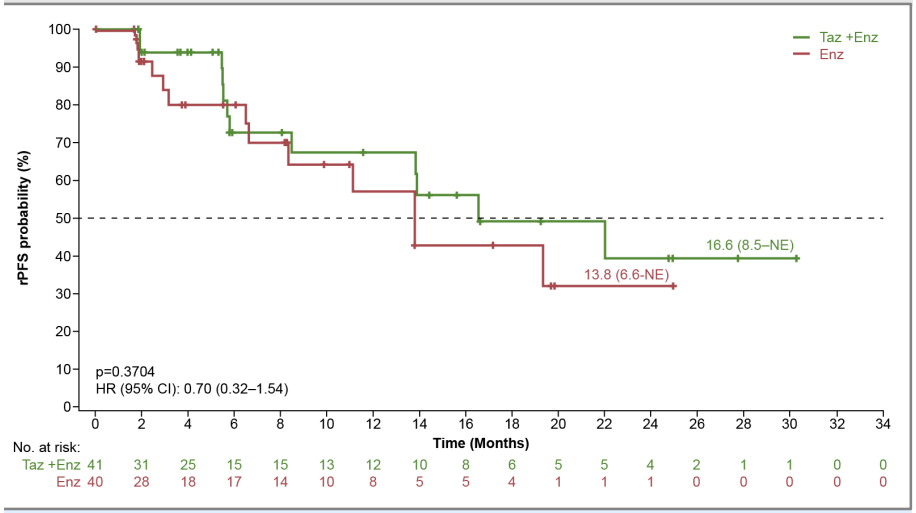
- **Primary endpoint** is change in rPFS by BCR
- **Secondary endpoints** included:
  - ORR by BCR
  - BOR by BCR
  - Percentage of participants with TEAEs

Results

Baseline demographics and disease characteristics

	Randomized	Median age	White	ECOG PS 0	Median time from last disease progression	Median PSA
TAZ+ENZ	41/81 patients	72.0 years	85.4%	56.1%	1.05 months	8.30 µg/L
ENZ	40/81 patients	68.5 years	77.5%	55.0%	0.94 months	7.68 µg/L

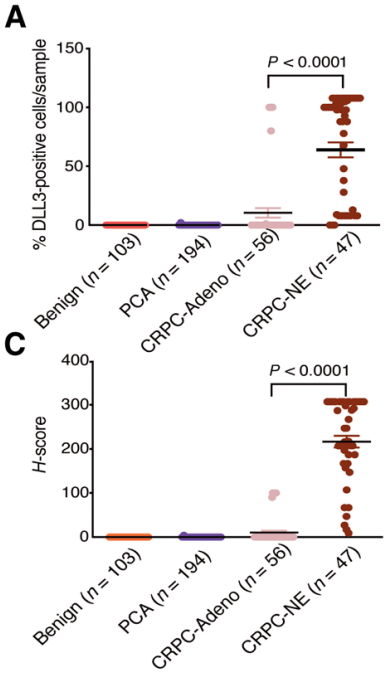
Figure 1. Kaplan-Meier curve for rPFS per BCR in the ITT population

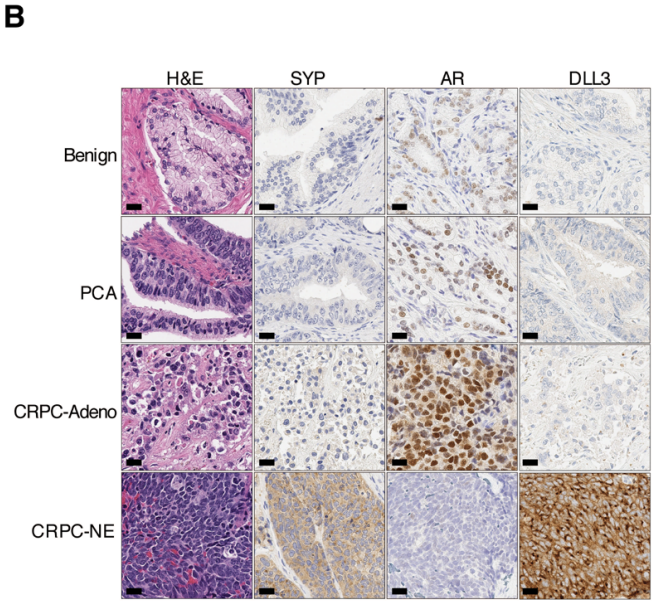


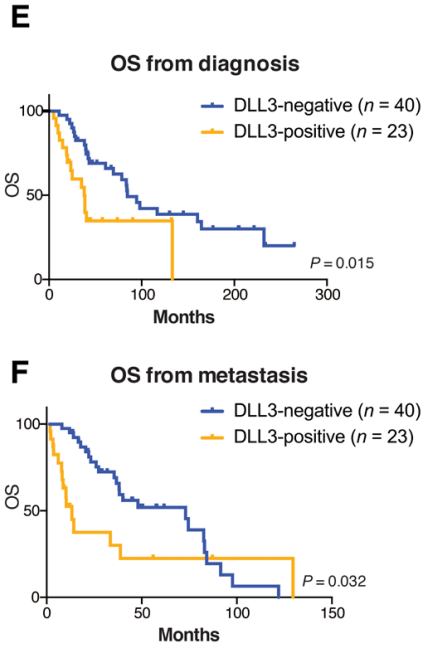
TAKE-HOME MESSAGE

- TAZ did not result in a statistically significant improvement in rPFS vs. ENZ in patients with mCRPC (HR [95% CI], 0.70 [0.32–1.54]; p=0.3704)
- No new safety signals observed

DLL3 is preferentially expressed in NEPC





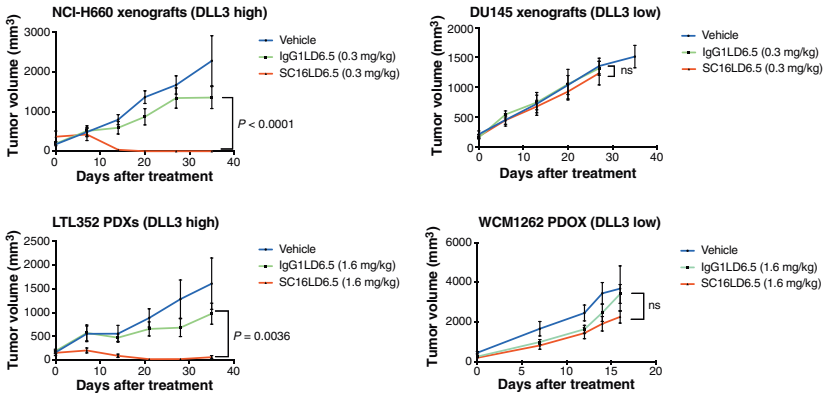


DLL3 in NEPC vs AdenoCRPC 76% vs 12.5%

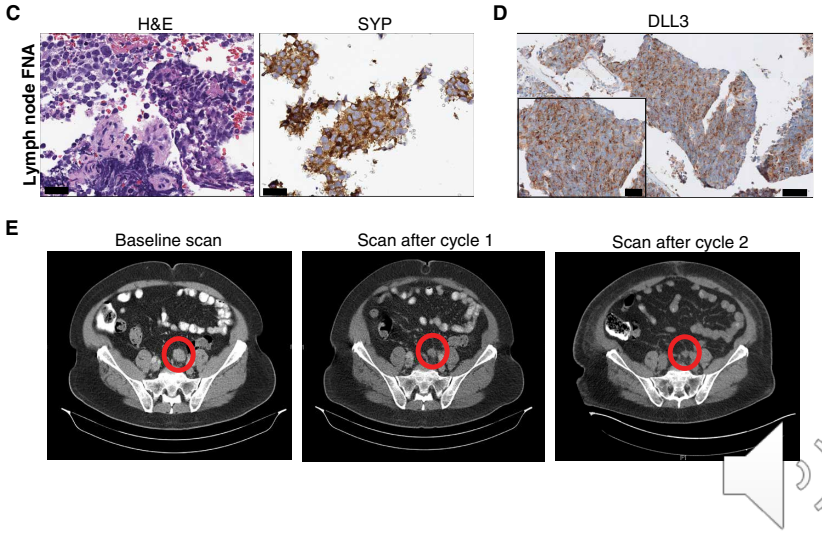
Puka L. Science Transl Med 2019
Chou J. Cancer Res 2022

DLL3 Antibody Drug Conjugate (ADC) Rovalpituzumab Tesirine (DLL3 – PBD)

DLL3 ADC mostly benefit DLL3 high PDX

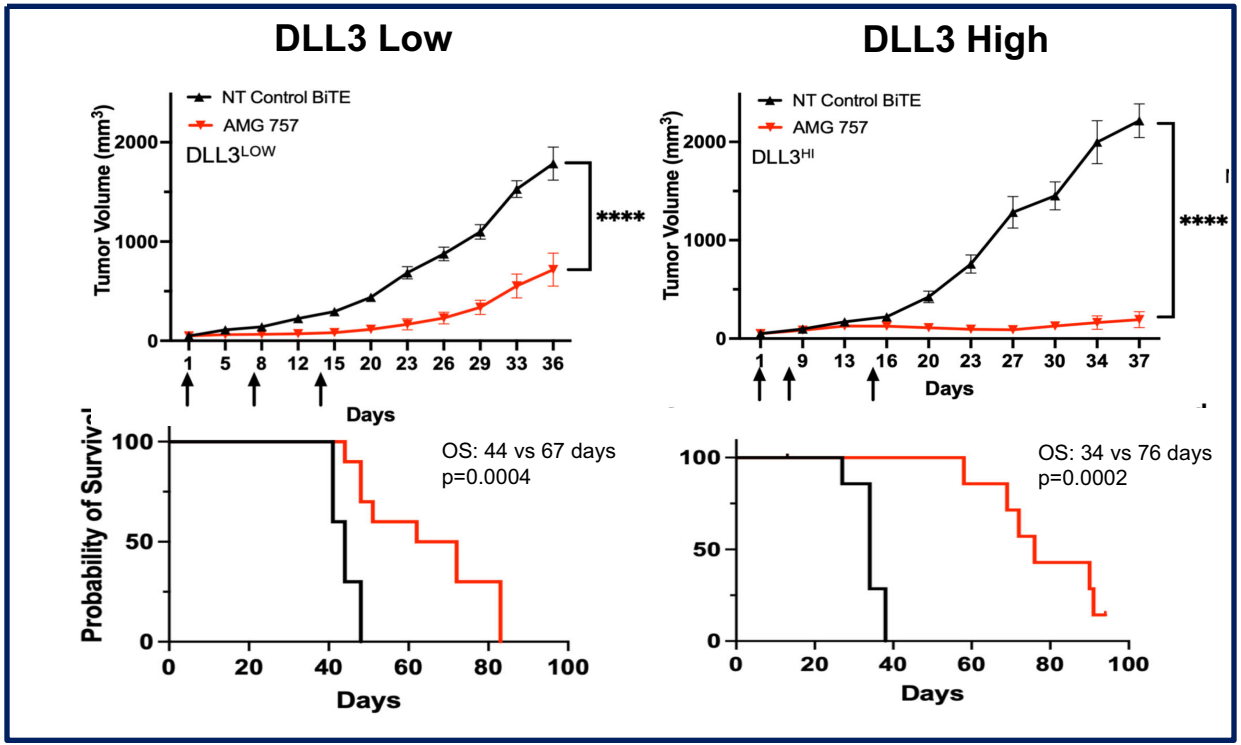


Patient enrolled in a phase 1 trial with Rovalpituzumab



Puka L. Science Transl Med 2019

AMG 757 (tarlatamab), a half-life-extended bispecific T cell engager (BiTE®) immunotherapy that redirects CD3-positive T cells to kill DLL3-expressing cells



Chou J. Cancer Res 2022

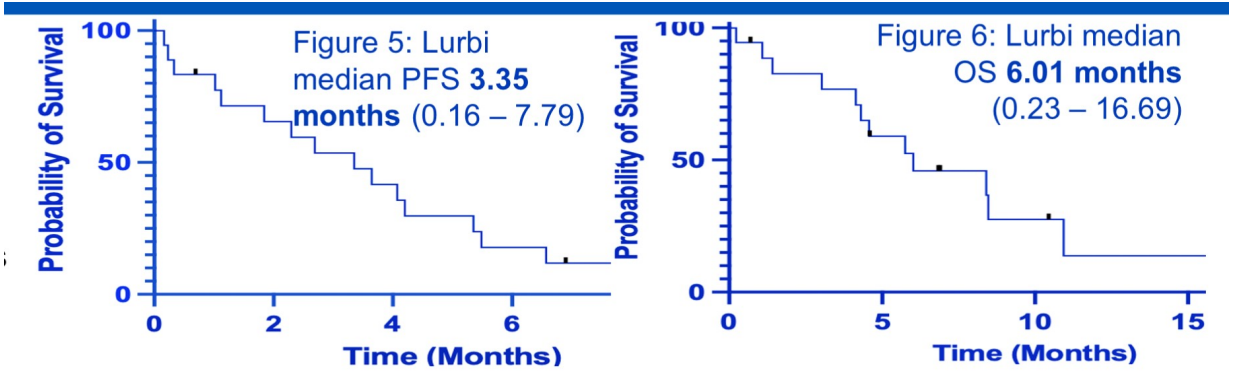
Abstract 164 (437556): Lurbinectedin in Prostatic Small Cell and Neuroendocrine Carcinoma

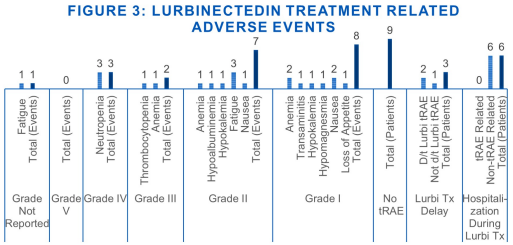
Haley Meyer[1], Rajitha Sunkara[2], Himisha Beltran[2], Emily Rothmann[2], Kevin Dale Courtney[3], Andrew J. Armstrong[4], Andrea Lippucci[5], Melissa L. Stanton[1], Alan Haruo Bryce[1]

[1]Mayo Clinic Arizona, [2]Dana-Farber Cancer Institute, [3]University of Texas Southwestern Medical Center, [4]Duke Cancer Institute Center for Prostate and Urologic Cancer, Duke University, Durham, NC [5]Duke University Medical Center

Contact: meyer.haley2@mayo.edu

Partial Response
5/16 pacientes (31.3%)





CONCLUSIONS SC/NEPC is an aggressive malignancy associated with a poor prognosis. PBC is an effective first-line treatment, but its duration of response is limited. Treatments second-line and beyond are major clinical challenges, as evidence to support subsequent therapies is lacking.

Lurbi is a well-tolerated and active treatment option for patients with SC/NEPC. Large-scale, prospective studies are needed to determine the role of Lurbi in the treatment of SC/NEPC.

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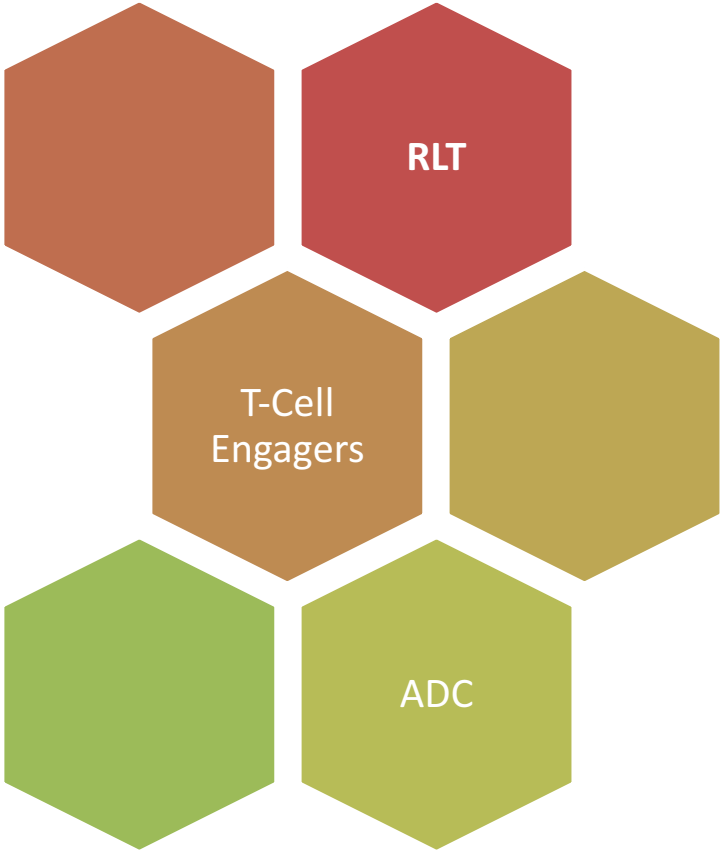
Other Treatments



ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

Centrally read PSMA PET imaging criteria

- ≥ 1 PSMA-positive metastatic lesion
  - Positive = ^{68}Ga uptake > liver
- No PSMA-negative metastatic lesions
  - Bone with soft tissue component ≥ 1.0 cm
  - Lymph node ≥ 2.5 cm
  - Solid organ ≥ 1.0 cm

Alternate primary endpoints	Key secondary endpoints	Other secondary endpoints
Radiographic progression-free survival (rPFS) per PCWG3	Time to first symptomatic skeletal event (SSE)	Safety and tolerability
Overall survival (OS)	RECIST v1.1 overall response rate	Biomarkers including PSA
	RECIST v1.1 disease control rate	Health-related quality of life and pain

Eligible patients

- Previous treatment with <u>both:</u>
  - ≥ 1 ARPI
  - 1–2 taxane regimens
- Protocol-permitted SoC planned before randomization
  - Excluding chemotherapy, immunotherapy, radium-223 or other investigational drugs[a]
- ECOG PS 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11[b]

2:1

^{177}**Lu-PSMA-617**[c]
7.4 GBq (200 mCi) Q6W
up to 6 cycles

+ Protocol-permitted SoC

Protocol-permitted SoC

Alternate primary endpoints

- rPFS (per PCWG3)
- OS

<u>Randomization stratification</u>

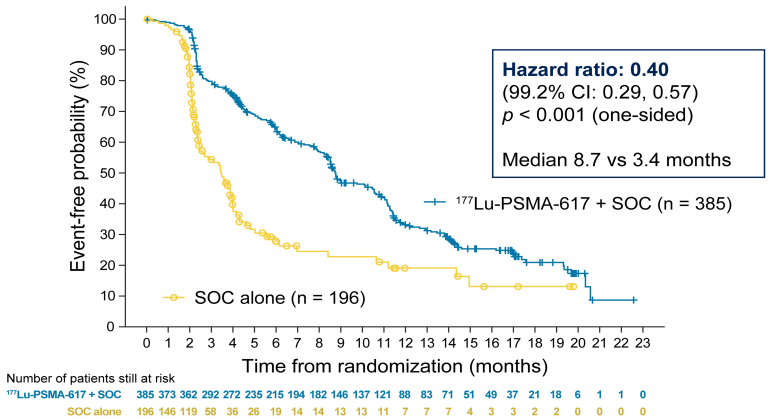
- ECOG PS (0–1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- **ARPI in SoC (yes or no)**

Sartor O. NEJM 2021

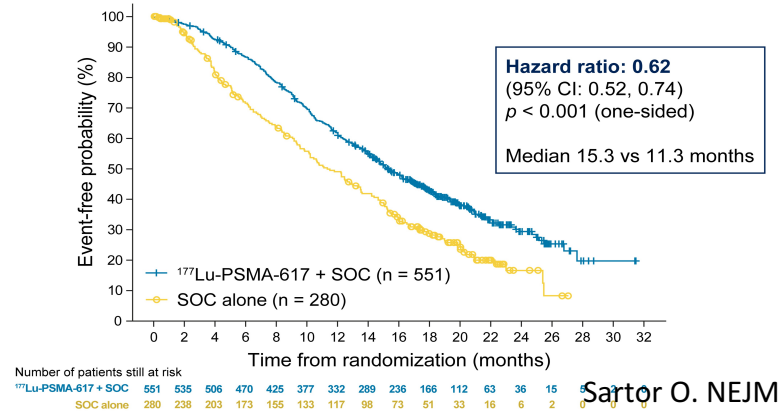
Primary Endpoint

	rPFS analysis set (n = 581)		All randomized (N = 831)	
	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
Age, median (range)	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
Race, n (%)				
White	336 (87.3)	166 (84.7)	486 (88.2)	235 (83.9)
Black/African-American	29 (7.5)	14 (7.1)	34 (6.2)	21 (7.5)
Asian	6 (1.6)	9 (4.6)	9 (1.6)	11 (3.9)
ECOG status, n (%)				
0 or 1	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
2	33 (8.6)	17 (8.7)	41 (7.4)	22 (7.9)
Site of disease, n (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Number received, median (range)				
Androgen receptor pathway inhibitor	1.0 (1–5)	1.5 (1–4)	1.0 (1–5)	2.0 (1–4)
Taxane regimen	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)
Patients who received more than one, n (%)				
Androgen receptor pathway inhibitor	172 (44.7)	98 (50.0)	253 (45.9)	152 (54.3)
Taxane regimen	178 (46.2)	94 (48.0)	226 (41.0)	124 (44.3)

rPFS

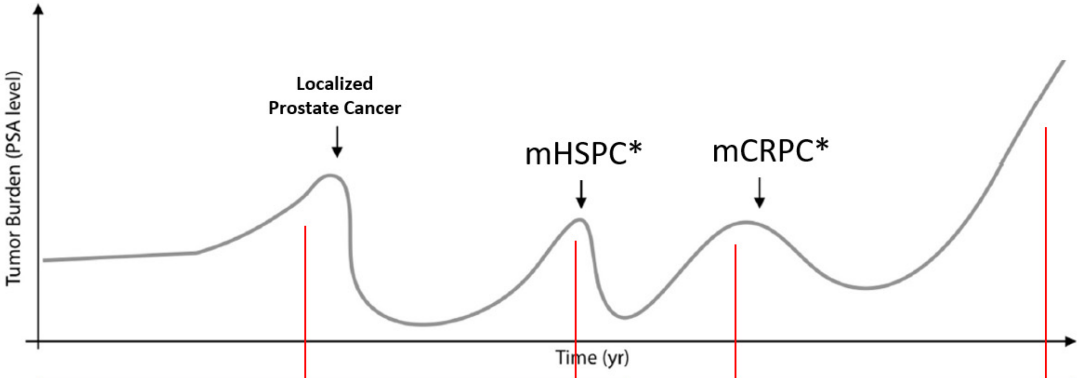


Overall Survival



Sartor O. NEJM 2021

What's next?



Neoadjuvant therapy for localized disease

1. ^{177}Lu-PSMA-617 (LuTectomy)

First-line therapy for mCRPC

1. ^{177}Lu-PSMA-I&T (Bullseye)
2. ^{177}Lu-PSMA-617 + enzalutamide (ENZA-P)

First-line therapy for mHSPC

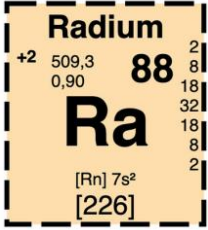
1. ^{177}Lu-PSMA-617 (UpFrontPSMA, PSMAddition)

Second-line or later therapy for mCRPC

1. ^{177}Lu-PSMA-617 (LuPSMA,TheraP, VISION)
2. ^{177}Lu-PSMA-617 + olaparib (LuPARP)
3. ^{177}Lu-PSMA-617 + pembrolizumab (PRINCE)
4. ^{177}Lu-PSMA-I&T (SPLASH)
5. ^{225}Ac-PSMA-617 (AcTION)
6. ^{177}Lu-J591 (NCT00538668)
7. ^{225}Ac-J591 (NCT04506567)
8. ^{227}Th-PSMA-TTC (NCT03724747)
9. ^{131}I-MIP-1095 + enzalutamide (ARROW)
10. ^{177}Lu-PSMA-R2 (NCT03490838)

*mHSPC (metastatic hormone-sensitive prostate cancer)
*mCRPC (metastatic castrate-resistant prostate cancer)
*Different colours represent various PSMA-targeted radiopharmaceuticals (^{177}Lu-PSMA-617, ^{177}Lu-PSMA-I&T, ^{177}Lu-J591, ^{225}Ac-J591, ^{227}Th-PSMA-TTC, ^{131}I-MIP-1095, ^{177}Lu-PSMA-R2)

6- More Phase 3 trials data to come for Radium-223?



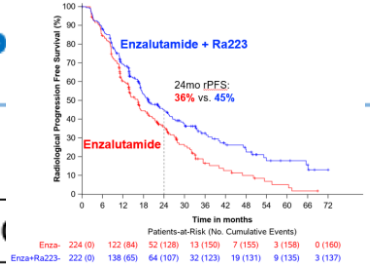
ARP

PSA relapse

High-risk localized

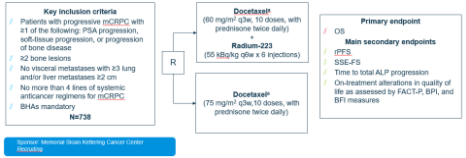
M0 (

M1 Castration-Sensitive



DORA

DOCE+Ra-223



PEACE-3

ENZA+Ra-223

Docetaxel

RADIANT

Ra-223
Post ARPI and DOCE

Metastati

Key Inclusion Criteria:

- Progression on/after one ARPI incl Abiraterone, Enzalutamide, Apalutamide, Darolutamide
- One prior taxane
- ≥ 2 bone mets
- Symptomatic based on BPI-SF
- No visceral disease
- LN <3cm
- Treatment with BPA

R

(Total n~700)

2nd ARPI

Stratified by ALP, prior chemotherapy, prior abiraterone

Radium-223 at 55 kBq/kg x 6 cycles

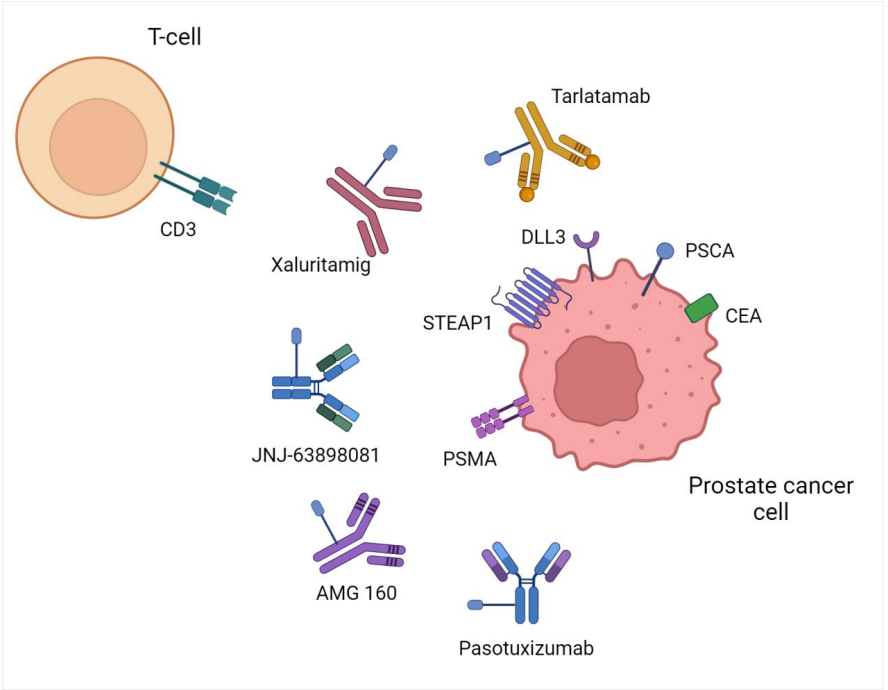
NCT04597125
NCT03574571

Tumor Antigen Targets in Prostate Cancer

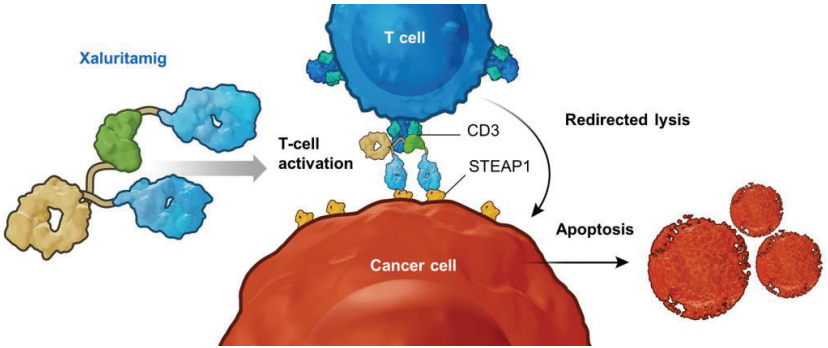
Table 1. TAAs and their expression in type of prostate cancer versus their normal distribution.

Tumor-associated antigen	Cell/tissue distribution
PSCA	**Prostate adenocarcinoma**, urothelial, skin, esophagus, neuronal, stomach
PSMA	**Prostate adenocarcinoma**, prostate acinar epithelium, proximal tubular cells, glial cells, jejunal brush border cells, salivary glandular cells
STEAP-1	**Prostate adenocarcinoma**, bladder, ovary, bone marrow, cardiac, respiratory
DLL3	**Neuroendocrine prostate cancer (NEPC)**, neurons, pancreatic islet cells, pituitary
CEA	**NEPC**, urogenital, respiratory, gastrointestinal

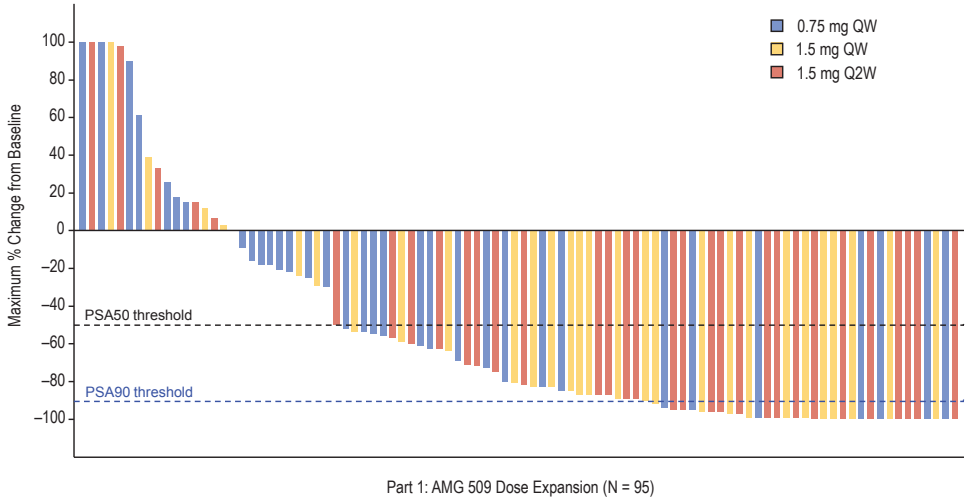
Dorff T et al. ***CCR***, 2022



Xaluritamig (STEAP1-CD3 BITE)



	0.75 mg QW	1.5 mg QW	1.5 mg Q2W	Total
PSA50, n/N (%)	12/33 (36.4)	18/30 (60.0)	17/32 (53.1)	47/95 (49.5)
PSA90, n/N (%)	7/33 (21.2)	9/30 (30.0)	11/32 (34.4)	27/95 (28.4)
ORR, n/N (%)	4/27 (14.8)	4/21 (19.0)	6/21 (28.6)	14/69 (20.3)



Kelly W. ESMO 2024

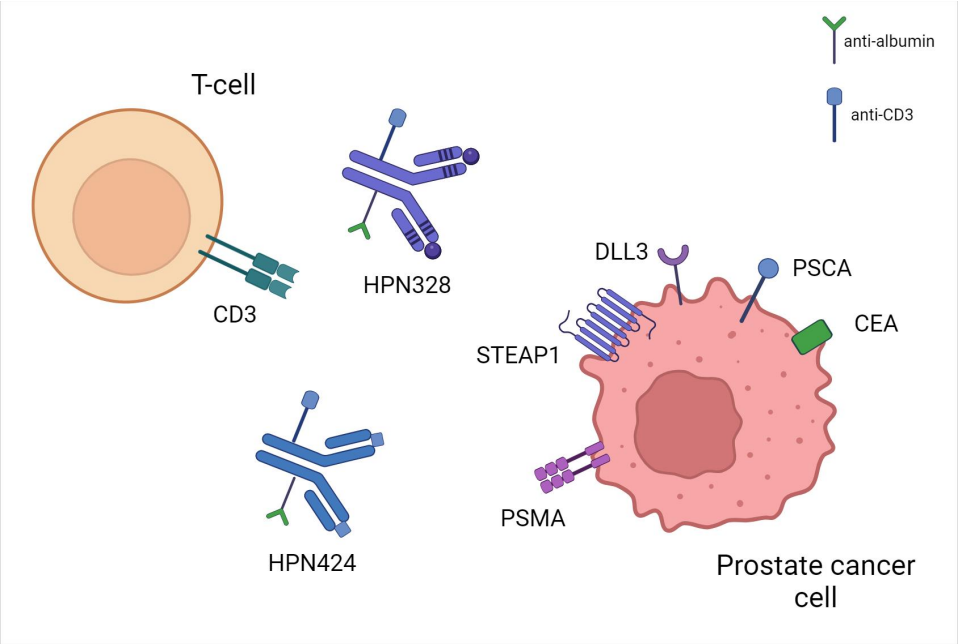
Bispecific T-Cell Engagers in Prostate Cancer

	Pasotuxizumab[1]	JNJ-63898081[2]	AMG 160[3]	LAVA-1207[4]	Xaluritamig[5]	Tarlatamab[6]
Patient Population	mCRPC with prior progression on ≥ 1 taxane and abiraterone and/or enzalutamide	mCRPC with prior progression on taxane or ARPI	mCRPC with prior progression on 1 to 2 taxane-based regimens and ARPI	Treatment refractory mCRPC	mCRPC with prior progression on ARPI and 1 – 2 taxane regimens	Metastatic de novo or treatment-emergent NEPC with prior progression on ≥ 1 platinum CT or ARPI
Study Design	Phase 1 Dose escalation	Phase 1 Dose escalation + dose expansion	Phase 1 Dose escalation + dose expansion	Phase 1/2a Dose escalation + dose expansion	Phase 1 Dose escalation	Phase 1b Dose expansion
Tumor Antigen Target	PSMA	PSMA	PSMA	PSMA	STEAP-1	DLL3
Primary Endpoint	Safety, MTD	Safety, anti-tumor response	Safety, MTD, RP2D	Safety, RP2D	Safety, MTD, RP2D	Safety
No. of Patients	47	39	133	20	97	40
Visceral Metastases, n (%)	-	-	22 (16.5)	-	51 (53)	-
Median number of prior lines of therapy, n (range)	-	-	-	4 (3 – 10)	4 (1 – 9)	3 (2 – 4)
Prior Taxane, n (%)	-	30 (76.9)	128 (96.2)	-	82 (85)	-
Prior ARPI, n (%)	-	38 (97.4)	132 (99.2)	-	96 (99)	-
PSA50 Responses, n (%)	12 of 39 (30.7)	2 of 26 (7.7)	42 of 133 (31.6)	-	43 of 87 (49)	-
ORR, n (%)	0 of 18 (0)	0 of 23 (0)	7 of 59 (10.6)	0	16 of 67 (24)	4 of 38 (10.5) in all pts, 4 of 18 (22.2) in DLL3+ pts
Median rPFS, months (95% CI)	-	-	3.8 (3.5 – 4.9)	-	-	2.1 for all pts, 3.7 for DLL3+ pts
Antidrug antibodies, n (%)	30 of 31 (96.7%) in SC cohort 0 of 16 (0) in IV cohort	17 of 27 (63%) in SC cohort 2 of 12 (16.7%) in IV cohort	30 of 81 (37%) in dose escalation 29 of 53 (55%) in dose expansion	-	49 of 90 (54%)	-
CRS, any G – G ≥ 3 (%)	6 – 2.1	66.7 – 0	97.7 – 20.3	~ 10 - 0	72 – 2	75 – 2.5
Fatigue, any G – G ≥ 3 (%)	34 – 2.1	41 – 0	53.2 – 23.4% of dose escalation cohort (n = 77)	~ 45 - 0	45 – 11	-

[1] Hummel H et al., ***Immunotherapy***, 2020; [2] Lim E et al., ***CGUC***, 2023; [3] Dorff T et al., ***CCR***, 2024; [4] Mehra N et al., ***ASCO 2023***; [5] Kelly W et al., ***Cancer Discovery***, 2023; [6] Aggarwal R et al., ***ASCO 2024***

Trispecific T-Cell Engagers

- The third binding domain can be used for[1]:
  - Dual targeting of tumor-associated antigens
  - Dual targeting of T-cell receptors
  - Fusion to human serum albumin
    - Extends half-life, allowing for more even drug concentration and less frequent dosing[2]



[1] Tapia-Galisteo A et al., ***Journal of Hematology & Oncology***, 2023

Trispecific T-Cell Engagers in Prostate Cancer

	HPN424[1]	HPN328[2]
Patient Population	mCRPC with receipt of > 2 prior systemic therapies Prior CT allowed but not required	Relapsed/refractory, metastatic NEPC, small cell lung cancer (SCLC), and other NEC associated with DLL3 expression
Study Design	Phase 1/2a Dose escalation + dose expansion	Phase 1/2 Dose escalation
Tumor Antigen Target	PSMA	DLL3
Primary Endpoint	Safety, tolerability and determination of MTD/RP2D	Safety, MTD, recommended dose for expansion, pharmacokinetics
No. of Patients	89	97
Visceral Metastases, n (%)	-	-
Median number of prior lines of therapy, n (range)	5 (1 – 12)	3 (1 – 7)
Prior Chemotherapy, n (%)	65 (73)	-
Prior ARPI, n (%)	87 (98)	-
PSA50 Responses, n (%)	4 of 74 (5)	-
ORR, n (%)	-	17 (41)
CRS, any G – G ≥ 3 (%)	69 - 4	63 - 3
Fatigue, any G – G ≥ 3 (%)	45 - 3	37 - 2
Anemia, any G – G ≥ 3 (%)	31 - 11	-

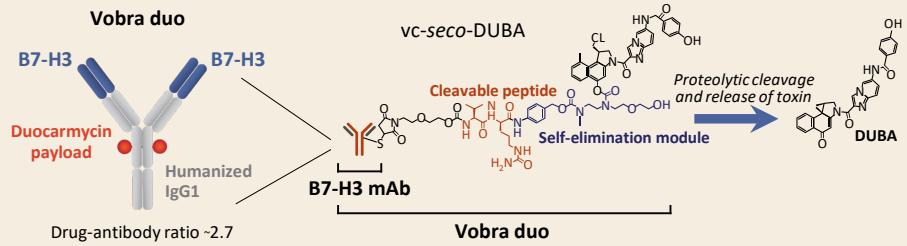
[1] De Bono J et al., ***ASCO 2021***; [2] Beltran H et al., ***ASCO GU 2024***

Agarwal N. ESMO 24

Antibody Drug Conjugates

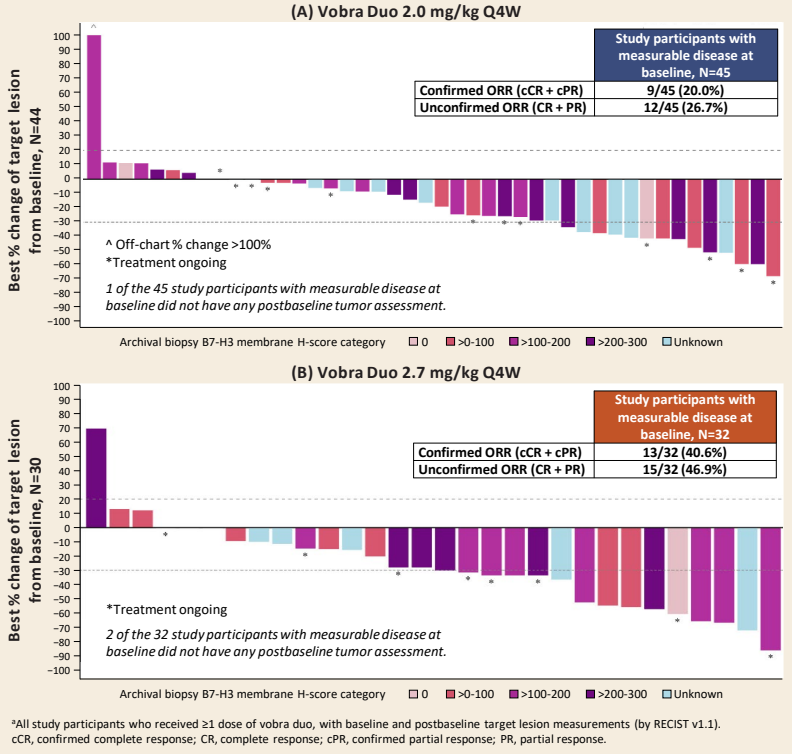
Vobra Duo

Figure 1. B7-H3–Directed ADC Vobra Duo With Duocarmycin-Based Linker Payload[4]



IgG1, immunoglobulin G1; mAb, monoclonal antibody.

Figure 4. TAMARACK Best % Change in Target Lesions From Baseline per Investigator (RECIST Response-Evaluable Population With Measurable Disease, N=77)[a]



[a]All study participants who received ≥1 dose of vobra duo, with baseline and postbaseline target lesion measurements (by RECIST v1.1).
cCR, confirmed complete response; CR, complete response; cPR, confirmed partial response; PR, partial response.

De Bono J. ESMO 2024

Take Home Messages

- **Pca treatment is moving towards personalization**
  - AR mut, HRD, MMR & NE
- **New targets are comming:**
  - RLT (PSMA, KLK2...)
  - T-Cell Engagers (STEAP1, PSMA, PSCA, KLK2..)
  - Antibody drug conjugates (B7H3, KLK2...)

¡Thank You!

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