Inaugural Southern California Genitourinary Cancer Research Forum

Key Updates in Prostate Cancer

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City of Hope

Disclosures

- Consultant for AstraZeneca, Bayer, Janssen, and Sanofi.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Cabozantinib + Atezolizumab, AMG509, and ARV766 will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Importance of addressing bias and barriers to care based on socioeconomic status and differences in responses that have been noted based on race.*
- *Patients who are underinsured can be treated with older generation drugs.*

New frontiers in prostate cancer

- Antigen targeting therapy
  - Radioligand (177-Lu-PSMA-617)
  - Bispecific T cell engaging antibodies
  - Antibody-drug conjugates (ABBV 969)
- Combination immunotherapy
  - Cabozantinib + Atezolizumab (CONTACT 02)
- PARP inhibitors
- AR degraders
  - ARV 110, ARV 766 and beyond

VISION: 177-Lu-PSMA-617 radioligand therapy selection by PET “theranostic”

>80% crossover!

Eligibility criteria

- Progressive mCRPC
- PSMA-positive with gallium 68-PSMA-11 PET/CT scan (per predefined criteria)
- Previous taxane (≤ 2 regimens) therapy and previous Abi/Enza (≥ 1 regimen)
- ECOG PS 0 to 2
- Life expectancy > 6 mo

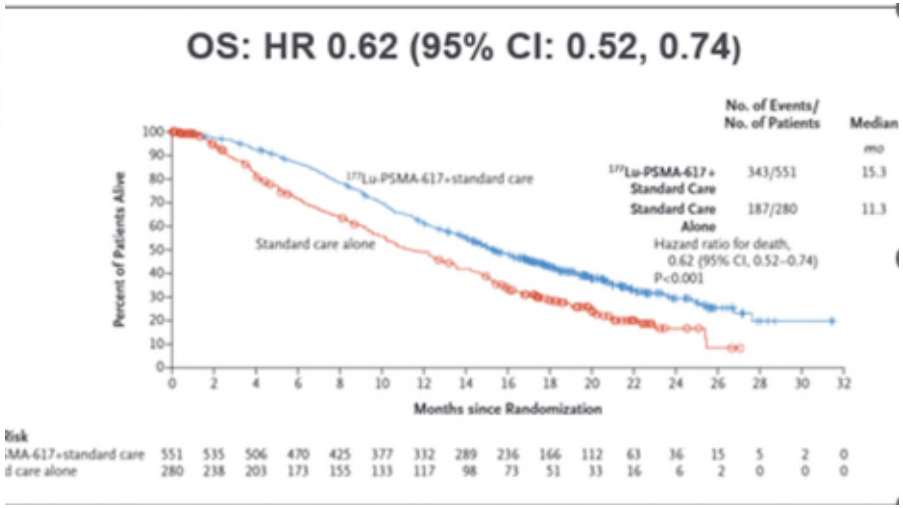
R 2:1

^{177}Lu-PSMA-617 + SOC (n = 551)

SOC alone (n = 280)

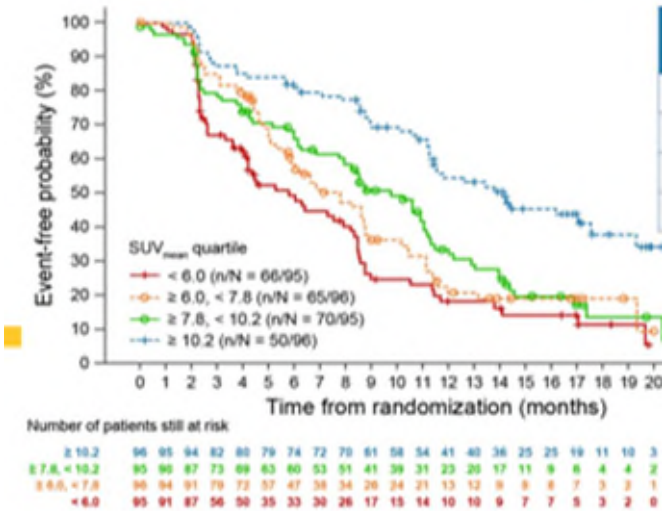
Primary endpoints:
OS, imaging-based PFS

Secondary endpoints:
ORR and DCR per RECIST response, time to SSE, safety



Sartor O, et al. N Engl J Med. 2021;385:1091-1103

- PSMA-positive metastatic lesion
  - PSMA-PET positivity defined as uptake ≥ liver
- No size criteria for PSMA-positive lesions
- No PSMA-negative visceral or lytic bone lesions ≥ 1 cm
- No PSMA-negative lymph node lesions ≥ 2.5 cm



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VISION: side effect profile

TEAEs Occurring in ≥ 5% of Patients, No. (%)	Safety Set (N = 734)			
	All Grades		Grade 3-5	
	Lutetium 177-PSMA-617 + SOC (n = 529)	SOC Alone (n = 205)	Lutetium 177-PSMA-617 + SOC (n = 529)	SOC Alone (n = 205)
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopenia	66 (12.5)	4 (2)	13 (2.5)	1 (0.5)

Marrow reserve will dictate sequences and combinations

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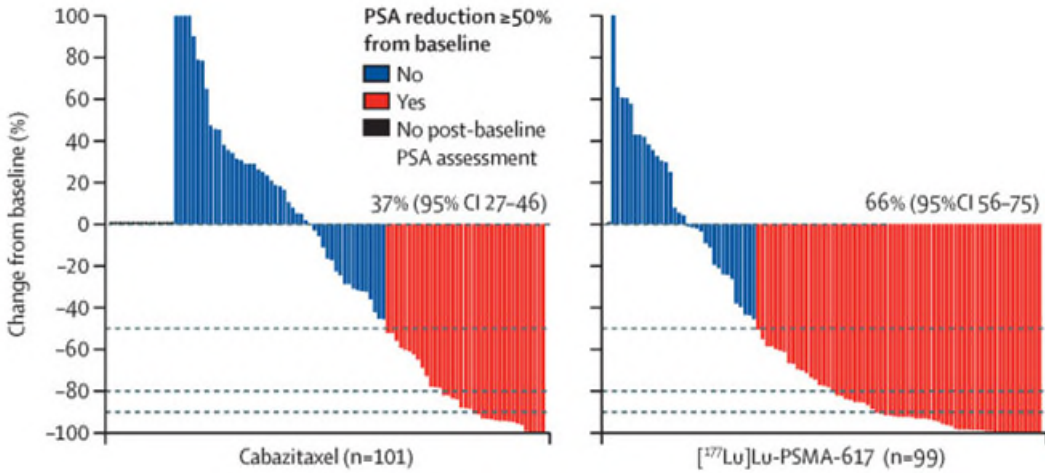
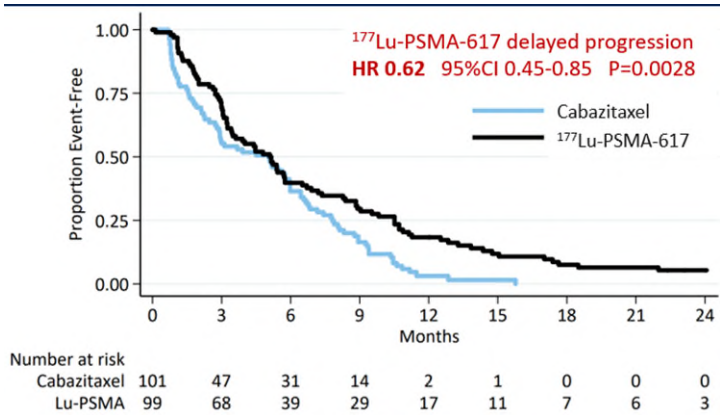
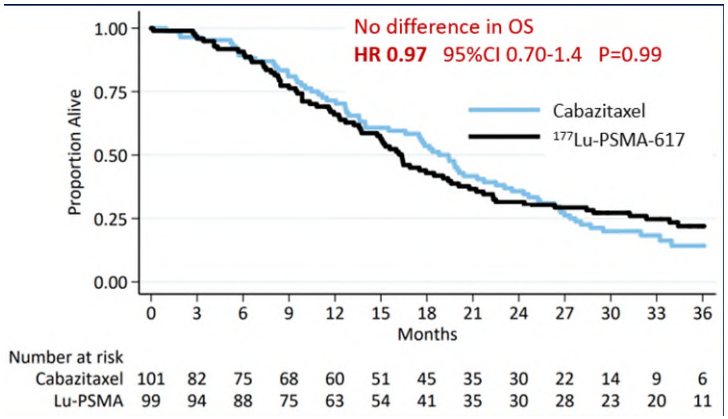
How does 177-Lu-PSMA-617 compare to chemotherapy?

TheraP: phase II Lu177-PSMA vs Cabazitaxel

- PSMA PET inclusion: SUVmax >20 at any site and no FDG+/PSMA- sites (28% excluded)
- Post docetaxel and ARPi







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Hofman MS, Lancet 2021; 27:797-801

Can we use177-Lu-PSMA-617 before chemotherapy?

PSMAfore

Sartor O, et al
ESMO 2023; LBA13

Eligibility criteria
- Progressive, mCRPC, taxane-naive in the metastatic setting and have received 1 prior ARPI and are candidates for a change in ARPI
- ECOG PS 0 or 1
- ≥ 1 PSMA-positive metastatic lesion on GA-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions

Stratification factors:
- Prior ARPI use
- Pain symptomatology score

PSMAfore (NCT04689828) is a multicenter, open-label, randomized phase 3 trial

Best supportive care is allowed in both arms.

R 1:1

- **^{177}Lu-PSMA-617** 7.4 GBq IV ± 10% once every 6 wk for 6 cycles (n = 234)
- **Change in ARPI to either abiraterone or enzalutamide** (n = 234)

Primary endpoints: rPFS according to PCWG3-modified RES

Key secondary endpoint: OS

Other secondary endpoints: rPFS2, PFS, PFS2, PSA50, time to SSE, time to soft tissue progression, time to chemo, HRQoL, and safety and tolerability

Participants with blinded independent centrally confirmed radiographic progression in the ARPI arm can cross over to the ^{177}Lu-PSMA-617 arm.

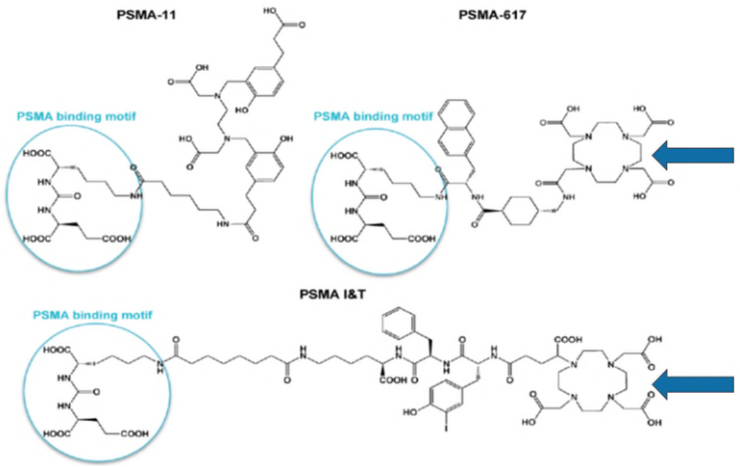
Baseline Characteristics	^{177}Lu-PSMA-617 (n = 234)	ARPI Change (n = 234)
Age, median (range), y	71 (43-94)	72 (53-91)
White, n	211	214
ECOG 0 ECOG 1	146 86	115 114
Gleason score 8 to 10, n	136	107
PSA, median (range), µg/L	18.4 (0-1197)	14.9 (0-4224)
Hemoglobin median, g/L	128	129
Alkaline phosphatase, median IU/L	100	100.3
Site of disease, n ▪ Liver ▪ Lymph node ▪ Bone	 13 76 205	 7 74 203
Prior ARPI, n ▪ Abiraterone ▪ Enzalutamide ▪ Other	 119 94 21	 130 84 20

Second OS IA (DCO, 21 Jun 2023; median follow-up, 15.9 months)	^{177}Lu-PSMA-617 (N=234)	ARPI change (N=234)
Cycles, median (range)	6.0 (1–6)	–
rPFS[a]		
Events, n (%)	115 (49.1)	168 (71.8)
Median (95% CI), months	12.02 (9.30, 14.42)	5.59 (4.17, 5.95)
HR (95% CI), *p*	0.43 (0.33, 0.54), <0.0001	

OS not mature, but trending in opposite direction

Ongoing clinical trials with radioactive targeted therapy

Name/NCT	Agents	Design (n)
PSMAddition	ADT + ARPi +/- 177Lu-PSMA-617	Randomized phase III, **mHSPC**
LUNAR NCT05496959	SBRT +/- 177Lu-PNT2002	Randomized phase II, **oligomet** prostate cancer
PRESERVE-006 NCT05682443	ONC392 + 177Lu-PSMA-617	Phase 1 mCRPC
PRINCE NCT03658447	177Lu-PSMA-617 + pembrolizumab	Phase 1b/II mCRPC
Mayo NCT06200103	177Lu-PSMA-617 de-escalation	Phase IV; stop after 5 vs 6 cycles
U W NCT06145633	Vorinostat and 177Lu-PSMA-617 for the Treatment of **PSMA-Low mCRPC**	Phase II
UPLIFT NCT05113537	Abemaciclib Before 177Lu-PSMA-617 for the Treatment of mCRPC	Phase I/II



What's next:

Different particles (ex: Ac^{225}, Pb, I^{131})
Different PSMA binders
Different protein targets (ex: hk2)
?Adaptive dosing
Combinations, mHSPC

Bispecific T cell engaging antibodies for prostate cancer

- **AMG 160: targets PSMA (1:1 with CD3)**
  - phase 1 showed robust response rate but limited by anti-drug antibodies
  - Toxicity limited ability to pursue phase 3
- **AMG 509: targets STEAP1 (2:1 with CD3)**
  - Dose escalation presented at ESMO 2023. better toxicity & efficacy
  - Likely going to phase 3
- JNJ-63898081: (PSMA 1:1 with CD3)
  - N=39, CRS in 65%, DLT transaminase elevation. 2 PSA 50, no objective response

AMG160: adverse events

TEAE	Dose expansion (N = 56)	
	Any grade n (%)	Grade ≥ 3 n (%)
Cytokine release syndrome	55 (98.2)	9 (16.1)*
Anemia	20 (35.7)	11 (19.6)
Hypophosphatemia	20 (35.7)	9 (16.1)
Alanine aminotransferase increased	12 (21.4)	3 (5.4)
Aspartate aminotransferase increased	11 (19.6)	3 (5.4)
Platelet count decreased	8 (14.3)	3 (5.4)*
Hypertension	4 (7.1)	3 (5.4)
Neutropenia	4 (7.1)	4 (7.1)*

*Includes one patient who experienced a grade 4 event
Abbreviation: TEAE: treatment-emergent adverse event

Dorff TB et al, Clin Cancer Res 2024
https://doi.org/10.1158/1078-0432.CCR-23-2978

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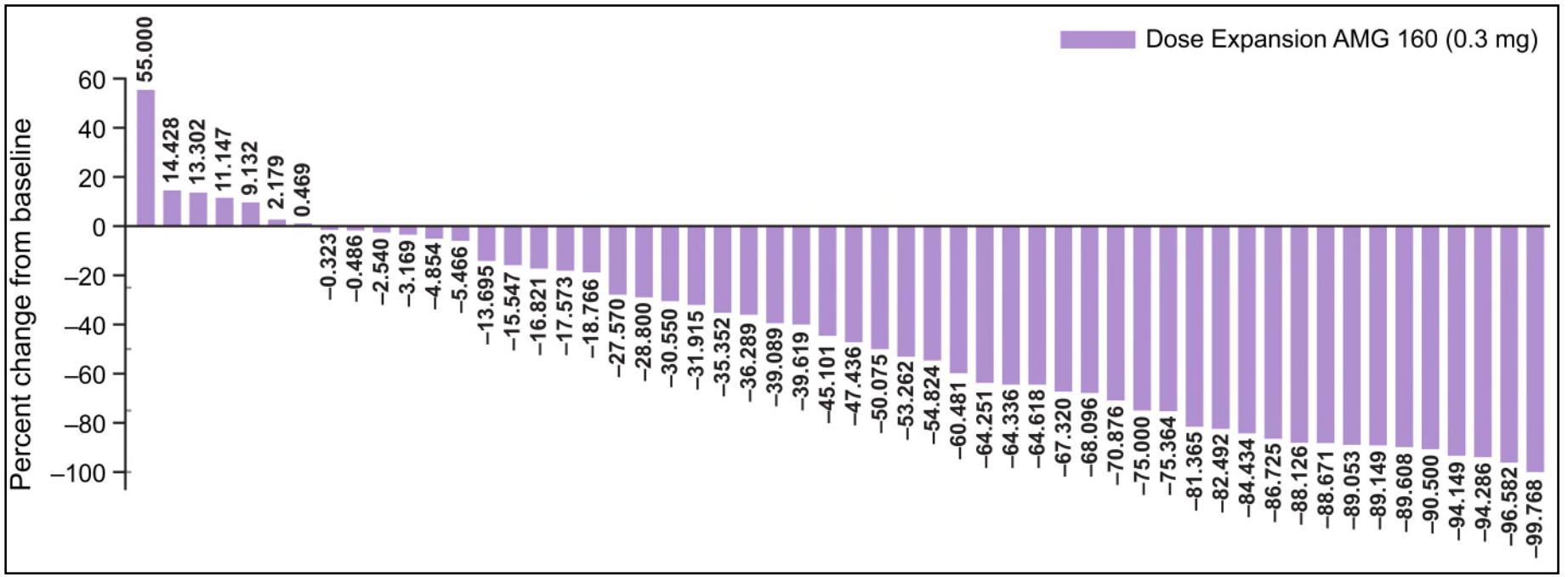
PSA response with AMG160 at full dose



Dorff TB et al, Clin Cancer Res 2024
https://doi.org/10.1158/1078-0432.CCR-23-2978

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AMG509 phase 1 dose escalation (Kelly WK et al, ESMO 2023)

Dosing schedule: 28-day cycles; QW dosing (except C7c); treatment until progression* or unacceptable toxicity

Dose exploration guided by BLRM for toxicity

No Step	1-Step	2-Step	3-Step
C1: 0.001 mg **C2:** 0.003 mg **C3:** 0.01 mg **C4:** 0.03 mg **C5:** 0.1 mg **C6:** 0.3 mg	**C7a:** 0.1 → 0.3 mg **C8:** 0.3 → 1.0 mg **C10:** 0.1 → 1.0 mg	**C7b:** 0.1 → 0.3 → 1 mg **C7c:** 0.1 → 0.3 → 1 mg (Q2W) **C9:** 0.1 → 0.3 → 0.75 mg	**C11:** 0.1 → 0.3 → 1 → 1.5 mg **C12:** 0.1 → 0.3 → 0.75 → 1.5 mg **C13:** 0.1 → 0.3 → 1 → 2 mg

MTD → **Xaluritamig dose expansion**

Pre-medication adjusted during C7a† →

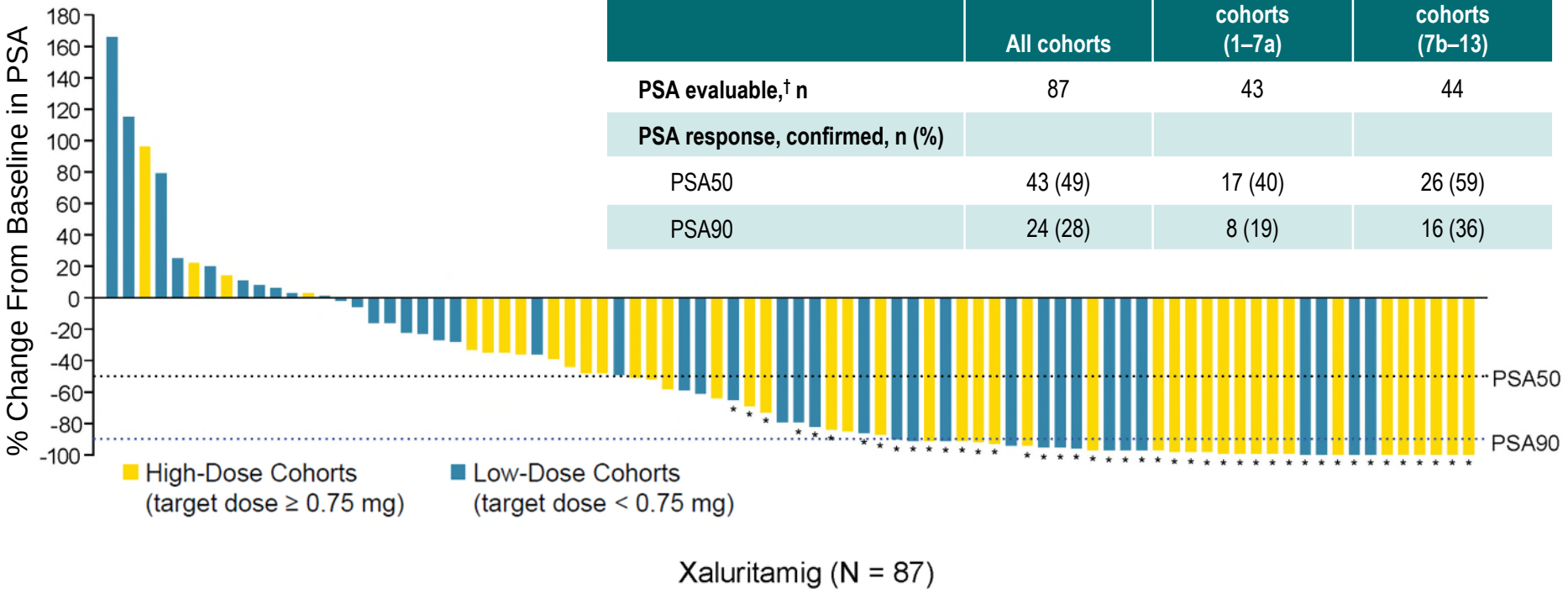
Not tolerable MTD

MTD was identified as 1.5 mg IV QW (3-step, D1 0.1 mg / D8 0.3 mg / D15 1.0 mg / D22+ 1.5 mg)

*Treatment beyond progression was allowed in patients deriving clinical benefit per PCWG3 criteria.
†Pre-medication post adjustment: steroids (2 doses) 6–12 hours and 1 hour pre-dose until target dose is reached; acetaminophen and IV hydration 1 hour prior for all doses in cycle 1.
BLRM, Bayesian logistic regression model; C, cohort; D, day; IV, intravenous; MTD, maximum tolerated dose; PCWG3; Prostate Cancer Working Group 3; QW, weekly; Q2W, every 2 weeks.

Confirmed PSA responses were observed across cohorts

	All cohorts	Low-dose cohorts (1–7a)	High-dose cohorts (7b–13)
PSA evaluable,† n	87	43	44
PSA response, confirmed, n (%)			
PSA50	43 (49)	17 (40)	26 (59)
PSA90	24 (28)	8 (19)	16 (36)



*Confirmed PSA responders of PSA50 or better.
†10 patients were not PSA evaluable: 6 patients were missing baseline PSA values, and 4 patients did not have sufficient follow-up duration.
PSA, prostate-specific antigen.

Antibody-drug conjugate (cytotoxic payload)

- PSMA ADC 2301 (Progenics) MMAE payload

Arm/Group Description	Prostate Specific Membrane Antigen Antibody Drug Conjugate (PSMA ADC) administered IV at 2.3 mg/kg Q3W for 8 cycles.... + Show more	Prostate Specific Membrane Antigen Antibody Drug Conjugate (PSMA ADC) administered IV at 2.3 mg/kg Q3W for 8 cycles.... + Show more
Overall Number of Participants Analyzed	79	34
>30% Decrease in PSA *Measure Type: Number | Unit of Measure: % of responders	29	32
>50% Decrease in PSA *	11	21

- ARX517 (NCT04662580) pAF-AS269 payload
  - recruiting at UCLA

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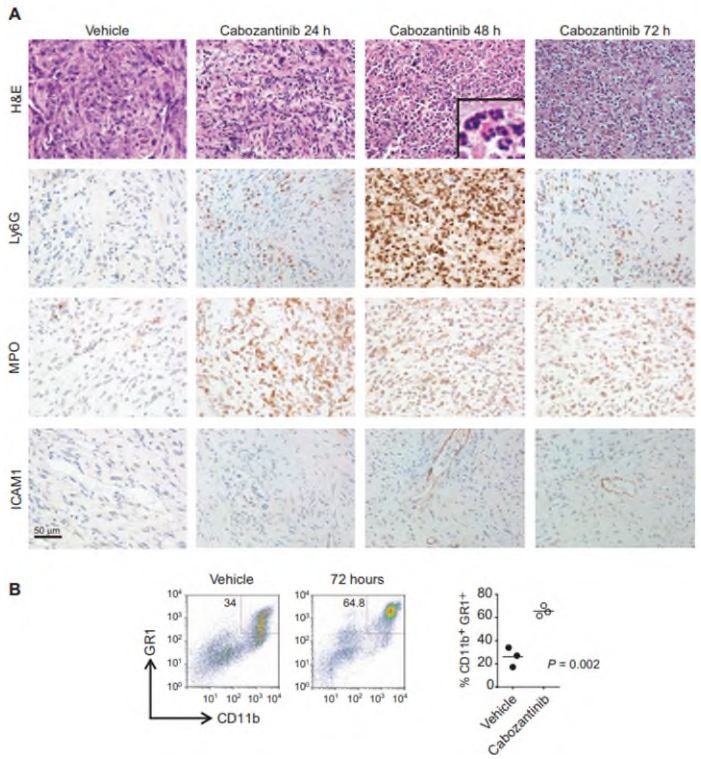
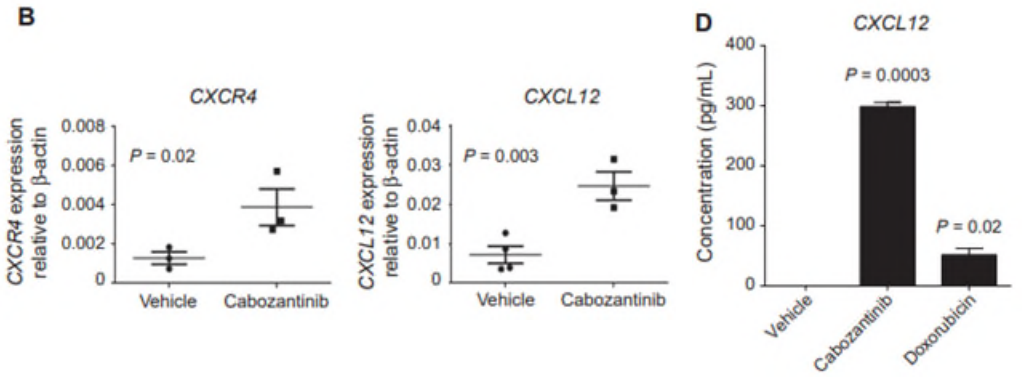
Clincaltrials.gov 2/21/24

Combination VEGF IO: coming to prostate?





Cabozantinib has been shown to induce favorable changes in tumor microenvironment and regression of prostate tumor in vivo

Patnaik A, et al. Cancer Discov 2017; 10.1158/2159-8290.CD-16-0778

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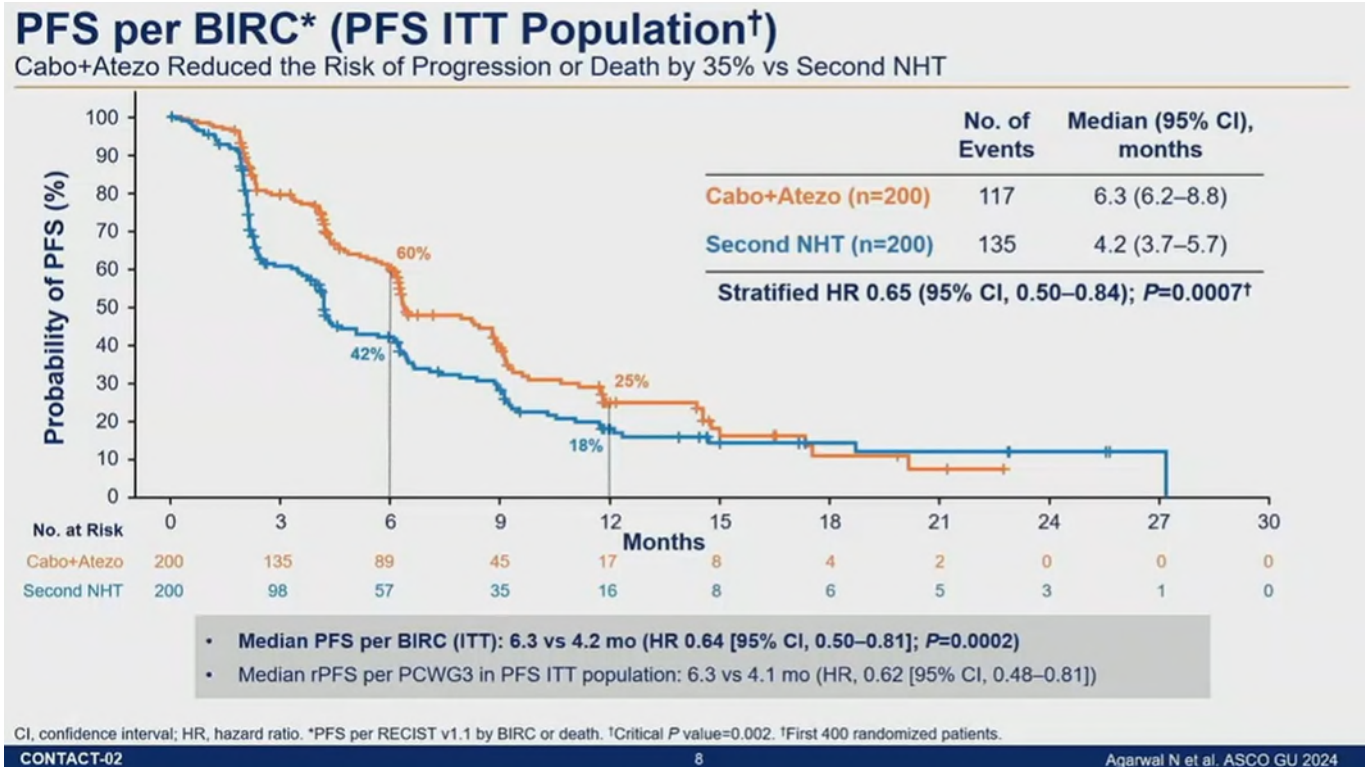
Cabozantinib + atezolizumab: phase 3 CONTACT-02



Agarwal N et al
GU ASCO 2024

mCRPC w/
measurable disease

OS not yet mature but trending in favor of cabo + atezo
HR 0.79 (0.58-1.07)

Weak control arm

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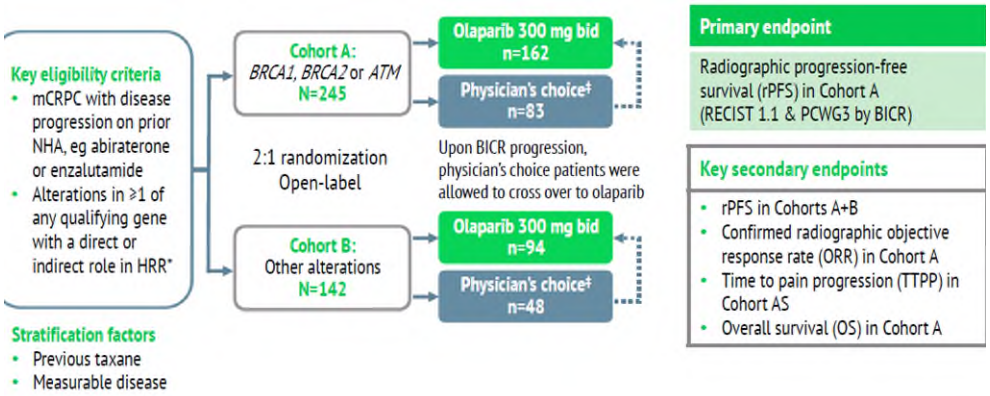
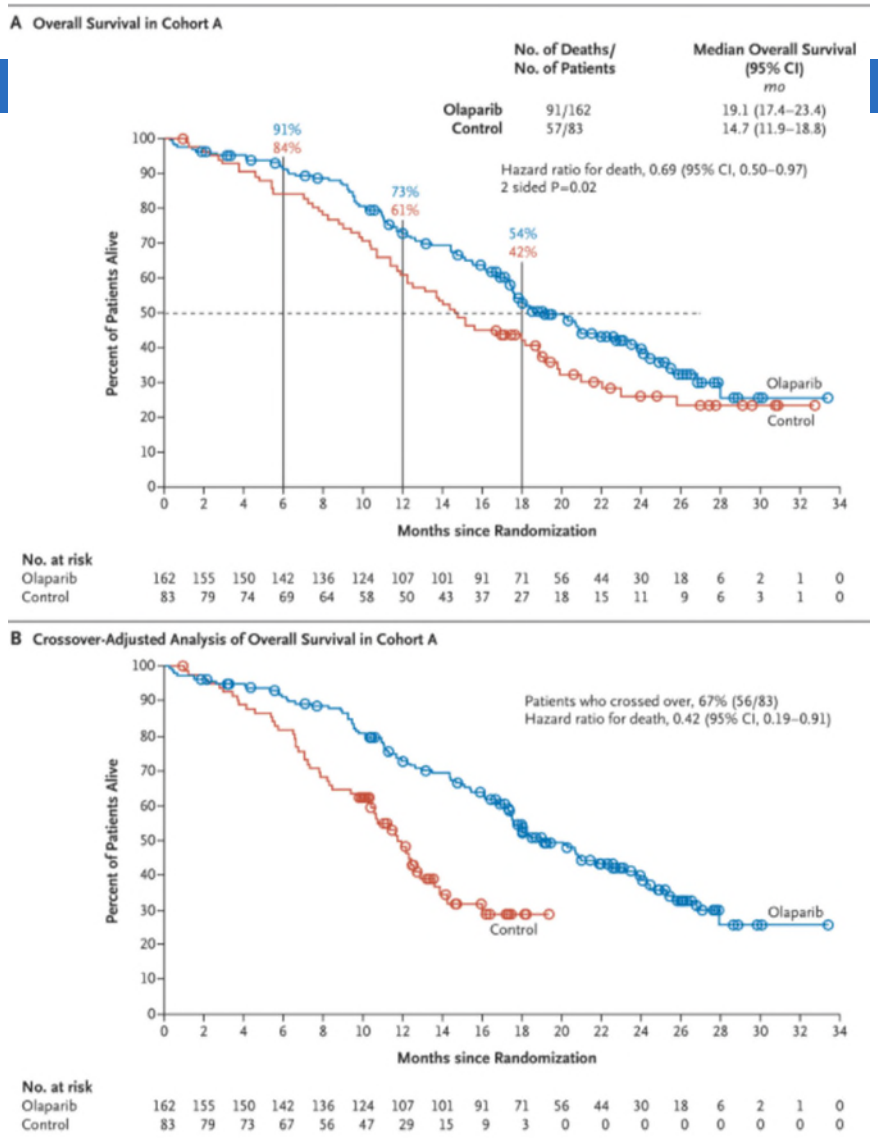
PARP inhibitor prolongs OS in mCRPC with HRR alteration

(PROFOUND: Olaparib vs ARPi post ARPi)

Weak control



>80% crossover!



deBono J et al. New Engl J Med 2020; 382:2091-102

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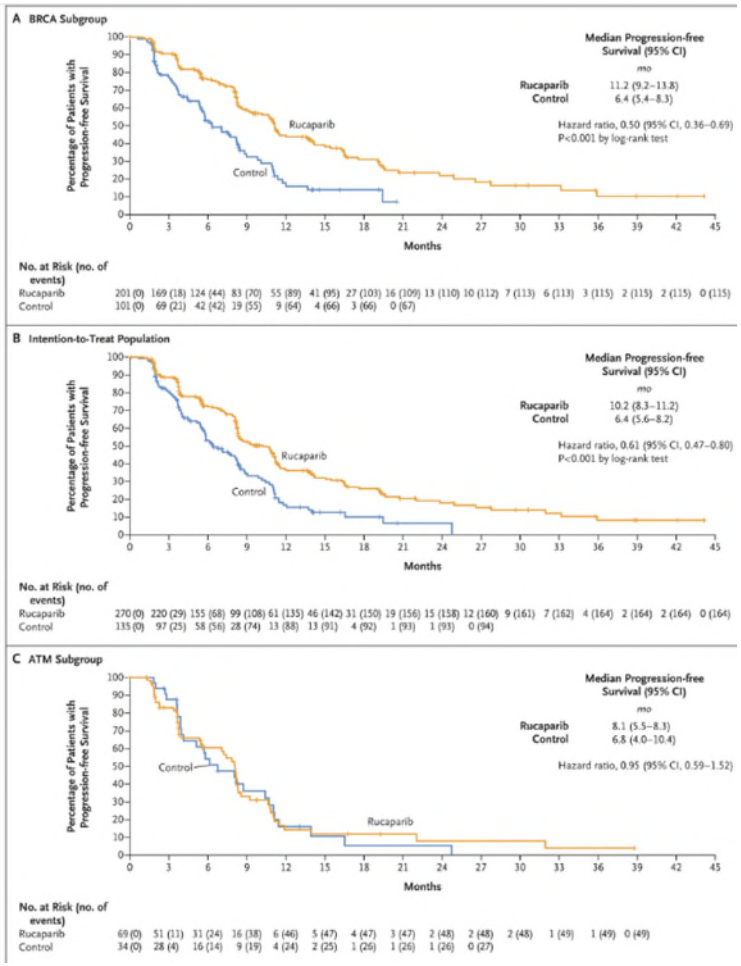
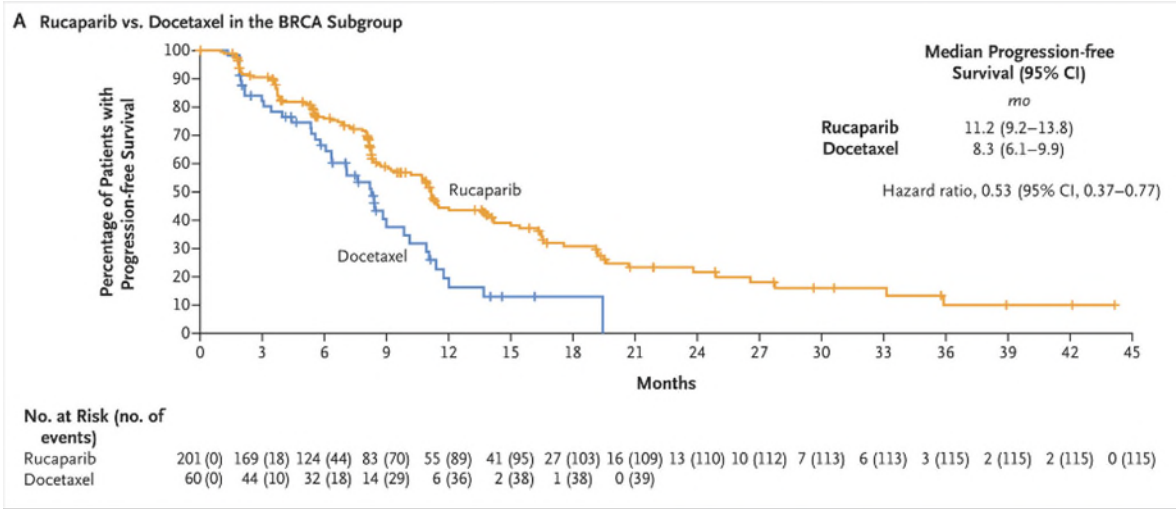
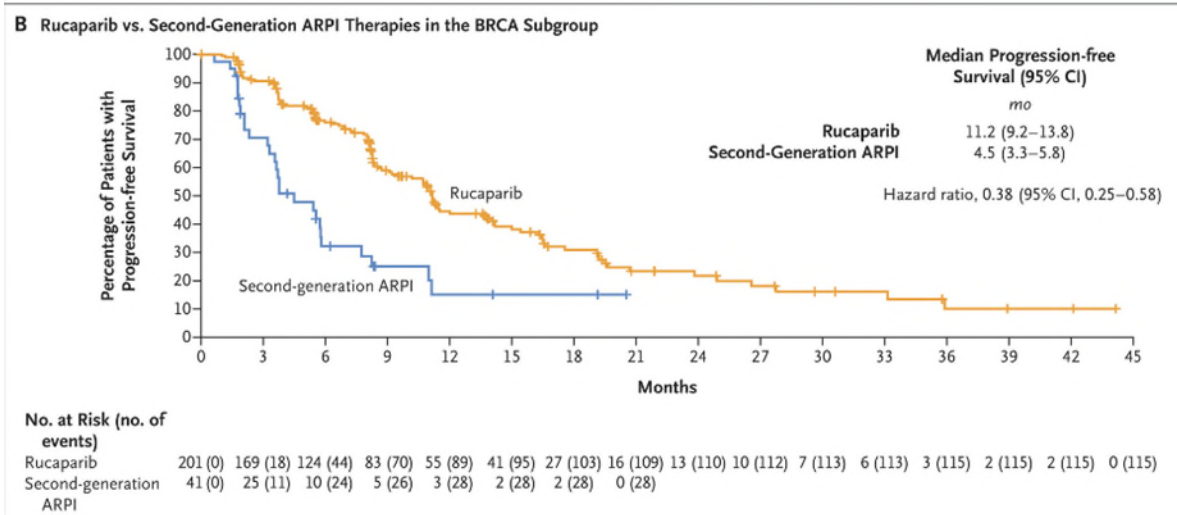
Hussain M, et al. N Engl J Med. 2020;383(24):2345-2357

Rucaparib monotherapy: more effective than docetaxel for BRCA altered mCRPC (TRITON-3)







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Fizazi K et al. NEJM 2023; 388:719-32

Notable toxicities of PARP inhibitors

Bone marrow toxicities are #1 cause of discontinuation

- Anemia
  - TALAPRO-1: 35% received ≥1 blood transfusion
  - PROfound: 21% grade 3+ anemia
  - TRITON2: 25.2% grade 3+ anemia, 28% ≥1 transfusion
- Leukopenia/infection
  - 8% grade 3 ANC talazoparib, 4% grade 3+ olaparib
- Pulmonary emboli
  - PROfound: 4% with olaparib vs 1% with abi/enza control; 6% in TALAPRO-1
- Very few MDS seen

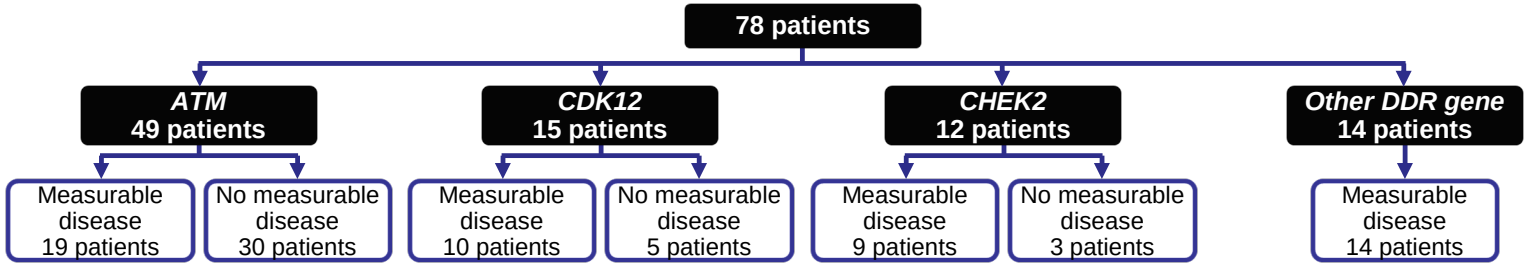
DeBono J, et al. N Engl J Med. 2020;382(22):2091-2102;
Abida W, et al. J Clin Oncol. 2020;38:3763-3772;
DeBono J, et al. Lancet Oncol. 2021;22:1250-1264

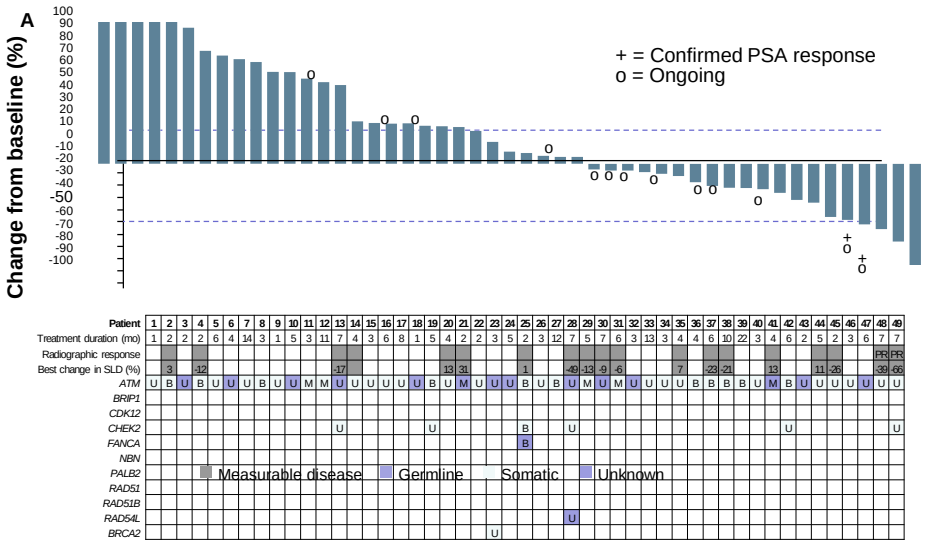
PARP: unanswered questions and what's next

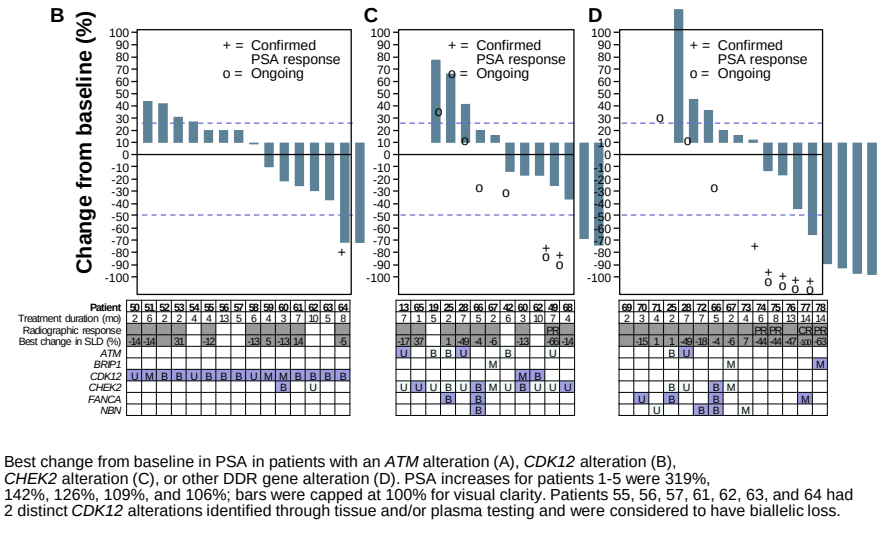
- How well does PARPi work in HRR+ aside from BRCA?
- Does it work in molecularly unselected patients with prostate cancer, when combined with ARPi?
- Financial implications and barriers

- Moving to mHSPC (for BRCA+ and ?others)
- Combining with radioligand therapy

TRITON2: Rucaparib in mCRPC non-BRCA DDR gene alterations







Best change from baseline in PSA in patients with an *ATM* alteration (A), *CDK12* alteration (B), *CHEK2* alteration (C), or other DDR gene alteration (D). PSA increases for patients 1-5 were 319%, 142%, 126%, 109%, and 106%; bars were capped at 100% for visual clarity. Patients 55, 56, 57, 61, 62, 63, and 64 had 2 distinct *CDK12* alterations identified through tissue and/or plasma testing and were considered to have biallelic loss.

ATM, ataxia telangiectasia mutated; BRCA (2), breast cancer type (2) susceptibility protein CR, complete response; DDR, DNA damage repair; mCRPC, metastatic castration resistant prostate cancer; mo, month; PR, partial response; PSA, prostate specific antigen; SLD, sum of the longest diameter

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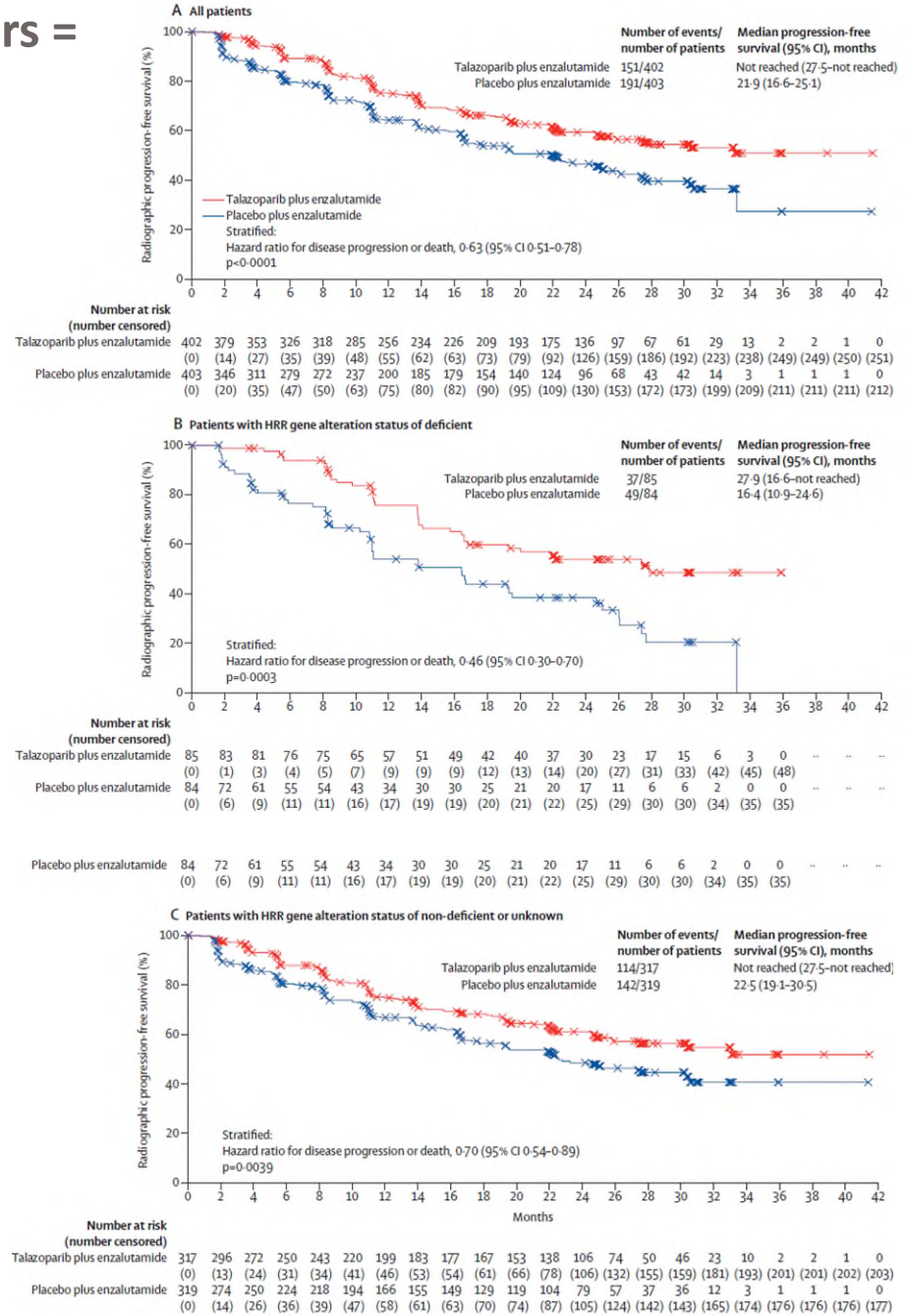
Abida W, et al. Clin Cancer Res. 2020;26:2487-2496

TALAPRO-2: Talazoparib + enzalutamide 1st line mCRPC vs placebo + enzalutamide (all comers = unselected for HRR alteration)

Agarwal N et al. Lancet 2023; 402:22-28

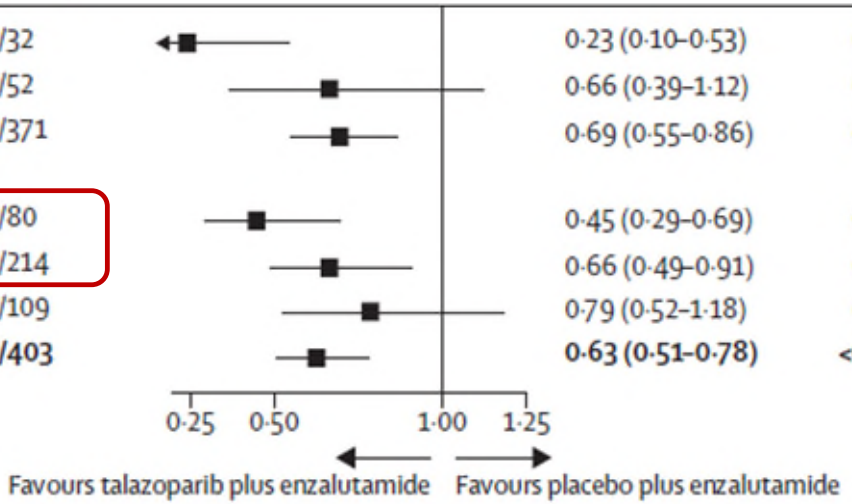
Baseline serum PSA, µg/L	18·2 (6·9–59·4)	16·2 (6·4–53·4)
Baseline circulating tumour cell count, cells per 7·5 mL of blood	1 (0–7)	1 (0–6)
Gleason score†		
<8	117 (29%)	113 (28%)
≥8	281 (70%)	283 (70%)
Disease site		
Bone (including with soft tissue component)	349 (87%)	342 (85%)
Lymph node	147 (37%)	167 (41%)
Visceral (lung)	45 (11%)	61 (15%)
Visceral (liver)	12 (3%)	16 (4%)
Other soft tissue	37 (9%)	33 (8%)
ECOG performance status		
0	259 (64%)	271 (67%)
1	143 (36%)	132 (33%)
Previous taxane-based chemotherapy§	86 (21%)	93 (23%)
Previous treatment with novel hormonal therapy	23 (6%)	27 (7%)
Abiraterone	21 (5%)	25 (6%)
Orteronel	2 (<1%)	2 (<1%)
HRR gene alteration status by randomisation stratification		
Deficient	85 (21%)	84 (21%)
Non-deficient or unknown	317 (79%)	319 (79%)
HRR gene alteration status by prospective tumour tissue testing¶		
Deficient	85 (21%)	82 (20%)
Non-deficient	207 (51%)	219 (54%)
Unknown	110 (27%)	102 (25%)
BRCA1/2 alteration	27 (7%)	32 (8%)



TALAPRO-2: primary endpoint by BRCA/HRR status

B By *BRCA*1/2 status, HRR gene alteration status, and prospective tumour tissue testing

*BRCA*1/2-altered, HRR-deficient	8/27	22/32	0·23 (0·10–0·53)	0·0002
Non-*BRCA*1/2-altered, HRR-deficient	29/58	27/52	0·66 (0·39–1·12)	0·12
Non-*BRCA*1/2-altered or unknown, intention-to-treat	143/375	169/371	0·69 (0·55–0·86)	0·0011
By prospective tumour tissue testing				
HRR-deficient	36/83	47/80	0·45 (0·29–0·69)	0·0002
HRR-non-deficient	70/198	96/214	0·66 (0·49–0·91)	0·0092
HRR-unknown	45/121	48/109	0·79 (0·52–1·18)	0·25
Overall	**151/402**	**191/403**	**0·63 (0·51–0·78)**	**<0·0001**



- BRCA alteration is still important biomarker to select those who benefit MOST

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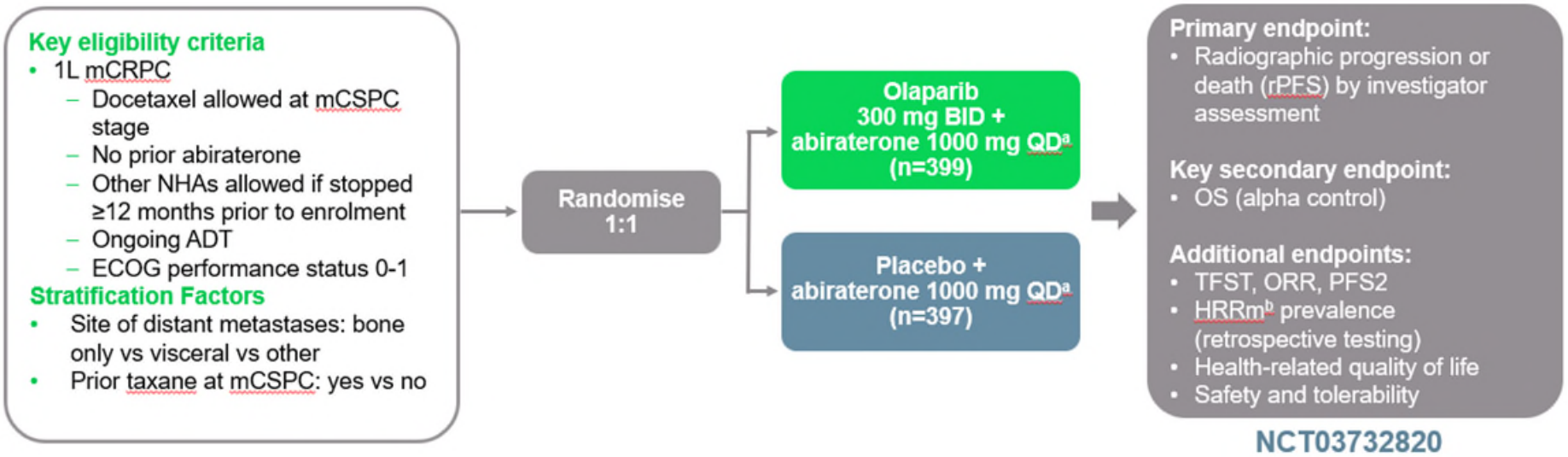
PROPEL trial: abiraterone +/- Olaparib in UNSELECTED mCRPC



	abi + olap n= 399	abi + placebo n = 397
HRRm	111 (27.8%)	115 (29%)
HRR non-mut	279 (69.9%)	273 (68.8%)

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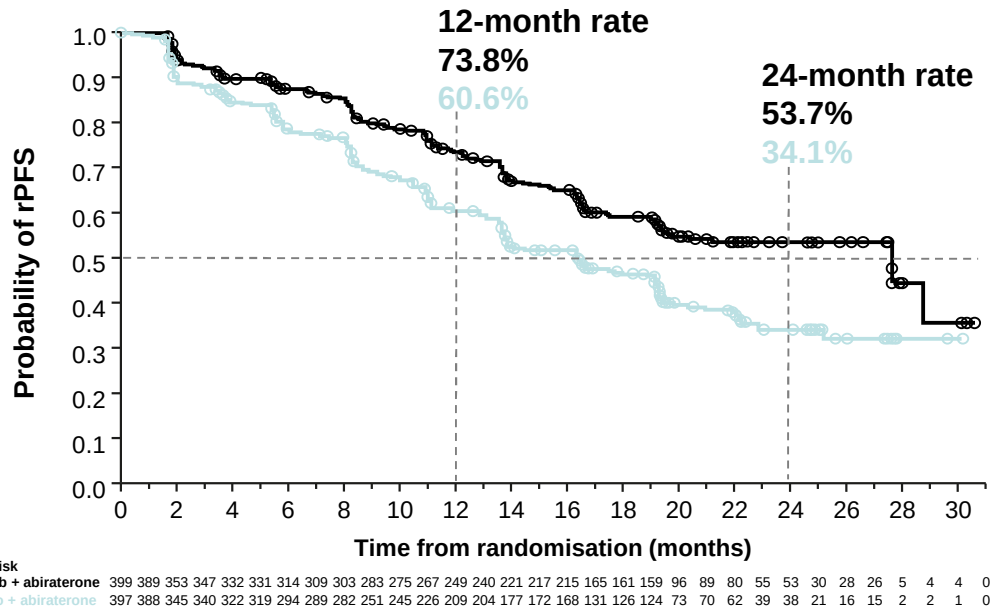
PROpel: rPFS by blinded independent central review[a]

39% RISK REDUCTION OF PROGRESSION OR DEATH WITH OLAPARIB + ABIRATERONE. HIGHLY CONSISTENT WITH THE PRIMARY ANALYSIS



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4

[a]Predefined sensitivity analysis. [b]Nominal. [c]In combination with prednisone or prednisolone

CI, confidence interval; HR, hazard ratio; rPFS, radiographic progression-free survival

Saad F, et al. J Clin Oncol. 2022; 40 (suppl 6; abstr 11)

OS trending in favor of combination, not yet statistically significant

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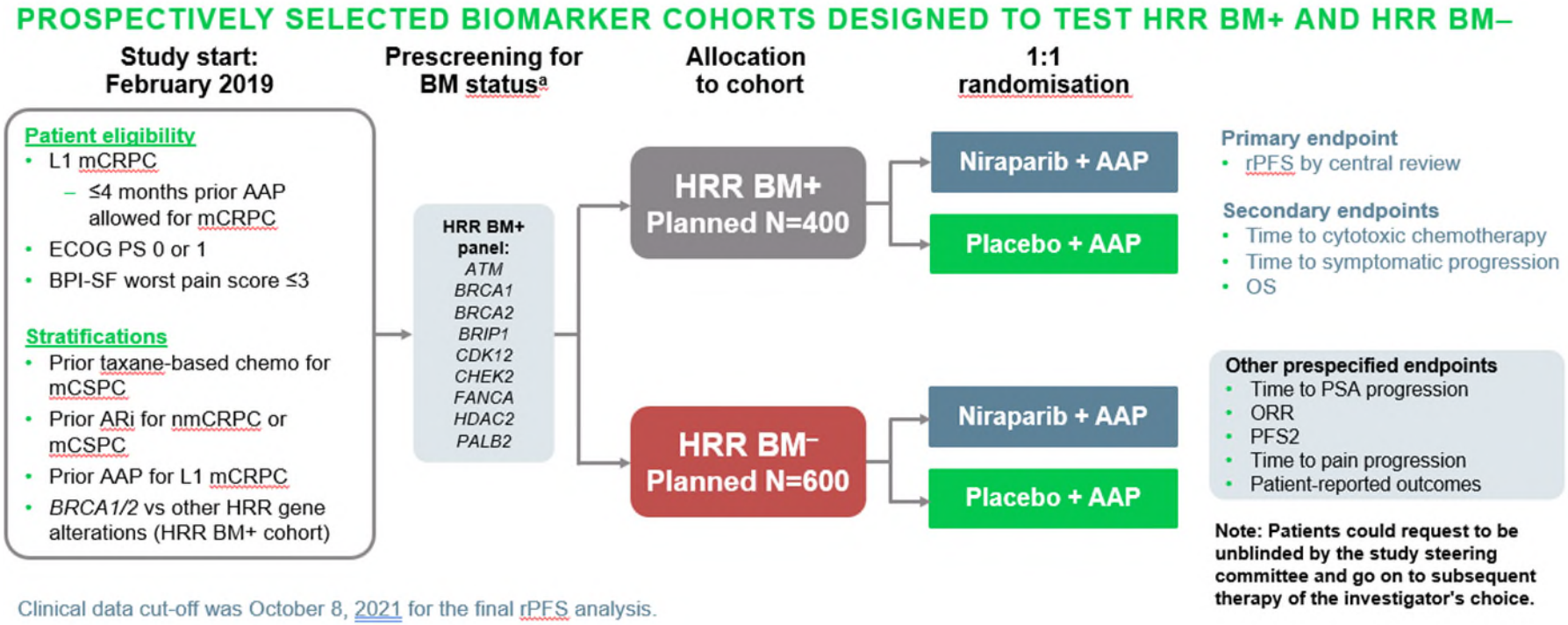
MAGNITUDE trial



Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

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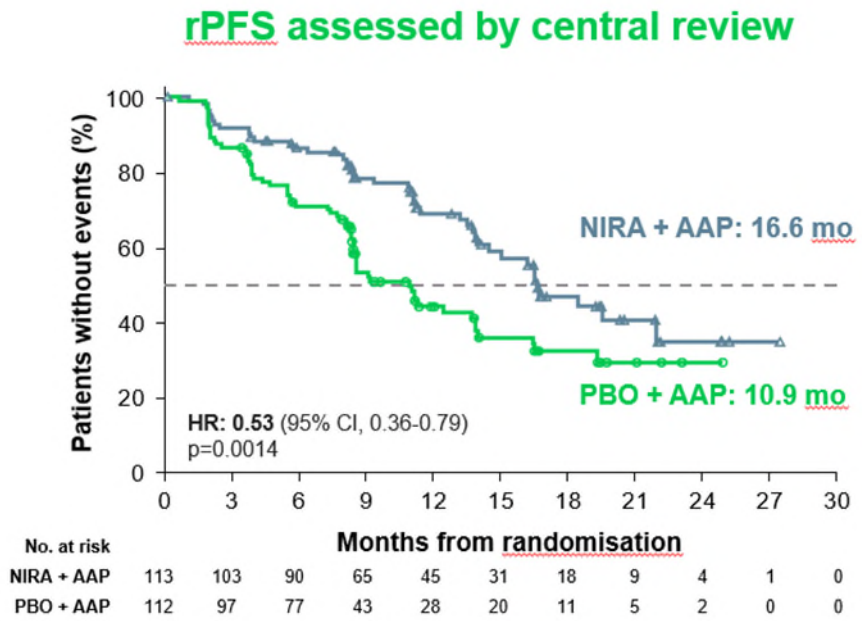
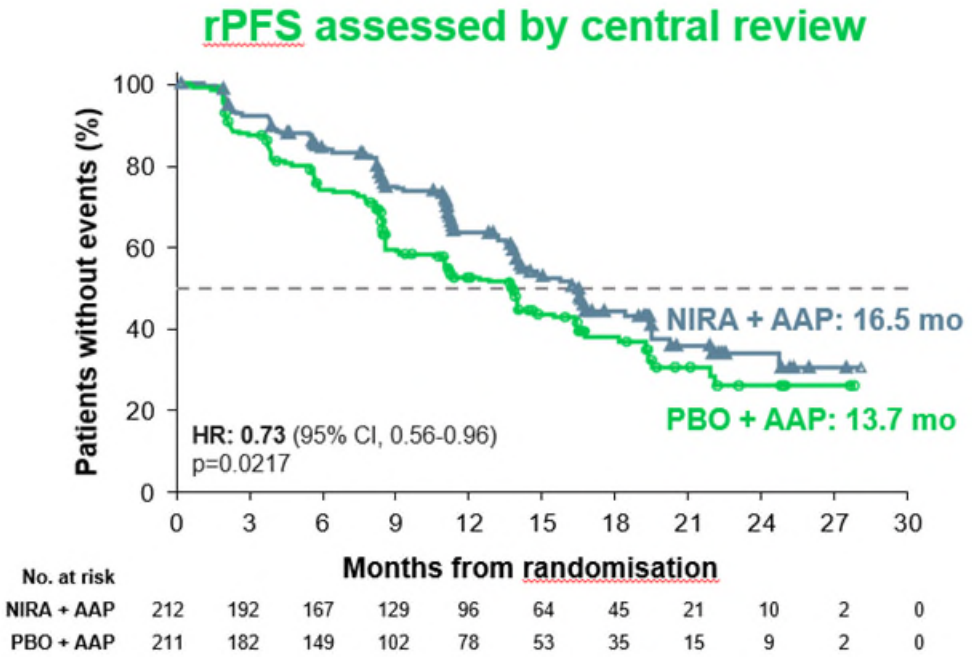
MAGNITUDE primary endpoint results





BRCA mutated

all HRR+

Prespecified futility analysis in **biomarker HRR- group** after ~200 enrolled (125 progression events) showed NO BENEFIT therefore this group stopped enrolling.

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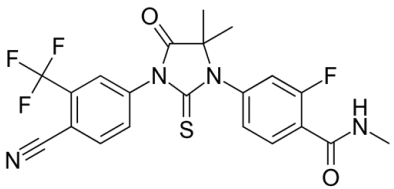
What's next for PARP: mHSPC and novel combinations

Name/Sponsor	PARPi	Combination	Design (n)
AMPLITUDE	Niraparib	Abiraterone	Randomized mHSPC, HRR+ (788)
TALAPRO-3	Talazoparib	Enzalutamide	Randomized mHSPC, HRR+ (550)
City of Hope PCF	Talazoparib	Abiraterone	Single arm mHSPC, Unselected (70)
NCT03076203	Niraparib	Radium-223	mCRPC prior abi/enza (chemo OK)
NCT03874884	Olaparib	177-Lu-PSMA-617	PSMA PET + mCRPC
NCT04253262	Rucaparib	Copanalisib	mCRPC, prior abi/enza. NEPC allowed
NCT04592237	Niraparib	Cabazi, Carbo, Cetrelimab	AVPC
NCT04846478	Talazoparib	Tazemetostat	Post ab/enza, post doce
NCT04336943	Olaparib	Durvalumab	BCR w/ high neoantigen load

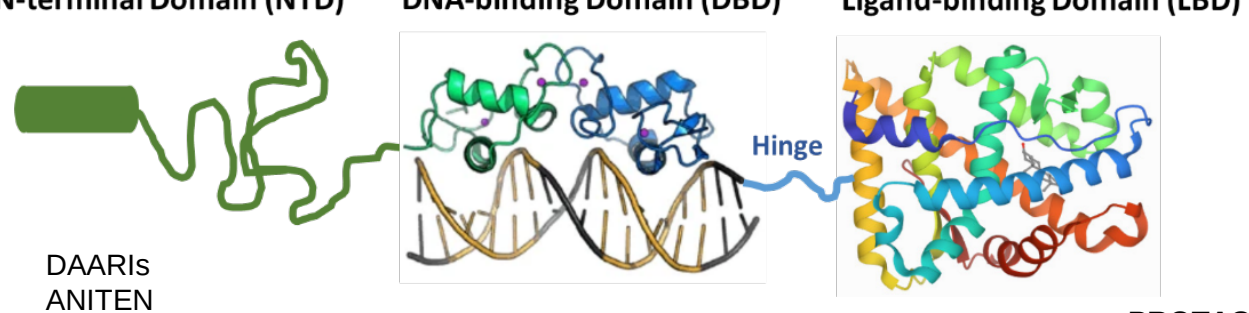
Overview of AR Targeting Modalities

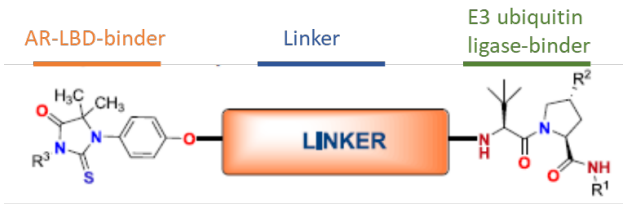
Decrease production of ligand (CYP17 inhibitors)
- abiraterone
- TAK700

Inhibit AR LBD
- Apalutamide
- Bicalutamide
- Darolutamide
- Enzalutamide

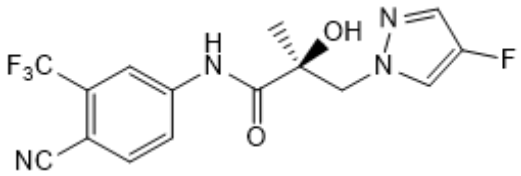


Commercial AR LBD Antagonists
Example: Enzalutamide





Generic AR-Targeting PROTAC Structure
Example: ARVINAS US 2020/005 5825 A1



ONCT-534

Slide courtesy of Evan Yu (UW/ Fred Hutch)

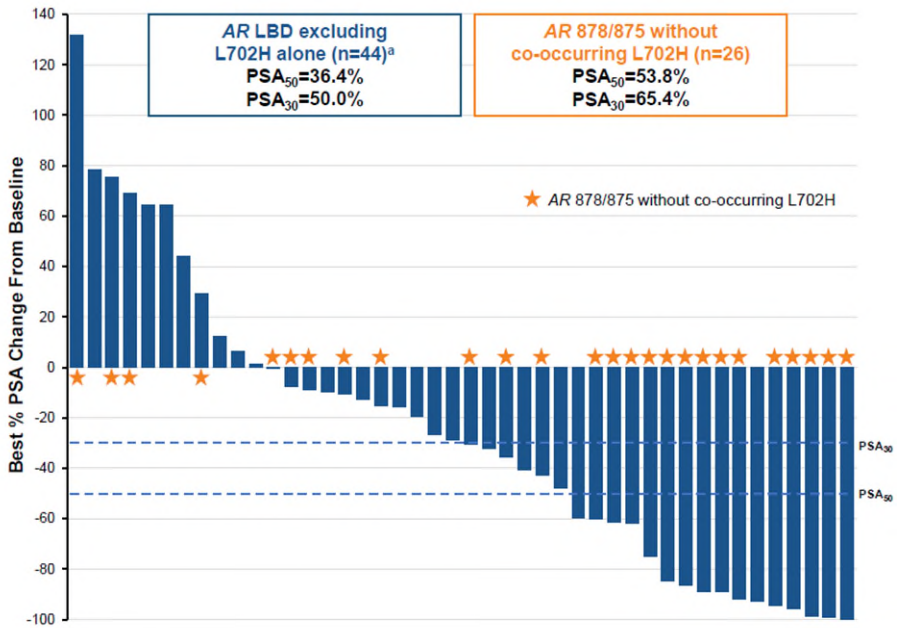
ARV-110

aka bavdegalutamide

- In phase 1, patients with mCRPC received bavdegalutamide 35–700 mg QD or 210–420 mg twice daily
- In phase 2 (ARDENT), patients with mCRPC were assigned to subgroups based on *AR* mutation status or a clinically defined subgroup (patients who had 1 prior NHA and no prior chemotherapy) and received bavdegalutamide 420 mg QD

Key eligibility criteria

- Confirmed mCRPC and disease progression on last line of treatment
  - Phase 1 dose escalation: Disease progression on ≥2 prior lines of systemic therapy, including abiraterone or enzalutamide
  - Phase 2 cohort expansion (ARDENT): 1–2 prior NHAs with ≤1 prior chemotherapy regimen each for castration-sensitive PC and CRPC



ESMO 2023 (Petrylak DP)

Phase 1/2 subset study results (AR LBD mutation excluding L702H alone)

ARV-110

Adverse Events

ESMO 2023 (Petrylak DP)

Phase 1/2 subset study results (AR LBD mutation + excluding L702H alone)

Table 2: TRAEs reported in ≥10% of patients treated with bavdegalutamide 420 mg QD in the phase 1/2 study (N=153)

n (%)	Total	Grade 1	Grade 2	Grade 3
Any TRAE	135 (88)	45 (29)	66 (43)	24 (16)
Nausea	85 (56)	59 (39)	24 (16)	2 (1)
Fatigue	53 (35)	36 (24)	16 (10)	1 (1)
Vomiting	50 (33)	38 (25)	11 (7)	1 (1)
Decreased appetite	39 (25)	21 (14)	18 (12)	0
Diarrhea	37 (24)	27 (18)	7 (5)	3 (2)
Alopecia	28 (18)	24 (16)	4 (3)	NA
Anemia	23 (15)	10 (7)	6 (4)	7 (5)
Decreased weight	19 (12)	10 (7)	9 (6)	0
Increased AST	18 (12)	13 (8)	4 (3)	1 (1)

Conclusions: updates for advanced prostate cancer

- Radioligand therapy prolongs OS, good toxicity profile
  - New agents may increase benefit (particle, binder, target)
- Other ways to target Prostate antigens are in trials
  - Immunotherapy (bispecific/CAR T), ADC - cytotoxic
- Combination of VEGF TKI + IO may become an option
  - Cabozantinib + atezolizumab (CONTACT-02)
- PARP inhibitors are powerful in some mCRPC
  - Even w/new data: germline+ somatic testing are important!
- AR PROTAC degraders (and other novel AR targeting strategies) may be another advance
  - ARV-766 trial open at COH