Presentaciones más destacadas en cáncer de próstata

Dr. David Lorente

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- Metastatic, castration-resistant prostate cancer
- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

- Metastatic, castration-resistant prostate cancer
  - TALAPRO-2 trial overall survival
  - ENZA-P trial overall survival
  - PSMAfore biomarker analysis
  - Mevrometostat + Enzalutamide
  - Metasases-directed therapy for mCRPC

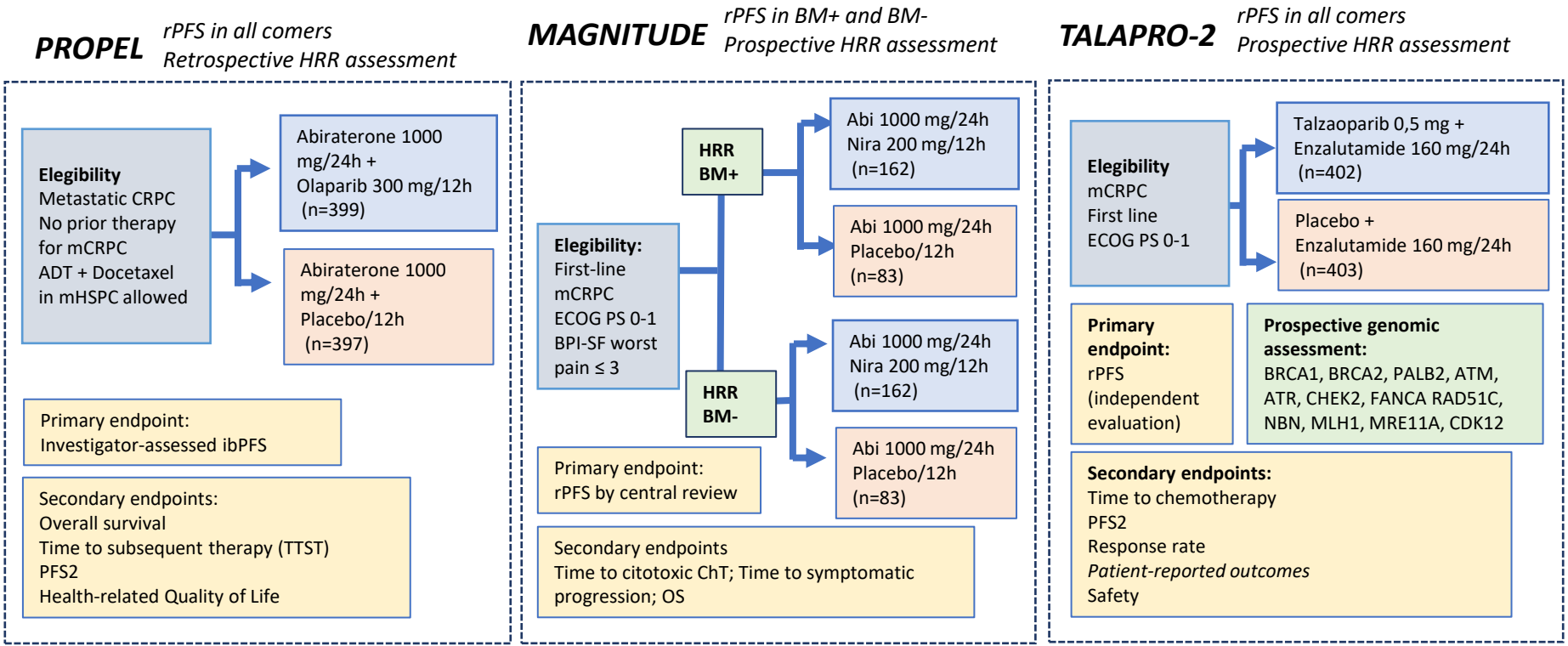
- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

- Metastatic, castration-resistant prostate cancer
  - **TALAPRO-2 trial overall survival**

    - Oral: LBA18. Neeraj Agarwal. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as firstline treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial.
    - Poster: LBA141. Karim Fizazi Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line (1L) treatment in patients (pts) with homologous recombination repair (HRR)-deficient metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial.
  - ENZA-P trial overall survival
  - PSMAfore biomarker analysis
  - Mevrometostat + Enzalutamide
  - Metasases-directed therapy for mCRPC

- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

PARP inhibitor + hormone therapy combinations

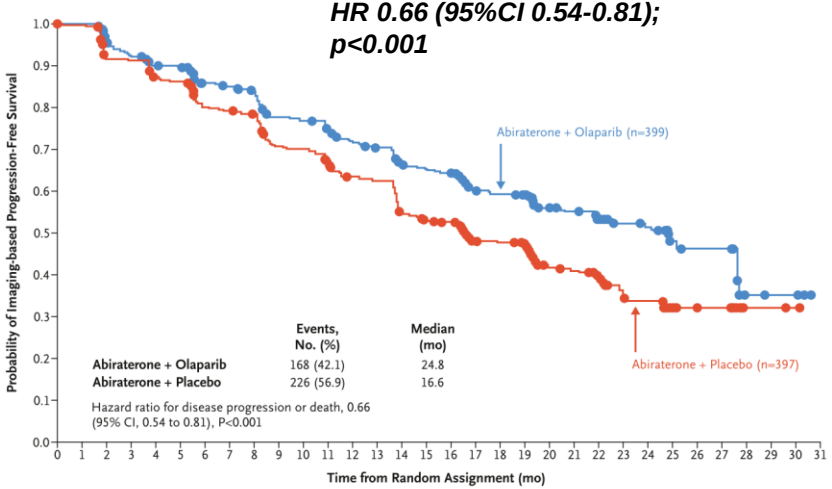


Clarke et al. N Eng J Med Evid 2022; Chi et al. J Clin Oncol 2023; Agarwal Lancet Oncol 2023

Significant rPFS benefit in all comers

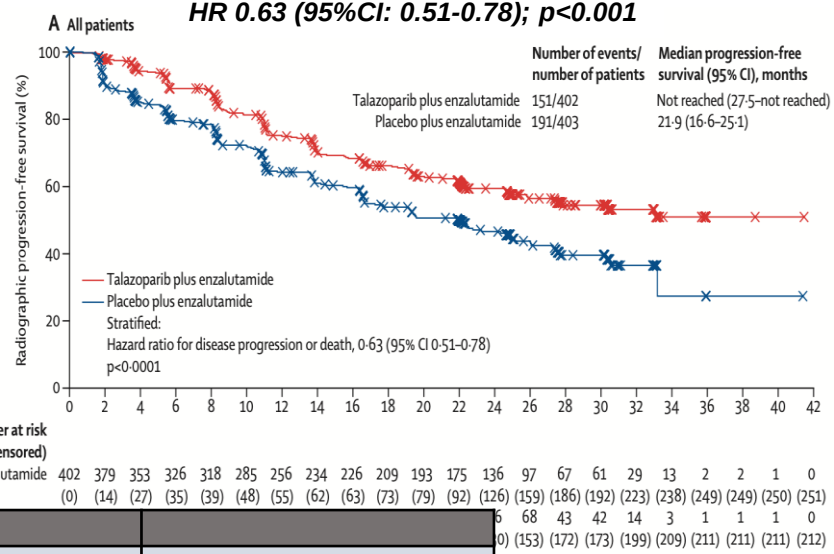
PROPEL

ibPFS in all patients
24.8 vs 16.6 months;
HR 0.66 (95%CI 0.54-0.81);
p<0.001



TALAPRO-2

All comers
NR vs 21.9 months
HR 0.63 (95%CI: 0.51-0.78); p<0.001



All comers	PROPEL	MAGNITUDE	TALAPRO-2
rPFS	HR 0.66 (95%CI 0.54-0.81)	Not assessed	HR 0.63 (95%CI: 0.51-0.78)
OS	HR 0.86 (95%CI: 0.66-1.12)	Not assessed	HR 0.89 (95%CI: 0.69-1.14)

Clarke et al. N Eng J Med Evid 2022; Chi et al. J Clin Oncol 2023; Agarwal Lancet Oncol 2023

Benefit is **greatest** with **BRCA mutations**

PROPEL	HR 0.23 (95%CI 0.12-0.43)
MAGNITUDE	HR 0.53 (95%CI 0.36-0.79)
TALAPRO-2	HR 0.20 (95%CI0.11-0.36)

Intermediate with **HRR mutations**

PROPEL	HR 0.50 (95%CI 0.34-0.73)
MAGNITUDE	HR 0.64 (95%CI 0.49-0.86)
TALAPRO-2	HR 0.45 (0.33-0.61)

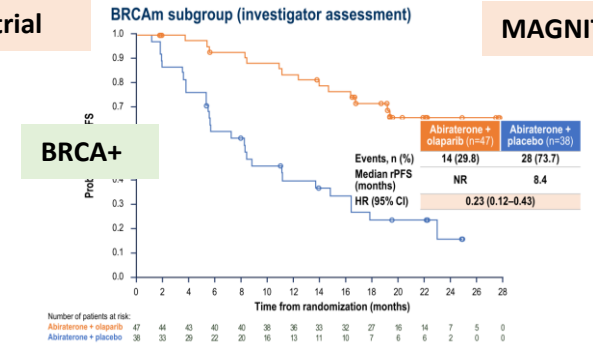
Lowest in patients **without HRR alterations**

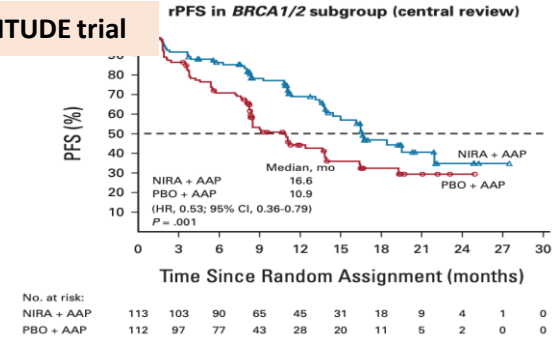
PROPEL	HR 0.76 (95%CI: 0.60-0.97)
MAGNITUDE	HR 1.03 (95%CI 0.63-1.67)
TALAPRO-2	HR 0.66 (95%CI: 0.49-0.91)

PROPEL trial

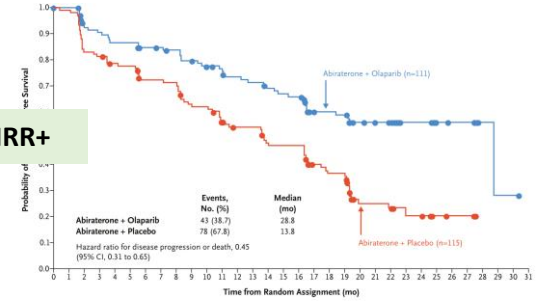
MAGNITUDE trial

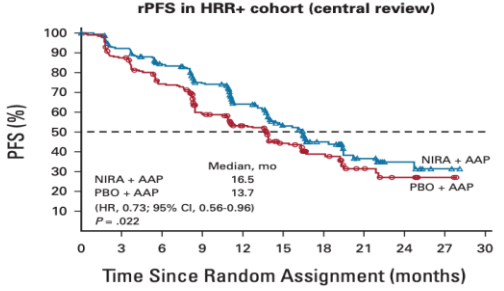
BRCA+



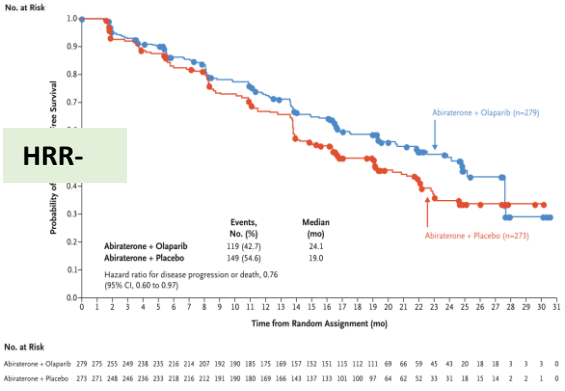


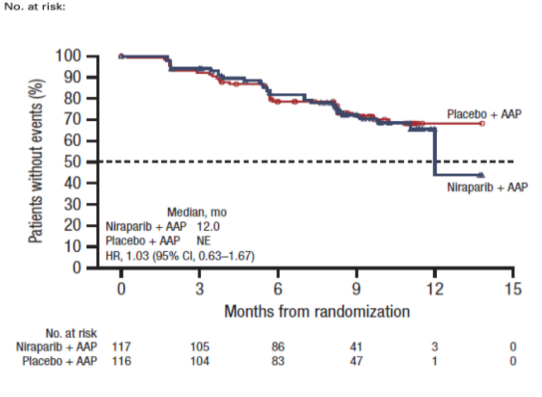
HRR+





HRR-

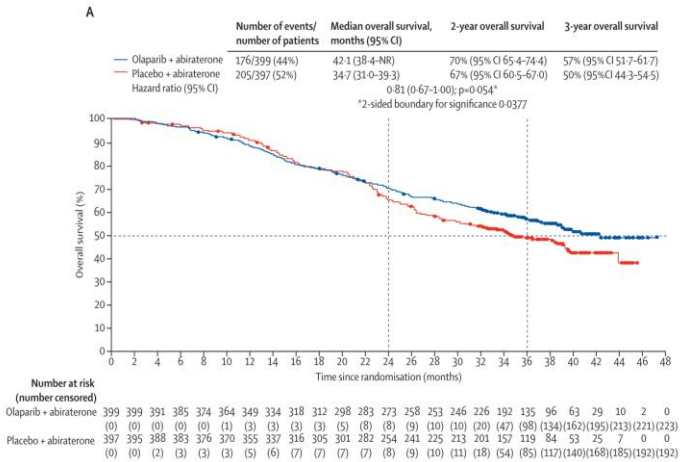




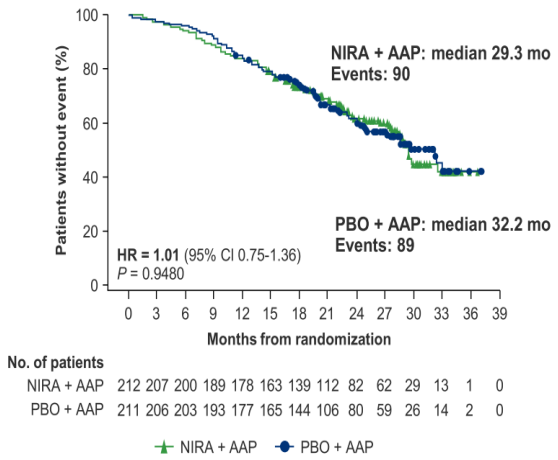
Clarke et al. NEJM Evidence 2023. Saad et al. Lancet Oncol 2023.
Chi et al. J Clin Oncol 2023. Chi et al. Ann Oncol 2023.
Agarwal et al. Lancet Oncol 2023. Fizazi et al. Nature Med 2024.

Overall survival

PROPEL (all comers)

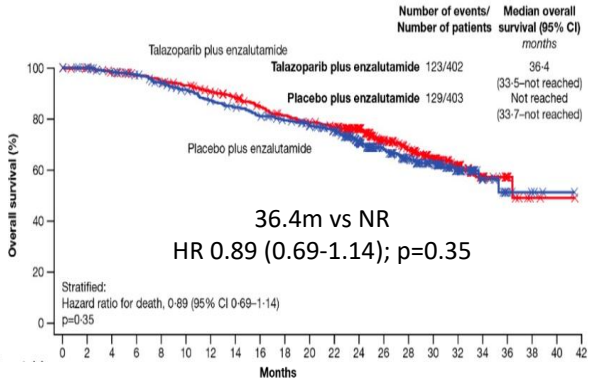


MAGNITUDE (HRR+)

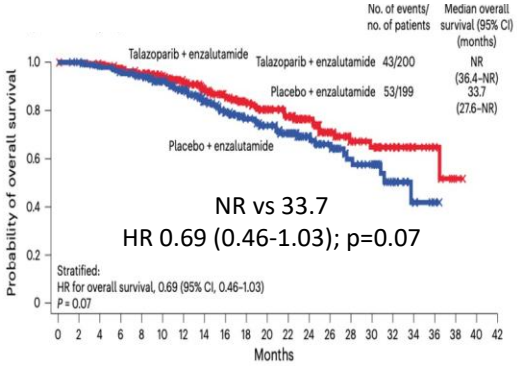


TALAPRO-2

All comers (cohort 1)



HRR mutant (cohort 2)



Saad et al. Lancet Oncol 2023. Chi et al. Ann Oncol 2023. Agarwal et al. Lancet Oncol 2023. Fizazi et al. Nature Med 2023

Presentation number LBA18

ASCO Genitourinary Cancers Symposium

Overall survival with talazoparib plus enzalutamide in unselected patients with metastatic castration-resistant prostate cancer in the Phase 3 TALAPRO-2 trial

Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Cezary Szczylik,[6,7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. C. Fong,[10,11] Eric Voog,[12] Robert J. Jones,[13] Neal D. Shore,[14] Curtis Dunshee,[15] Stefanie Zschäbitz,[16] Jan Oldenburg,[17] Xun Lin,[18] Cynthia G. Healy,[19] Matko Kalac,[20] Dana Kennedy,[21] Karim Fizazi[22]

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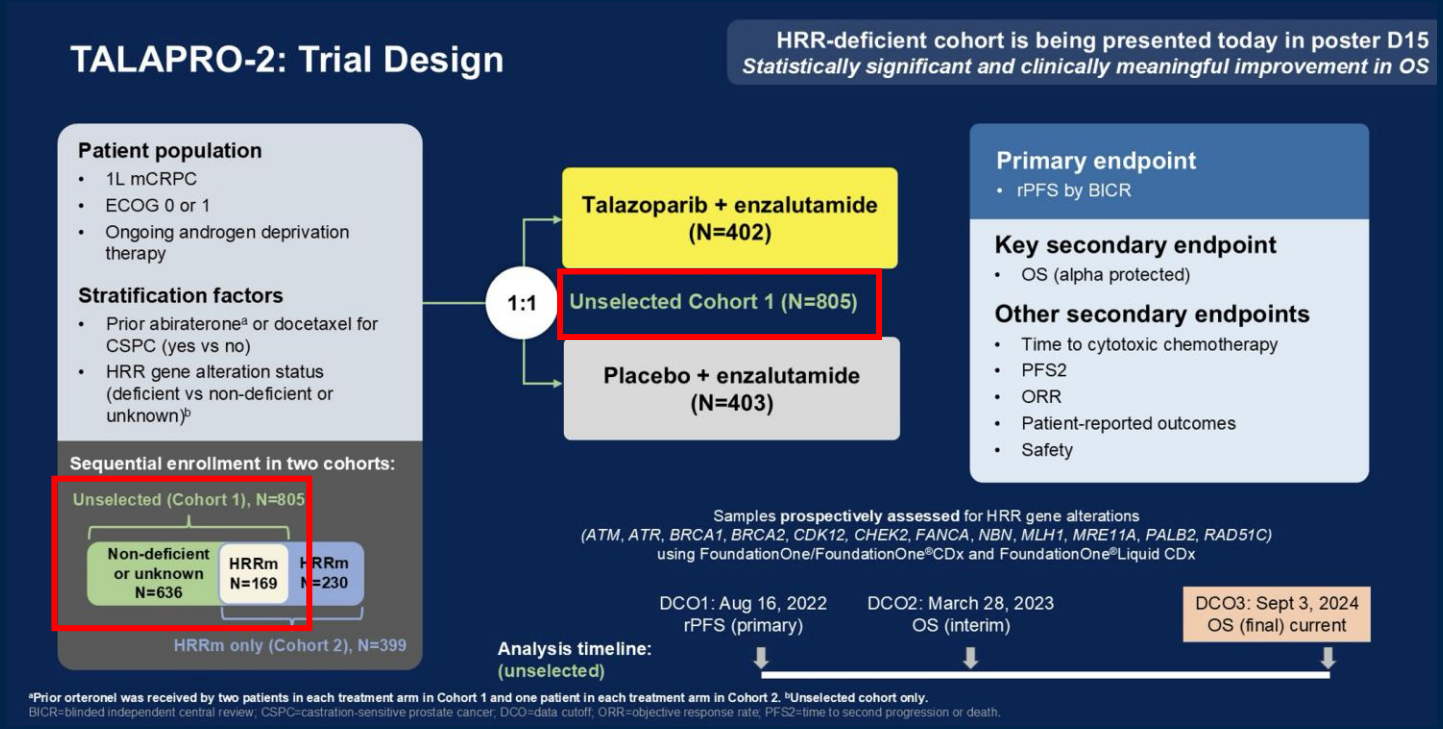
ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.



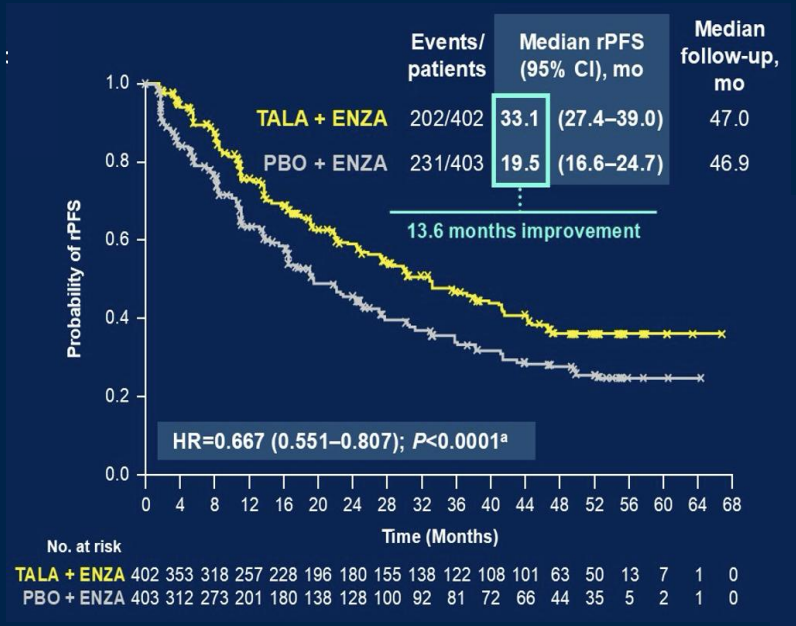
- No differences across treatment groups
- 21% prior Docetaxel
- 5.5% prior Abiraterone
- HRR alterations:
  - HRRd: 21% (N=169)
  - HRRp: 79% (N=636)

	Tala + Enz	Enz
CDK12	5.7%	7.2%
BRCA2	5.7%	6.9%
ATM	5.7%	3.5%
CHEK2	1.5%	1.2%
BRCA1	1.2%	1%

rPFS

Primary analysis (Aug 16 2022)
NR vs 21.9 months; HR: 0.63 (0.51-0.78); p<0.001

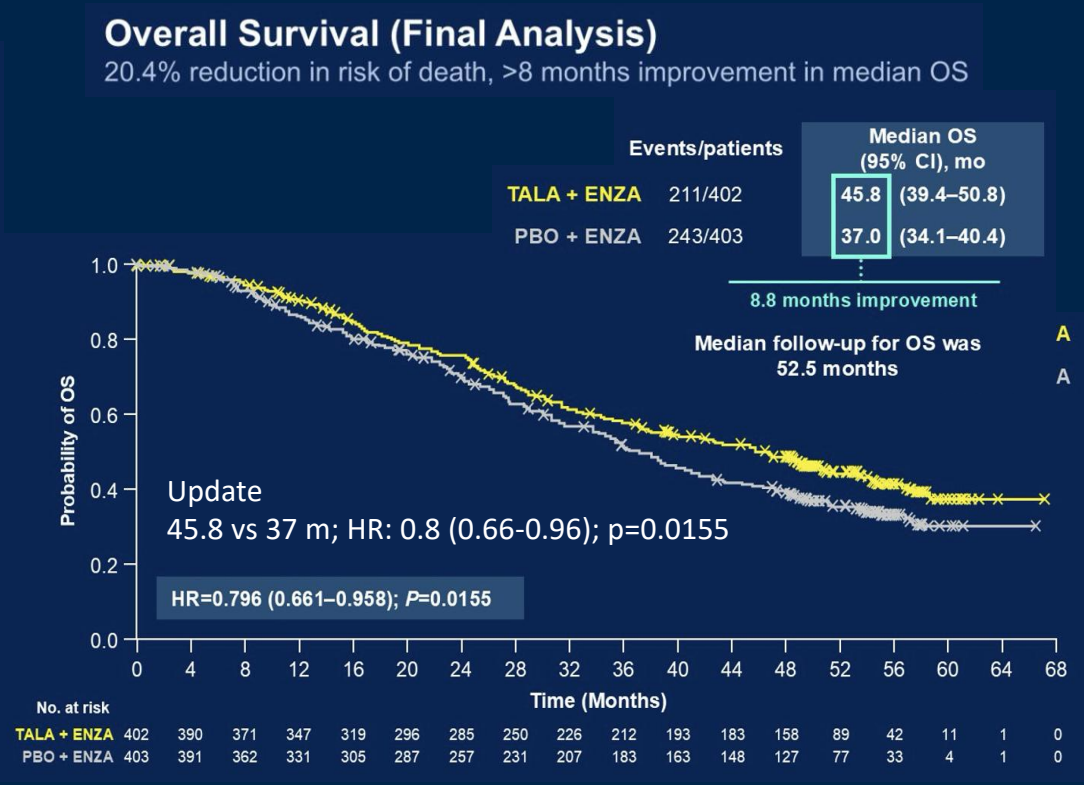
Update (DCO: Sept 3, 2024)



Update:
33.1 vs 19.5 months; HR: 0.67 (0.55-0.81); p<0.001

OS (all comers)

Primary analysis (Aug 16 2022)
NR vs 36.4m; HR: 0.89 (0.69-1.14); p=0.35

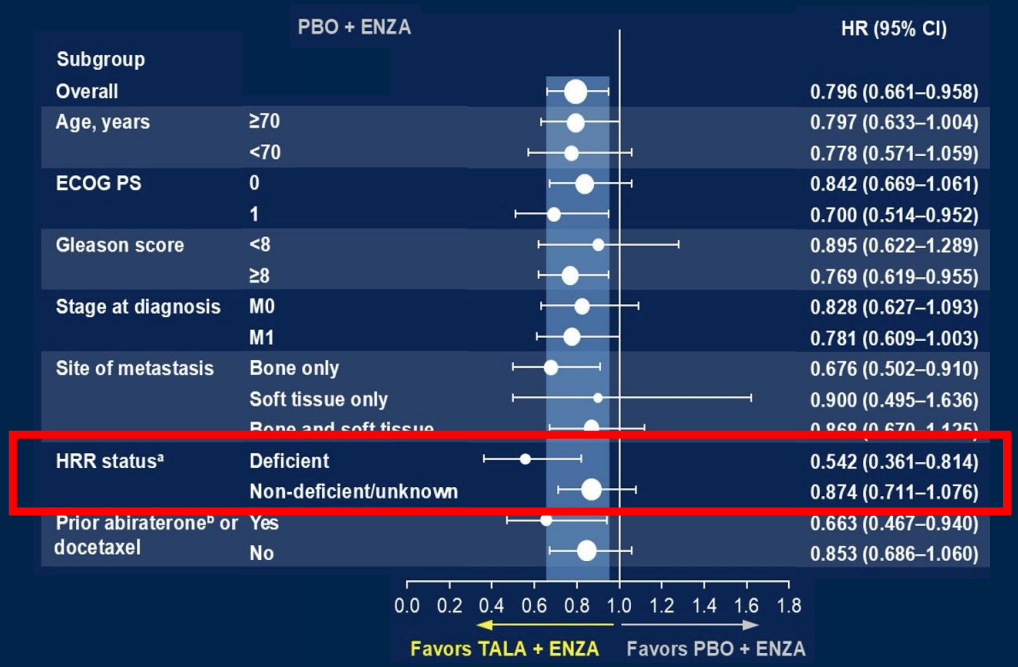


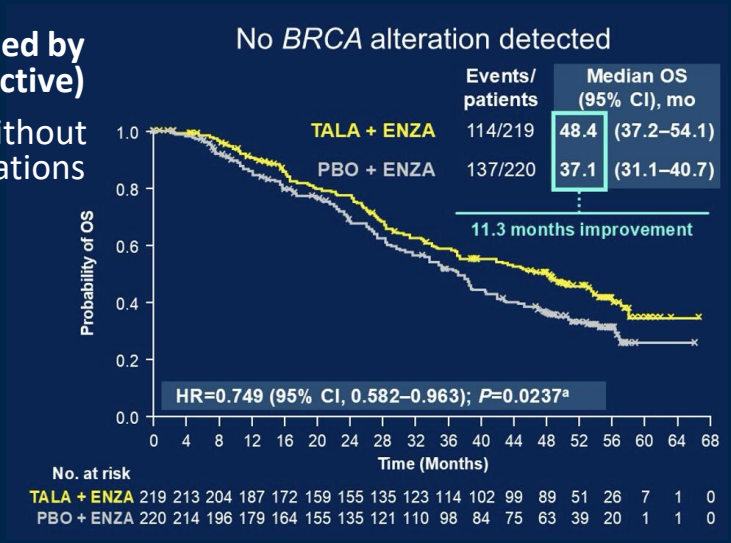
Update
45.8 vs 37 m; HR: 0.8 (0.66-0.96); p=0.0155

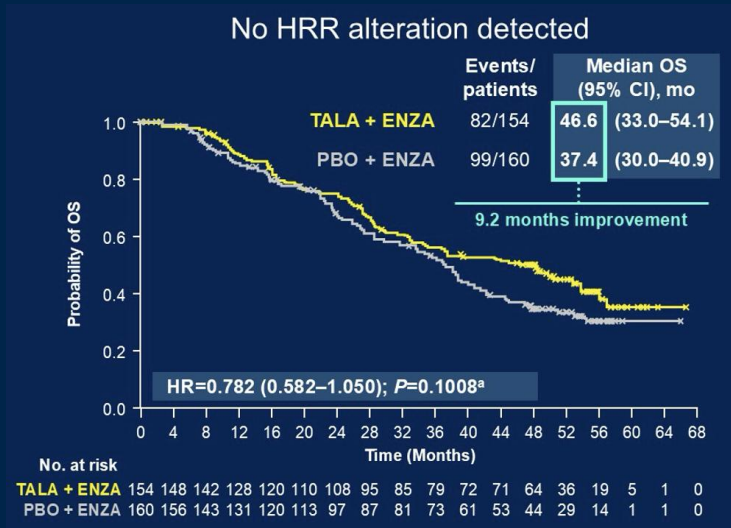
Overall Survival in Subgroups With No Alterations Detected by Both ctDNA and Tumor Tissue (prospective & retrospective)

Clinically meaningful reduction in risk of death in patients without *BRCA* or HRR alterations

Overall Survival: subgroup analysis





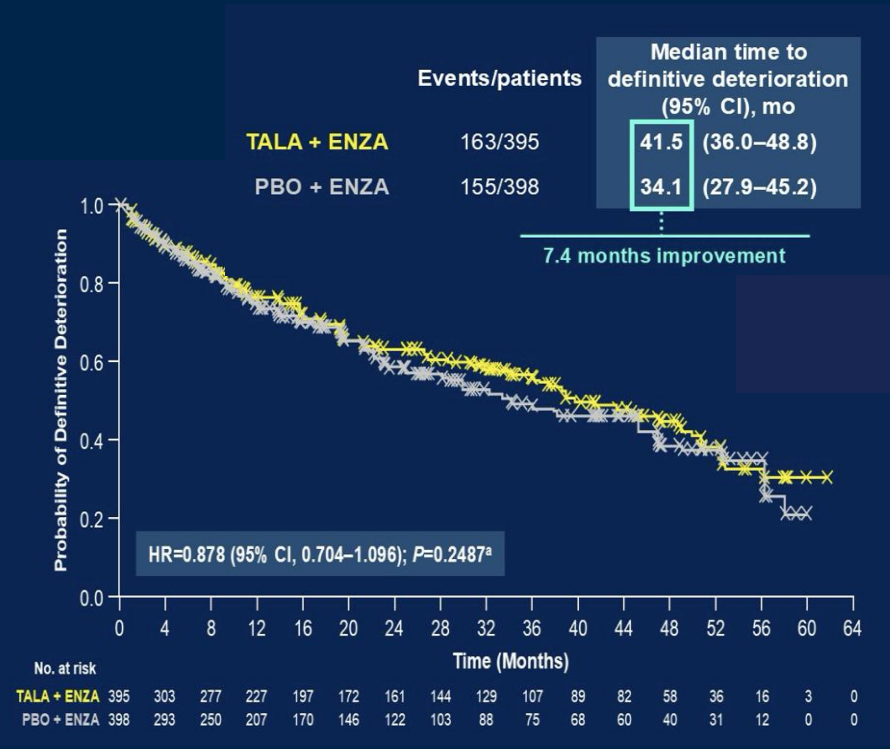


Subsequent therapy

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)
Any subsequent antineoplastic therapy	149 (37.4)	211 (52.6)
Patients taking any of the following post-baseline antineoplastic therapies with demonstrated overall survival benefit		
Docetaxel	90 (22.6)	133 (33.2)
Cabazitaxel	46 (11.6)	66 (16.5)
Carboplatin	4 (1.0)	15 (3.7)
Paclitaxel	1 (0.3)	2 (0.5)
Cisplatin	1 (0.3)	6 (1.5)
Abiraterone	44 (11.1)	68 (17.0)
Radium	20 (5.0)	27 (6.7)
Lutetium-177	15 (3.8)	16 (4.0)
Other[a]	1 (0.3)	3 (0.7)
Enzalutamide	20 (5.0)	22 (5.5)
Apalutamide	1 (0.3)	3 (0.7)
Darolutamide	1 (0.3)	1 (0.2)
Rezvilutamide	1 (0.3)	0
Olaparib	6 (1.5)	15 (3.7)
Sipuleucel-T	1 (0.3)	1 (0.2)

How many are BRCA mutant?

Quality of life is maintained with the combination (EORTC-QLQ-C30)



Final Overall Survival With Talazoparib Plus Enzalutamide as Initial Treatment in Patients With Homologous Recombination Repair-Deficient Metastatic Castration-Resistant Prostate Cancer in the Phase 3 TALAPRO-2 Trial

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,[8,9] Eric Voog,[10] Robert J. Jones,[11] Neal D. Shore,[12] Curtis Dunshee,[13] Stefanie Zschäbitz,[14] Jan Oldenburg,[15] Dingwei Ye,[16] Xun Lin,[17] Matko Kalac,[18] A. Douglas Laird,[19] Dana Kennedy,[20] Neeraj Agarwal[21]

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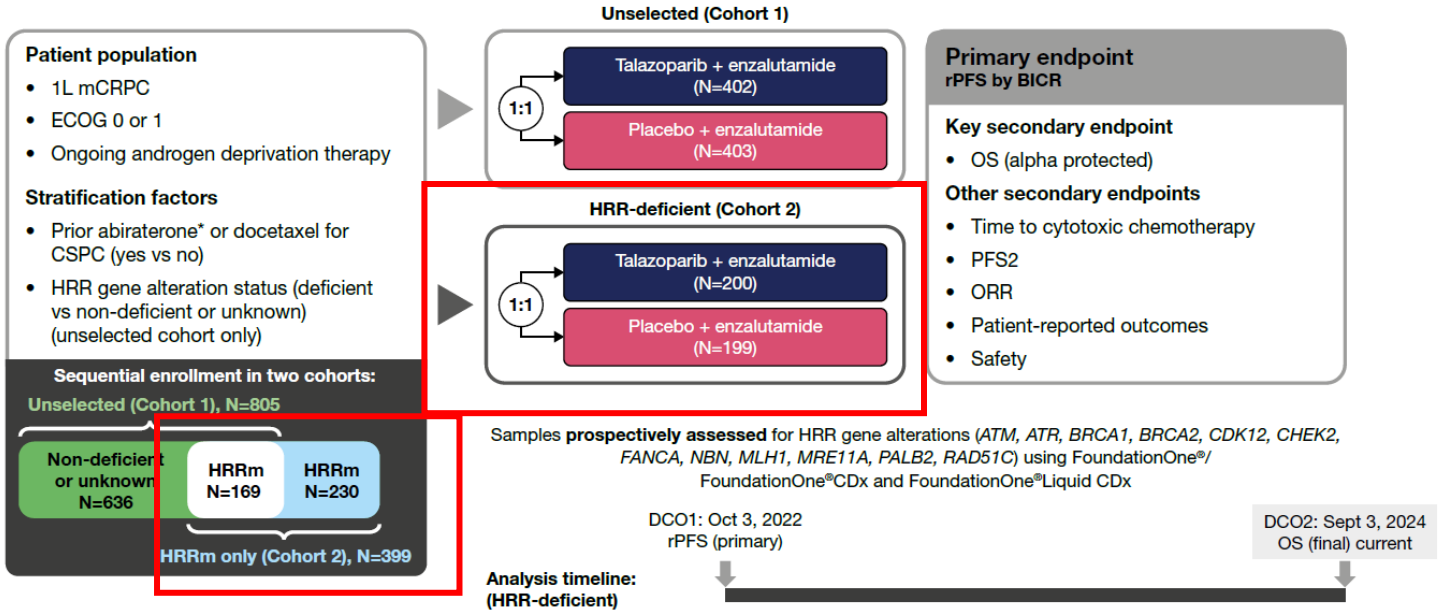
1. Fizazi K, et al. "Final Overall Survival With Talazoparib Plus Enzalutamide as Initial Treatment in Patients With Homologous Recombination Repair-Deficient Metastatic Castration- Resistant Prostate Cancer in the Phase 3 TALAPRO-2 Trial." Poster D15 Supplement. *ASCOGU 2025 Feb 13–15, 2025*

Figure 1. Trial Design

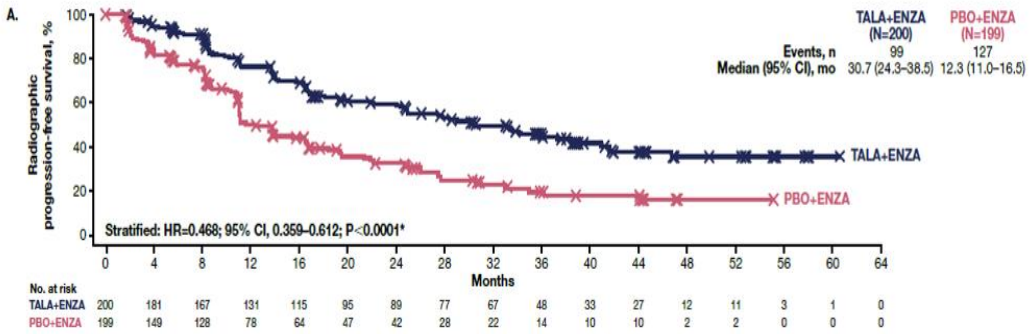


1L=first line; BICR=blinded independent central review; CSPC=castration-sensitive prostate cancer; DCO=data cutoff; HRR=homologous recombination repair; HRRm=HRR gene alterations; mCRPC=metastatic castration-resistant prostate cancer; ORR=objective response rate; OS=overall survival; PFS2=based on investigator assessment (time from randomization to the date of documented progression on the first subsequent antineoplastic therapy for prostate cancer or death from any cause, whichever occurs first); rPFS=radiographic progression-free survival.

*Prior orteronel was received by two patients in each treatment arm in Cohort 1, and by one patient in each treatment arm in Cohort 2.

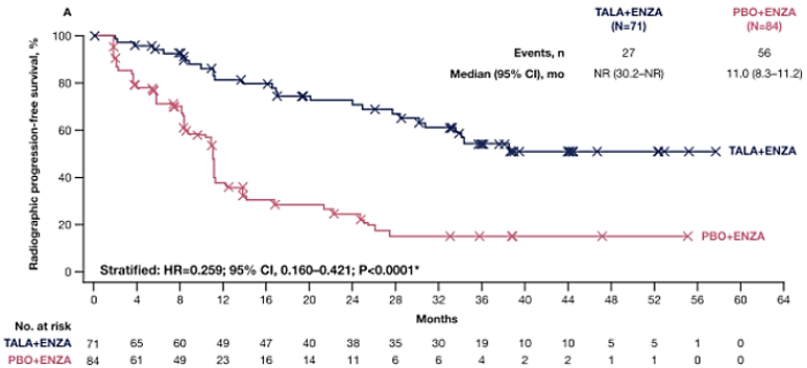
Radiographic progression-free survival

All HRR patients (N=399)

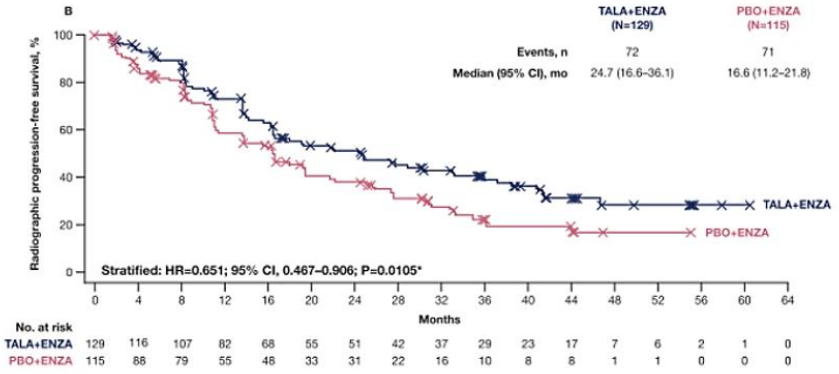


	Talazo-Enza	Enza	HR (95%CI); p-val
All HRR	*N=200* 30.7 m	*N=199* 12.3 m	0.47 (0.36-0.61); p<0.0001
BRCA +	*N=71* NR	*N=84* 11 m	0.26 (0.16-0.42); p<0.0001
HRR non-BRCA	*N=129* 24.7 m	*N=115* 16.6 m	0.65 (0.47-0.91); p=0.012

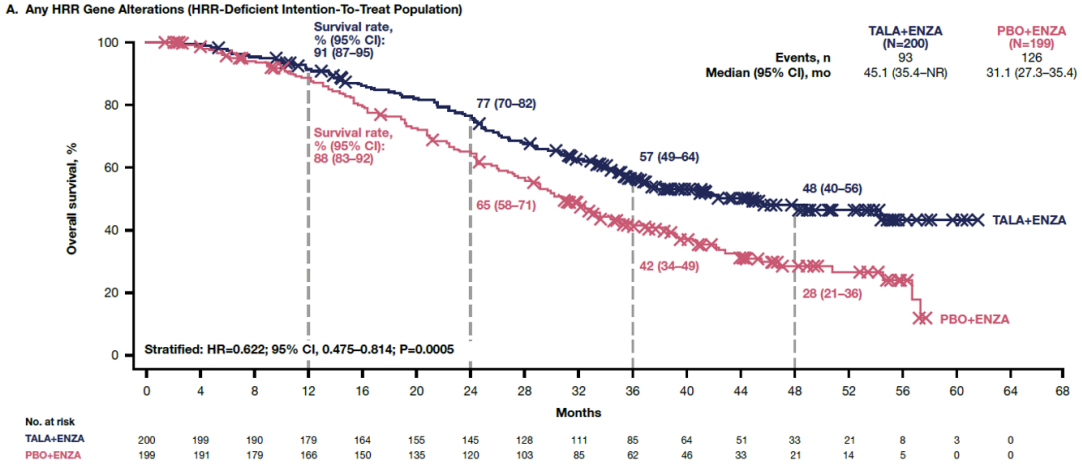
BRCA+ (N=155)



HRR non-BRCA (N=244)

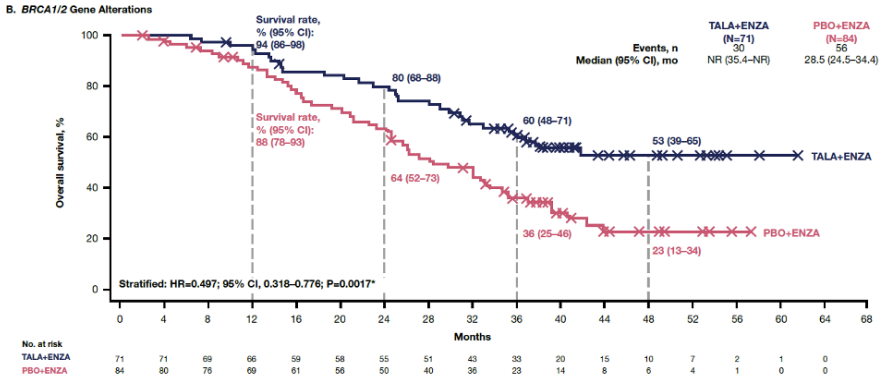


Overall survival

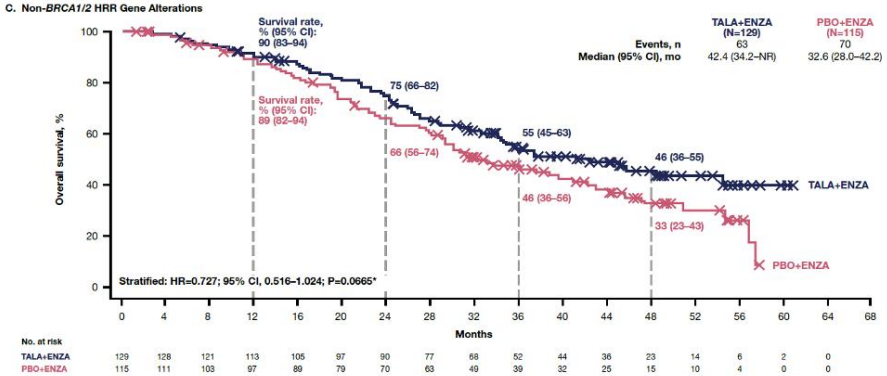


	Talazo-Enza	Enza	HR (95%CI); p-val
All HRR	*N=200* 45.1 m	*N=199* 31.1 m	0.62 (0.48-0.81); p=0.0006
BRCA +	*N=71* NR	*N=84* 28.5 m	0.50 (0.32-0.78); p=0.0017
HRR non-BRCA	*N=129* 42.4 m	*N=115* 32.6 m	0.73 (0.62-1); p=0.067

BRCA+ (N=155)



HRR non-BRCA (N=244)



Toxicity (cohort 1 + cohort 2)

No new safety findings identified after an additional 2 yrs of follow-up

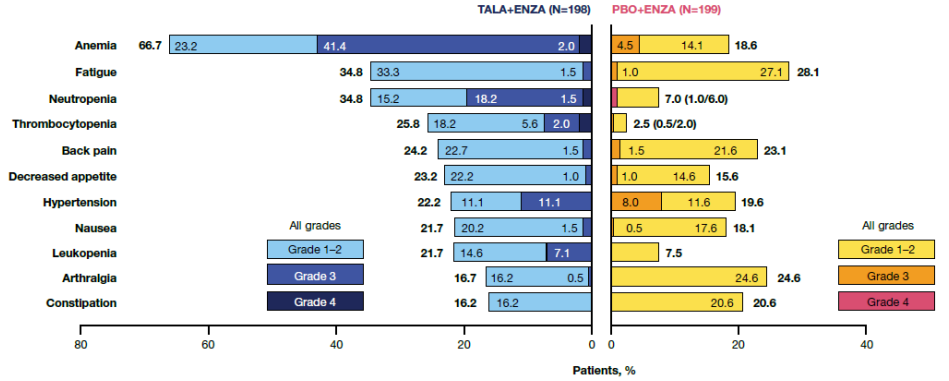
- No additional cases of MDS
- Discontinuation rate for Talazo-Enza similar to previous reports
- Rate of VTE unchanged with longer follow-up (2.4 / 100 paticipant-yr)

TEAEs, n (%)	TALA + ENZA (N=398)	PBO + ENZA (N=401)
Any TEAE	394 (99.0)	384 (95.8)
Treatment-related	360 (90.5)	286 (71.3)
SAEs	182 (45.7)	126 (31.4)
Treatment-related	85 (21.4)	13 (3.2)
Grade 3–4 TEAEs	302 (75.9)	179 (44.6)
Grade 5 TEAEs	14 (3.5)	20 (5.0)
Treatment-related	1 (0.3)	2 (0.5)
Dose interruption of talazoparib or placebo due to AE	260 (65.3)	99 (24.7)
Dose reduction of talazoparib or placebo due to AE[a]	217 (54.5)	29 (7.2)
Discontinuation of talazoparib or placebo due to AE	86 (21.6)	52 (13.0)

In the talazoparib arm:

- TEAEs leading to a dose reduction of talazo:
  - Anemia (44.9%)
  - Neutropenia (15.7%)
  - Thrombocytopenia (5.6%)
- Grade 3–4 anemia
  - Reported in 43.4% of patients
  - Median time to onset was 3.4 months
- 4.5% discontinued talazoparib due to anemia
- Median duration of treatment with talazoparib was 20.3 months

Figure 4. Summary of Most Common All-Cause TEAEs* (HRR-Deficient Safety Population)



TEAE=treatment-emergent adverse event.
*TEAEs reported in ≥20% of patients in either treatment arm.

TALAPRO-2: Conclusions

Cohort 1: all comers

- TALAPRO-2 is the first PARPi plus ARPI combination study to show a **statistically significant and clinically meaningful improvement in OS** vs standard-of-care ARPI in mCRPC – in patients unselected (cohort 1) and selected for HRR gene alterations (cohort 2 – poster D15)
    - **Median OS** in the talazoparib group was 45.8 months – **8.8 months longer** than active control
- Median OS with talazoparib plus enzalutamide was **similar across the ITT, and HRR-deficient and HRR–non-deficient** subgroup populations, ranging from 46 to 47 months
- **Median rPFS** in the talazoparib group was 33.1 months — **13.6 months longer** than active control
- No new safety signals were identified with extended follow-up

Cohort 2: HRR mutant

In patients with HRR-deficient mCRPC, talazoparib plus enzalutamide resulted in a **statistically significant and clinically meaningful improvement in OS** vs enzalutamide plus placebo

- Median OS in the talazoparib group was 45.1 months – **14 months longer** than active control
- To our knowledge, this is the longest median OS reported in men with HRR-deficient mCRPC and is similar to the median OS in the unselected cohort of patients from TALAPRO-2 (#LBA18; ASCO GU 2025),a which is the **longest-reported median OS in mCRPC overall**
- **Median rPFS** in the talazoparib group was 30.7 months — **~18 months longer** than active control
- No new safety signals were identified with extended follow-up

TALAPRO-2: Conclusions

- Talazoparib + Enzalutamide **improves overall survival** in a **non-selected population** of mCRPC patients in 1st line
  - *Benefit:* ***BRCA*** *(HR: 0.50 greatest) >* ***HRR nonBRCA*** *(HR: 0.73) >* ***nonHRR*** *(HR: 0.78) lowest*
- Expertise in the management of **adverse events** key to ensure quality of life
  - 75% grade 3-4 AEs (mainly hematologic - anemia)
  - 65% interrupt dose → 20% discontinue

- **Molecular characterization** is **still required** to balance expected benefit (based on BRCA/HRR status) with toxicity (hematologic, GI)

- **Questions** still pending:
  - What is the benefit with individual HRR alterations (CDK12, PALB2, ATM)?
  - Is this benefit applicable to patients treated with ARPIs in mHSPC/nmCRPC?
  - How many BRCA+ patients received PARPi at progression?
  - What is the benefit of PARPi + ARPi over PARPi monotherapy in BRCA+ (BRCAAWAY)?

- Metastatic, castration-resistant prostate cancer
  - TALAPRO-2 trial overall survival
  - **ENZA-P trial overall survival**

    - Oral. #17. Louise Emmett. Overall survival and quality of life with [177Lu] Lu PSMA-617 plus enzalutamide versus enzalutamide alone in poor-risk, metastatic, castration-resistant prostate cancer in ENZA-p (ANZUP 1901)
  - **PSMAfore biomarker analysis**

    - Oral. #16. Johann de Bono. Association of baseline and on-treatment ctDNA fraction with clinicaloutcomes in patients with mCRPC in the PSMAfore study of 177Lu-PSMA-617
  - Mevrometostat + Enzalutamide
  - Metasases-directed therapy for mCRPC

- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

Lutetium-based PSMA radiopharmaceuticals in advanced prostate cancer

	Phase / N	Population	Exp	Control	rPFS	OS
VISION	Phase III	mCRPC, post-ARPi, post-chemo	Lu-177-PSMA-617 + SoC	Soc	8.7 vs 3.4m; HR 0.4; p<0.001	15.3 vs 11.3m; HR 0.62; p<0.001
Thera-P	Phase II	mCRPC, post-ARPi, post-chemo	Lu-177-PSMA-617	Cabazitaxel	HR 0.63; p=0.005	RMST 19.1 vs 19.6m; NS
PSMAfore	Phase III	mCRPC, post-ARPi	Lu-177-PSMA-617	2nd ARPi	9.3 vs 5.6m; HR 0.41; p<0.001	23.7 vs 24.9m; HR 0.98; p=0.44*
Enza-P	Phase II	mCRPC, ARPi naïve**	Lu-177-PSMA-617 + Enza	Enza	16 vs 12m; HR 0.68 (0.45-1.03)	???

**Crossover to 177-Lu-PSMA-617 at progression in control arm*

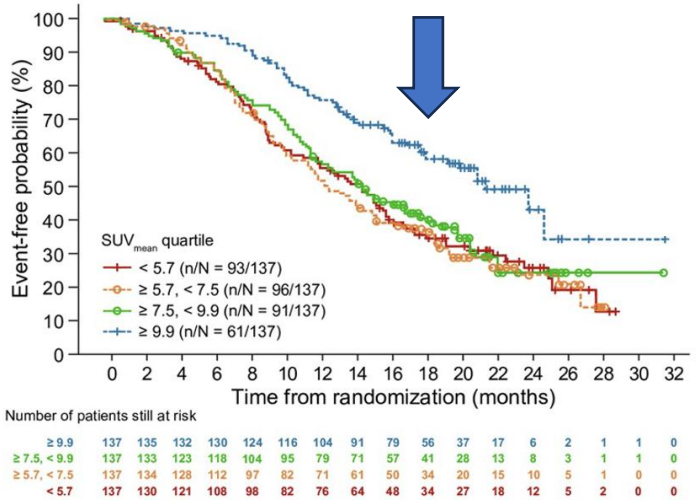
***1st line mCRPC with adverse prognostic features*

The challenge of adequate patient selection

SUVmean has prognostic value in 177-Lu-PSMA treated patients

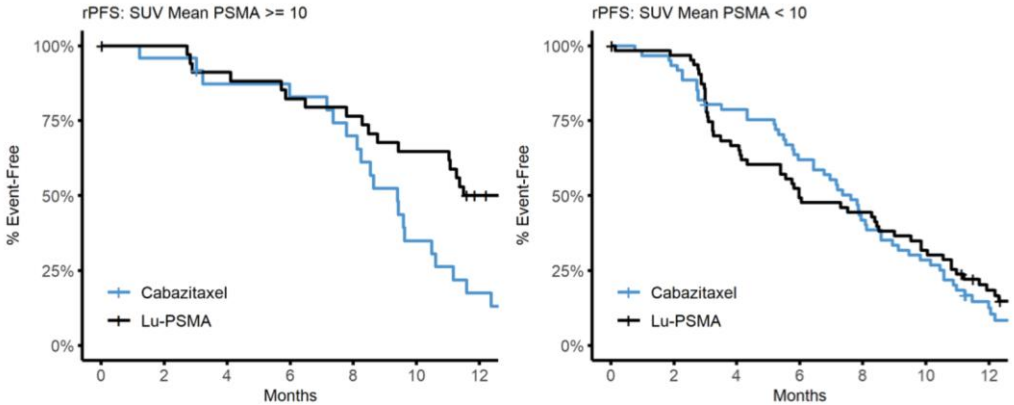
VISION

SUV_{mean} quartile	Median OS (months)
≥ 9.9 (highest)	21.4
≥ 7.5, < 9.9	14.6
≥ 5.7, < 7.5	12.6
< 5.7 (lowest)	14.5



Thera-P

Predictive value is unclear



B Radiographic progression-free survival

	Cabazitaxel (n/N)	Cabazitaxel, median, months (95% CI)	[177Lu]Lu-PSMA-617 (n/N)	[177Lu]Lu-PSMA-617, median, months (95% CI)	HR (95% CI)
PSMA SUVmean <10	57/71	7·6 (6·4–8·6)	57/64	6·0 (4·3–9·5)	0·85 (0·59–1·24)
PSMA SUVmean ≥10	23/30	9·4 (8·1–11·2)	23/35	12·7 (11–NE)	0·46 (0·25–0·84)
Q1: PSMA SUVmean <6·9	22/28	8·1 (6·4–10·6)	19/21	5·6 (2·8–10·8)	1·21 (0·65–2·26)
Q2: PSMA SUVmean ≤6·9 to <8·5	15/20	5·7 (4·3–NE)	27/29	8·5 (5·6–11)	0·65 (0·34–1·26)
Q3: PSMA SUVmean ≤8·5 to <10·8	24/30	7·5 (6·8–9·5)	18/22	8·9 (6–13·8)	0·53 (0·28–1·00)
Q4: PSMA SUVmean ≤10·8	18/23	9·6 (8·1–12·4)	16/27	14·2 (8·3–NE)	0·52 (0·26–1·04)

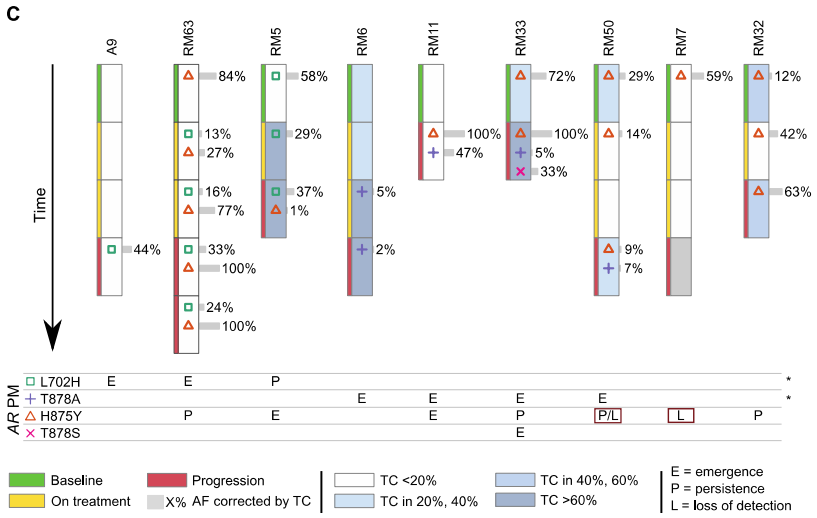
0·25 0·50 1·0 2·0 4·0

Favours [177Lu]Lu-PSMA-617 Favours cabazitaxel

Armstrong et al. ASCO 2022. Buteau et al. Lancet Oncol 2022

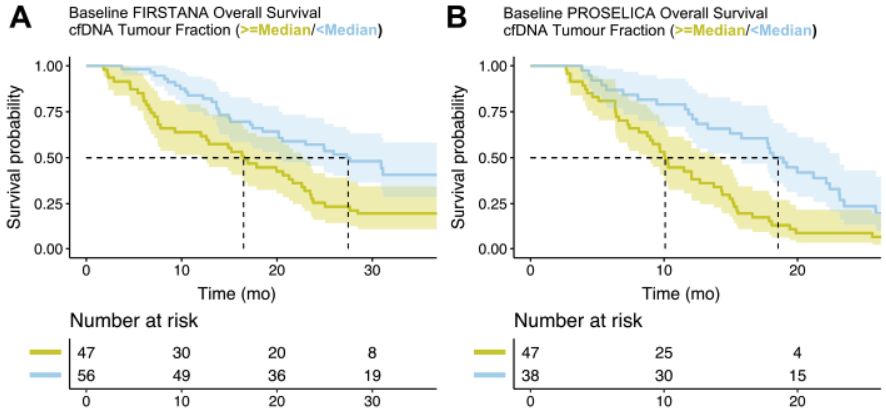
ctDNA as a biomarker in advanced prostate cancer

Idenfitication of predictive biomarkers / drug targets
Dynamic monitoring of changes in the AR



ctDNA levels as prognostic indicator (baseline) or treatment response biomarker (change)

PROSELICA / FIRSTANA trials (cabazitaxel)



Sumanasuriya et al. Eur Urol 2021

Overall survival and quality of life with [^{177}Lu]Lu-PSMA-617 plus enzalutamide in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from an open-label, multicentre, randomised, phase 2 trial

ENZA-P

Louise Emmett, Shalini Subramaniam, Megan Crumbaker, Andrew Nguyen, Anthony M. Joshua, Andrew J. Weickhardt, Sze-Ting Lee, Siobhan Ng, Roslyn J. Francis, Jeffrey C. Goh, David A. Pattison, Thean Hsiang Tan, Ian D. Kirkwood, Shahneen Sandhu, Alison Yan Zhang, Michael S. Hofman, Hayley Thomas, Andrew J. Martin, Ian D. Davis* & Martin R. Stockler*

Clinicaltrials.gov NCT04419402

NHMRC Clinical Trials Centre

ANZUP Cancer Trials Group Limited

ASCO Genitourinary Cancers Symposium #GU25

PRESENTED BY: Prof Louise Emmett #ENZAp

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ^{68}Ga PSMA PET/CT

R 1:1

- Enzalutamide 160 mg
- Enzalutamide 160 mg + [^{177}Lu]Lu- PSMA-617 7.5 GBq 2-4 doses

Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Risk Factors for Early Treatment Failure on Enzalutamide

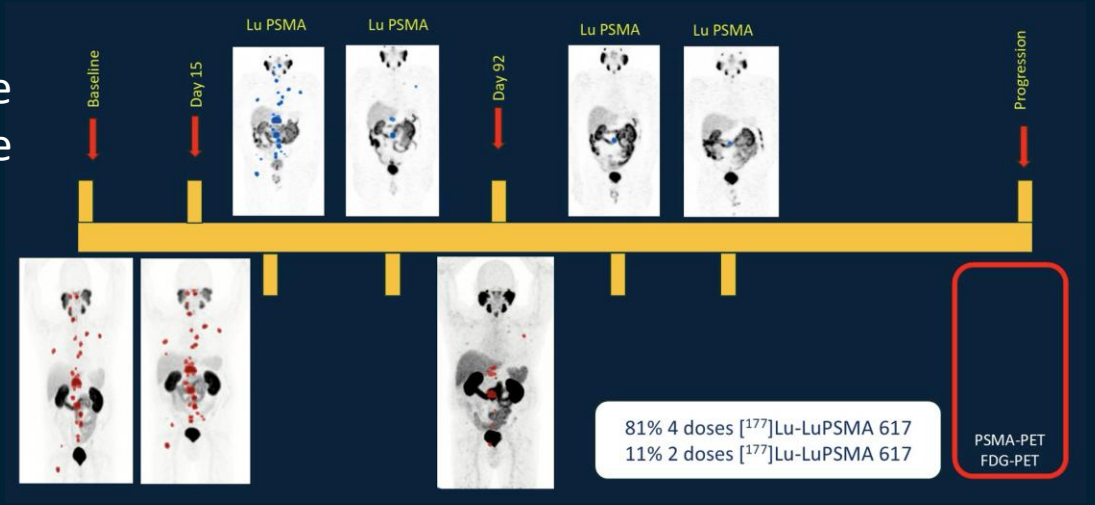
- LDH ≥ULN
- ALP ≥ULN
- Albumin <35g/L
- De novo metastatic disease at diagnosis
- <3 Years since initial diagnosis
- >5 Bone metastases
- Visceral metastases
- PSA doubling time <84 days
- Pain requiring opiates >14 days
- Prior abiraterone

	Enza	Enz + LuPSMA
PSA (ng/mL)	33	39
>20 mts	59%	61%
De novo	58%	52%
Doce mHSPC	57%	53
BRCA1	1.2%	1%

Objectives

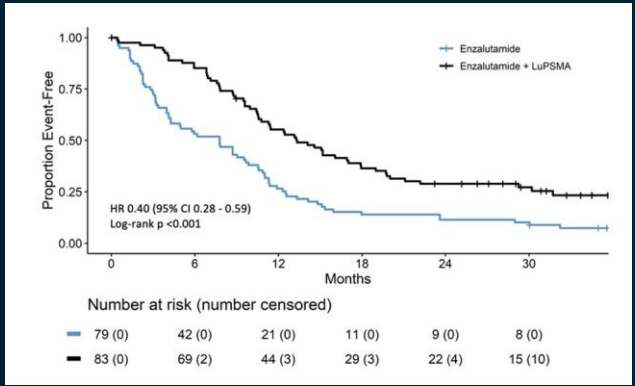
PSA-PFS (primary endpoint)
Overall survival
Health-related Quality of Life
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
Adverse events
Health economic analyses
Translational/correlative

Adaptive schedule



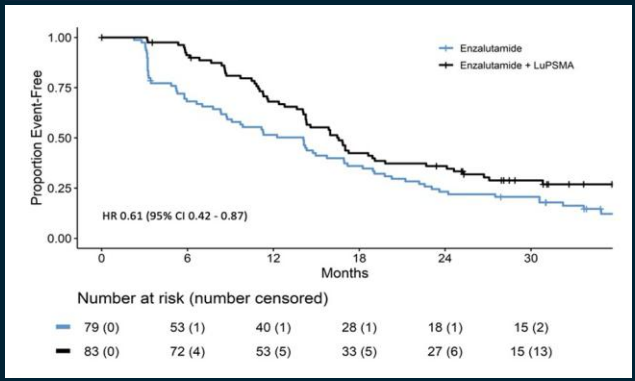
PSA-PFS

HR 0.40 (95%CI 0.28-0.59) p=0.000001

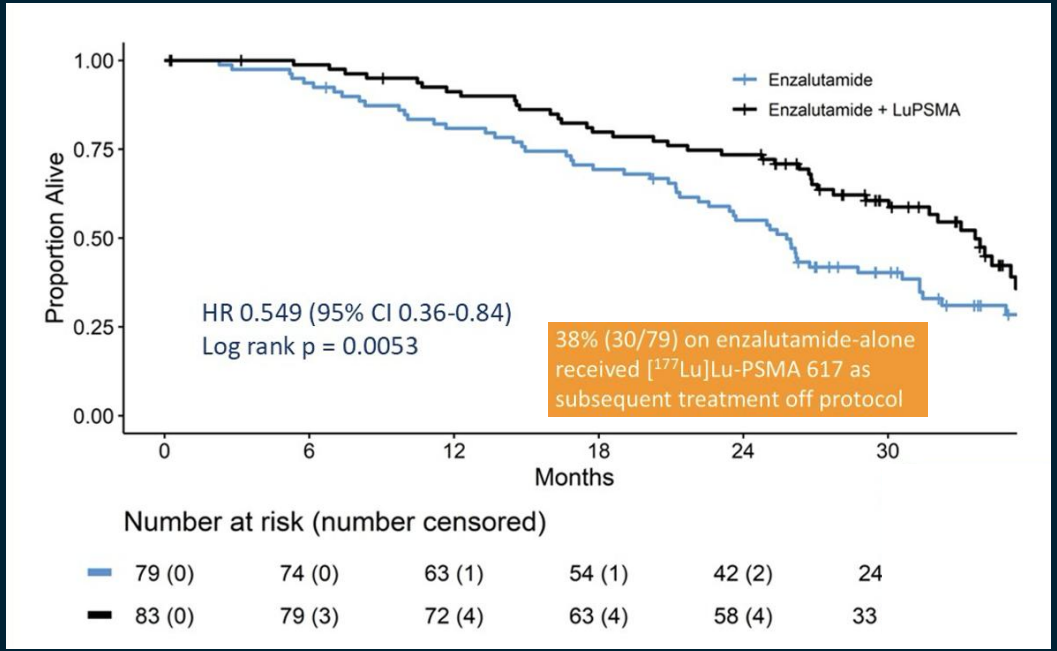


R-PFS

HR 0.61 (95% CI 0.42-0.87)

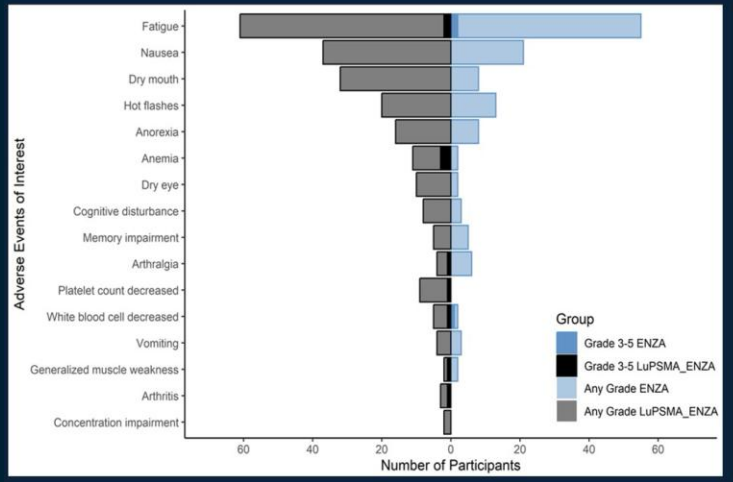


Overall Survival



Overall Survival	Participants	Events	Censored	Median Months
Enzalutamide	79	53	26	26 (C195% 23-31)
Enzalutamide + Lu-PSMA 617	83	43	40	34 (CI95% 30-37)

No new safety findings

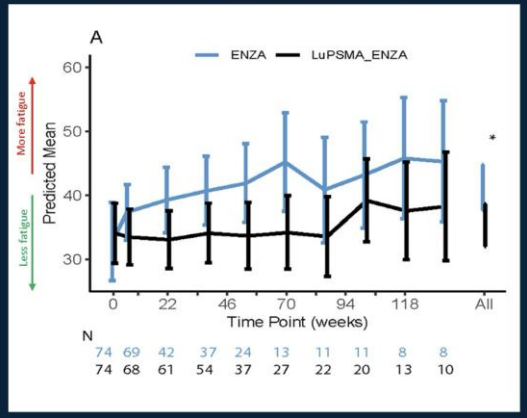


Adverse Events of Interest	Enzalutamide n (%)			Enzalutamide + [^{177}Lu]Lu-PSMA-617 n (%)		
	Grade 1-2	Grade 3	Overall	Grade 1-2	Grade 3	Overall
Any AE	64 (81)	3 (4)	67 (85)	67 (83)	8 (10)	77 (95)
Anemia	4 (5)	_	2 (3)	9(11)	3(4)	11(14)
Fatigue	53 (67)	2 (3)	55 (70)	60(74)	2 (2)	61 (75)
Platelets decreased	_	_	_	7(9)	1 (1)	9 (11)
WCC decreased	1(1)	1(1)	2(3)	4(5)	1(1)	4(6)
Nausea	24(30)	_	_	39(48)		3(4)
Dry Mouth	8(10)	_	8(10)	33(41)	_	32 (40)

Improvement in quality of life parameters

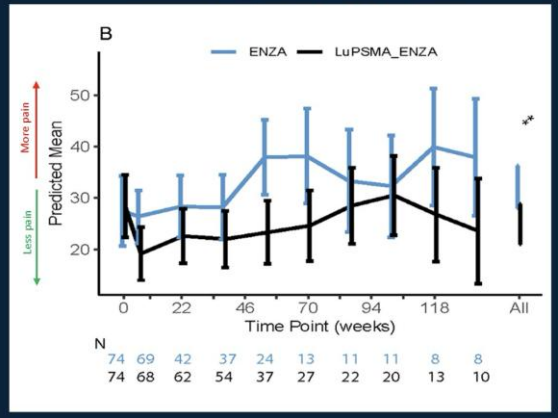
Fatigue

Difference 5.9, 95%CI 1.1 to 11; p=0.02



Pain

Difference 7.3, 95%CI 1.6 to 13; p=0.01



Conclusions

Limitations
First line enzalutamide in the early mCRPC pre-chemo setting.
Selective population
Impacts broad applicability of the findings

Directions
Should PSMA RLT in prostate cancer be administered more broadly in conjunction with ARPI?
Paves the way for phase III trials leveraging these complementary therapies

- Combining ^{177}Lu-PSMA-617 and enzalutamide significantly improves overall survival in men with mCRPC and risk factors for early treatment failure on enzalutamide alone.
- 8-month overall survival benefit compared to an active comparator arm
- The combination improved both deterioration-free survival and health-related quality of life indicators for:

Pain | Fatigue | Physical function | Overall health and quality of life

- First trial to show overall survival benefit for a 177-Lu-PSMA + hormonal agent combo.
- Confirms quality of life benefit (Thera-P)
- Benefit of adaptive dosing scheme
- Are combos better than monotherapy?

But:

- Primary endpoint is PSA response → not powered for overall survival
- Selected patient population with adverse prognostic features → not applicable for all
- 1st line mCRPC patients are not ARPi naïve → can it reflect our current clinical practice?
- How does it compare to recent PEACE-3 results (HR: 0.69 in a population with less adverse prognostic features)

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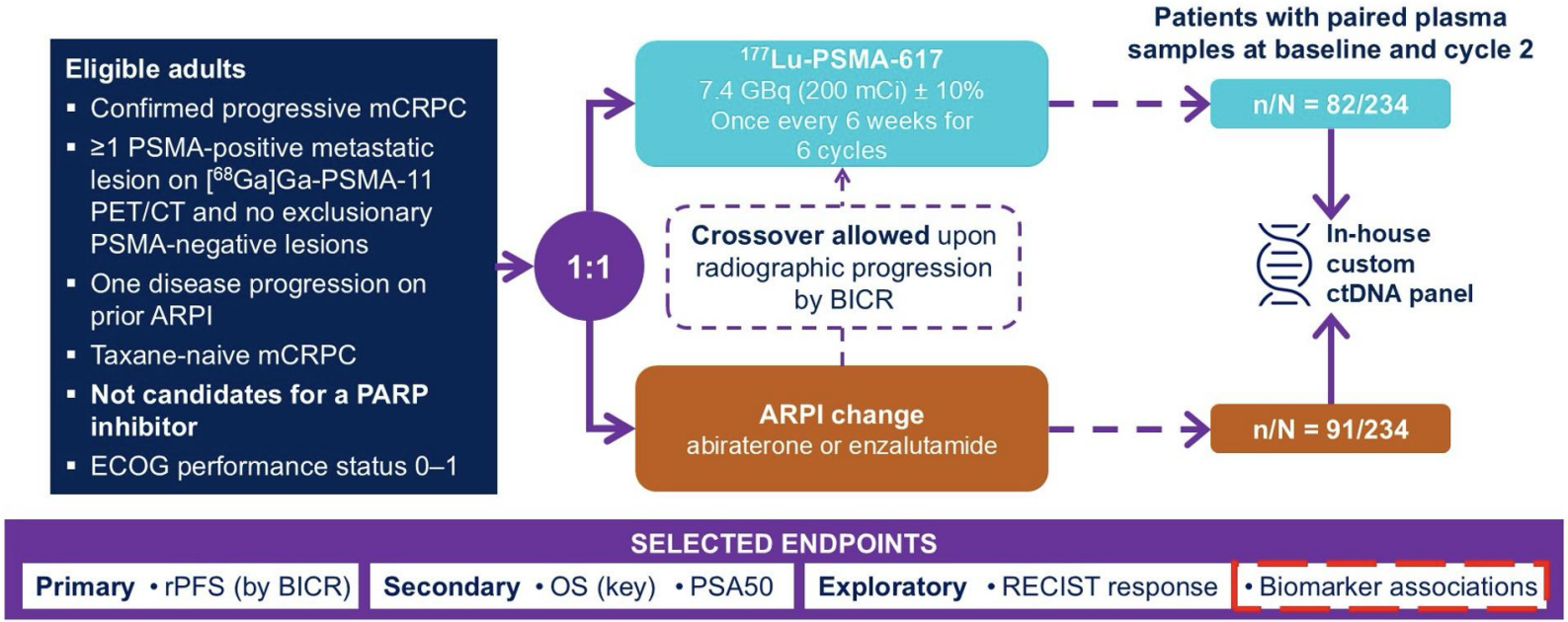
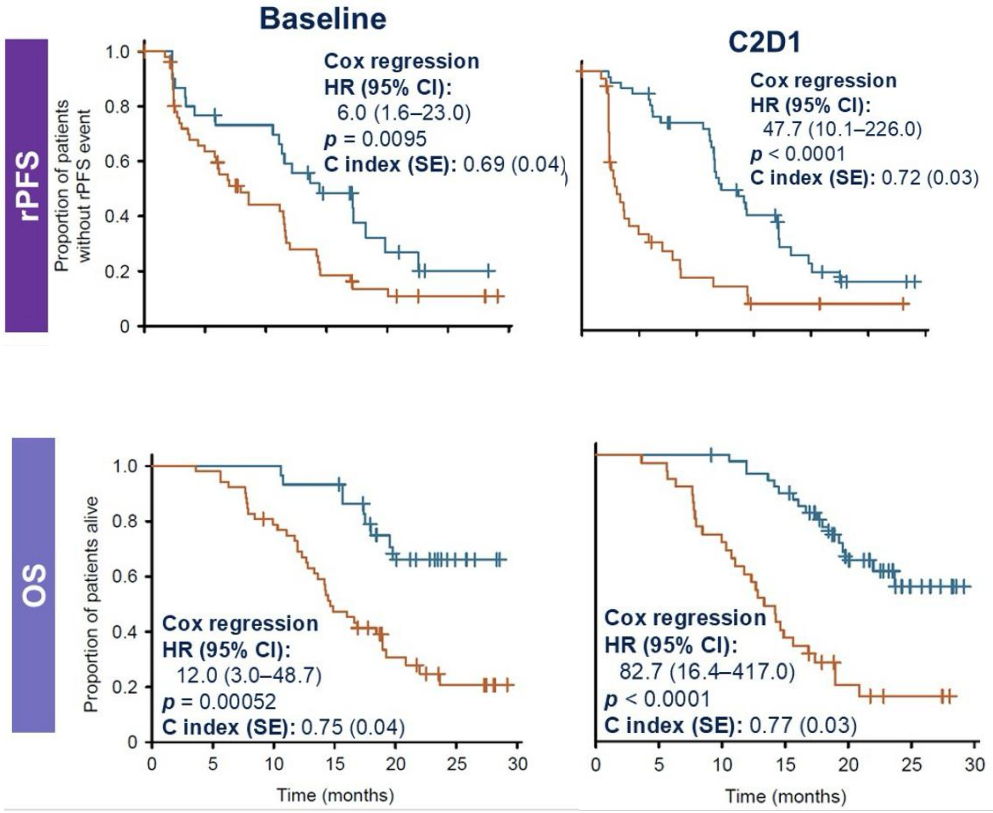
Association of baseline and on-treatment ctDNA fraction with clinical outcomes in patients with mCRPC in the PSMAfore study of ^{177}Lu-PSMA-617

Presenter: Johann S de Bono
The Institute of Cancer Research and The Royal Marsden Hospital, London, UK

Co-authors: MJ Morris, O Sartor, XX Wei, K Fizazi, K Herrmann, JM Piulats, H Mahammedi, C Logothetis, DJ George, CC Wong, L Barys, N Rajagopal, S Alanee, KN Chi,
on behalf of the PSMAfore investigators


Eligible adults
▪ Confirmed progressive mCRPC
▪ ≥1 PSMA-positive metastatic lesion on [68Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
▪ One disease progression on prior ARPI
▪ Taxane-naive mCRPC
▪ Not candidates for a PARP inhibitor
▪ ECOG performance status 0–1
1:1
177Lu-PSMA-617
7.4 GBq (200 mCi) ± 10%
Once every 6 weeks for
6 cycles
Crossover allowed upon radiographic progression by BICR
ARPI change
abiraterone or enzalutamide
Patients with paired plasma samples at baseline and cycle 2
n/N = 82/234
n/N = 91/234
In-house custom ctDNA panel
SELECTED ENDPOINTS
Primary • rPFS (by BICR)
Secondary • OS (key) • PSA50
Exploratory • RECIST response
• Biomarker associations

ctDNA fraction as a prognostic biomarker in patients treated with ^{177}Lu-PSMA-617



Baseline	Events/patients, n/n	Median rPFS, months (95% CI)
ctDNA detected	41/52	7.9 (5.8–11.6)
ctDNA not detected	20/30	14.4 (11.3–22.5)

C2D1		
ctDNA detected	29/36	3.4 (2.5–7.9)
ctDNA not detected	32/46	14.2 (11.6–18.2)

rPFS

Baseline Cox regression HR (95% CI); *p*	3.1 (0.7–14.0); 0.14
C2D1 Cox regression HR (95% CI); *p*	35.9 (7.2–180.0); < 0.0001
Cox regression C-index (SE)	0.72 (0.03)

Baseline	Events/patients, n/n	Median rPFS, months (95% CI)
ctDNA detected	37/52	14.6 (13.3-19.3)
ctDNA not detected	9/30	NE

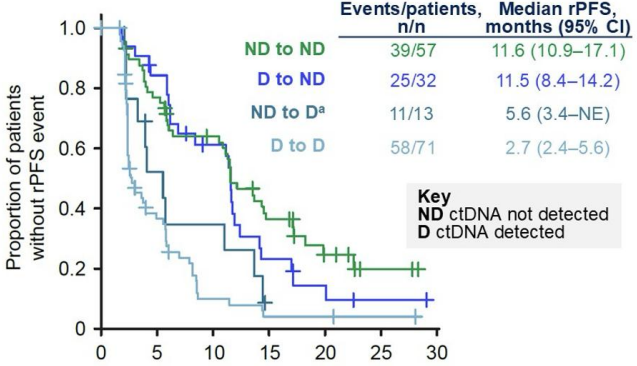
C2D1		
ctDNA detected	29/36	13.1 (10.7–16.9)
ctDNA not detected	17/46	NE

OS

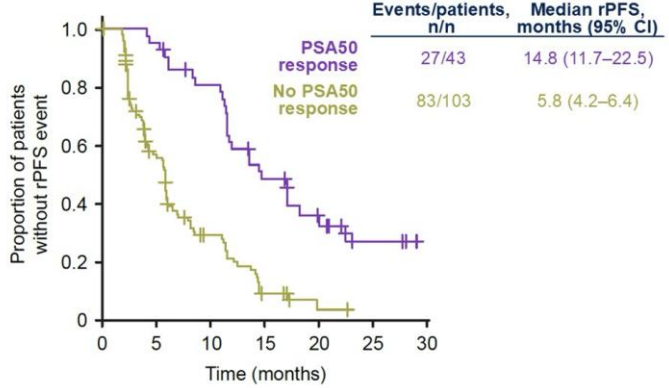
Baseline Cox regression HR (95% CI); *p*	2.1 (0.4–12.7); 0.41
C2D1 Cox regression HR (95% CI); *p*	52.5 (7.6–362.0); < 0.0001
Cox regression C-index (SE)	0.79 (0.03)

ctDNA clearance from baseline to C2D1 and PSA50 response were associated with longer rPFS

ctDNA clearance



PSA50 response



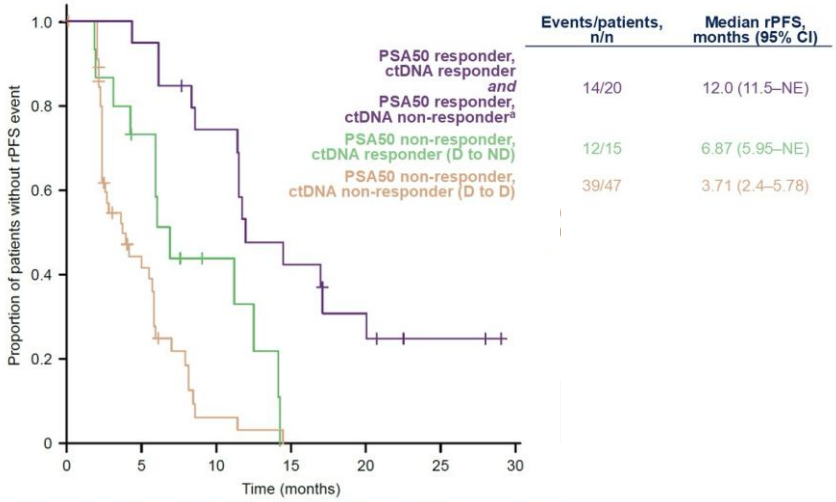
Overall population

	rPFS		OS	
	ctDNA fractional decrease[a]	PSA50[b]	ctDNA fractional decrease[a]	PSA50[b]
Patients, n	145		68	
Cox regression HR (95% CI)	0.17 (0.05–0.56)	0.32 (0.2–0.53)	0.07 (0.01–0.59)	0.44 (0.17–1.1)
p	0.0035	< 0.0001	0.015	0.09

^{177}Lu-PSMA-617 arm

All models were adjusted for baseline clinical risk variables
[a]Fractional decrease in ctDNA was measured from baseline to C2D1 (~6 weeks)
[b]PSA50 response was defined as per the protocol, including PSA timepoints at 12 weeks and beyond

What information does ctDNA add?



Conclusions

In exploratory analyses of PSMAfore in patients with taxane-naive mCRPC who had experienced one disease progression on prior ARPI:

- Higher ctDNA fraction was associated with shorter rPFS and OS in patients treated with ^{177}Lu-PSMA-617
  - The association was stronger with C2D1 than baseline ctDNA fraction
- Higher ctDNA fraction was associated with worse tumor response
- ctDNA clearance from baseline to C2D1 was associated with longer rPFS and OS
- Early ctDNA fraction dynamics contributed additional information in models of rPFS and OS beyond PSA
- Post-treatment changes in ctDNA fraction merit evaluation as an intermediate endpoint for clinical benefit
  - FDA recently released guidance on the use of ctDNA as a biomarker for response in clinical trials[1]

- ctDNA **sequencing** may help identify targets (AR, BRCA) especially when no tumor available

- ctDNA **levels** have **prognostic value**: higher ctDNA levels = higher tumor burden = worse prognosis
  Is this prognostic value better than what we can already estimate

- Does ctDNA have **predictive value** or value as a treatment response biomarker?
- What is the **clinical utility**?
  Can we use information from ctDNA changes (response/progression) to make changes to therapy that will improve patient outcomes? Are we ready to stop therapy based on an increase in ctDNA if other markers ok?
  Is it proven that information from ctDNA is superior to, for example, PSA change?

- Metastatic, castration-resistant prostate cancer
  - TALAPRO-2 trial overall survival
  - ENZA-P trial overall survival
  - PSMAfore biomarker analysis
  - **Mevrometostat + Enzalutamide**
  - Metasases-directed therapy for mCRPC

- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

ASCO® Genitourinary Cancers Symposium

Slide deck

Plain Language Summary

Mevrometostat (PF-06821497), an EZH2 inhibitor, in combination with enzalutamide in patients with mCRPC: A randomized dose-expansion study

Michael Thomas Schweizer,[1,2] Mariona Calvo,[3] Victor Moreno,[4] Begoña Mellado,[5] Daniel Castellano,[6] Alexander I. Spira,[7] Qiang Wei,[8] Joan Carles,[9] Benjamin Garmezy,[10] Cheol Kwak,[11] Iwona Ługowska,[12] Konstantin Penkov,[13] Neal D. Shore,[14] Li Liu,[15] Rajendar K. Mittapalli,[15] Jessica Tougias,[16] Claudia Andreu-Vieyra,[17] Neelesh Soman,[18] Teresa Alonso Gordoa[19]

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Funding: This study is sponsored by Pfizer Inc. Enzalutamide for the study was provided by Astellas Pharma Inc.
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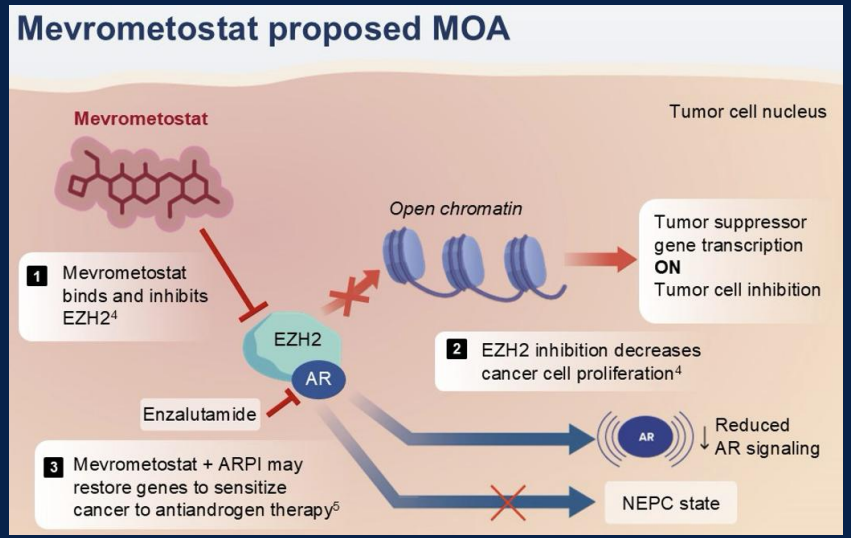
The authors thank all patients, their families, and investigators and investigational site members involved in this study
Additional findings from this study presented by Dr. Schweizer during Poster Session A: Prostate Cancer on Thursday, February 13, from 11:25 AM–12:45 PM and 5:45–6:45 PM (Poster D20).

Mevrometostat: EZH2 inhibitor

EZH2: catalytic subunit of the PRC2 → methylates H3K27 to regulate expression of tumor suppressor genes

Canonical (polycomb-associated) and non-canonical EZH2 functions are different in adenocarcinoma and NEPC



Study design: randomized phase II

Patient population:
- mCRPC
- Prior abiraterone
- ≤1 regimen of prior chemotherapy in any setting
- Evidence of progression per modified PCWG3 criteria
- Ongoing ADT

R 1:1

N=81

Mevrometostat
1250 mg orally BID empty stomach + Enzalutamide 160 mg orally QD
n=41

Enzalutamide
160 mg orally QD
n=40

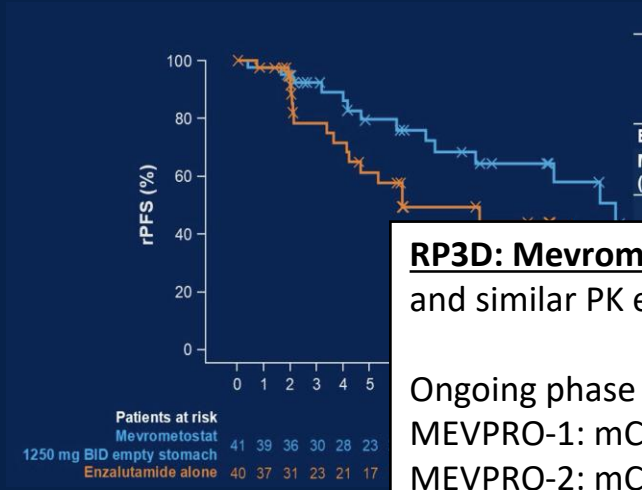
Stratification factor:
- Prior chemotherapy

Primary endpoints:
- rPFS per investigator assessment
- Safety

Secondary endpoints:
- OR†
- PSA_{50}
- Pharmacokinetics‡

rPFS benefit with combination vs enza monotherapy

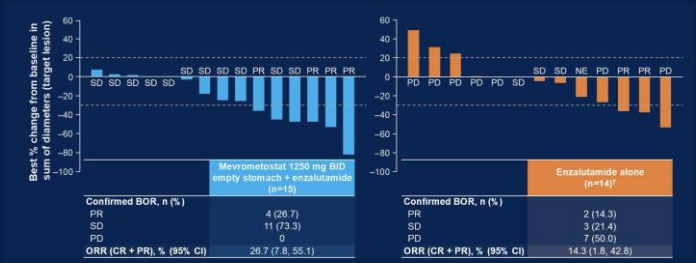
14.3 vs 6.2m; HR 0.51



	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41)	Enzalutamide alone (n=40)
Events, n (%)	15 (36.6)	19 (47.5)
Median rPFS (95% CI), months	14.3 (7.5, NE)	6.2 (4.1, 13.9)

HR 0.51 (90% CI: 0.28, 0.95)

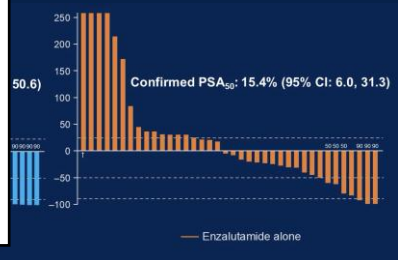
ORR: 26.7% VS 14.3%



RP3D: Mevrometostat 875 mg with food had improved safety profile and similar PK exposure to mevrometostat 1250 mg on empty stomach

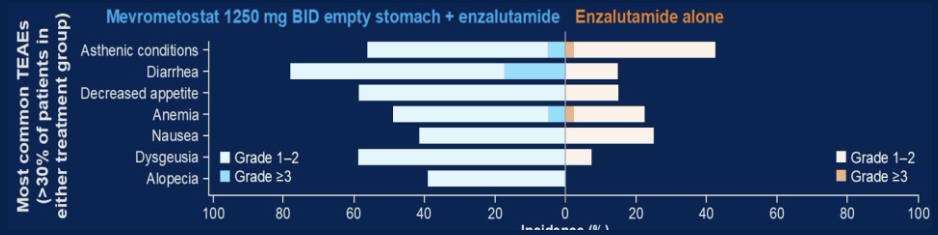
Ongoing phase III trials:
MEVPRO-1: mCRPC post abiraterone
MEVPRO-2: mCRPC ARPi naïve

15.4%



Mevrometostat 1250 mg BID empty stomach + enzalutamide has a manageable safety profile

Event, n (%)	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) All grades	Mevrometostat 1250 mg BID empty stomach + enzalutamide (n=41) Grade ≥3	Enzalutamide alone (n=40) All grades	Enzalutamide alone (n=40) Grade ≥3
Any TEAE	40 (97.6)	22 (53.7)	37 (92.5)	17 (42.5)
Treatment-related TEAE	39 (95.1)	20 (48.8)	33 (82.5)	9 (22.5)
Serious AE	14 (34.1)	13 (31.7)	11 (27.5)	10 (25.0)
Treatment-related serious TEAE†	10 (24.4)	10 (24.4)	1 (2.5)	1 (2.5)
TEAE leading to dose reduction	15 (36.6)	7 (17.1)	3 (7.5)	0
TEAE leading to study discontinuation	1 (2.4)	0	2 (5.0)	1 (2.5)



- Metastatic, castration-resistant prostate cancer
  - TALAPRO-2 trial overall survival
  - ENZA-P trial overall survival
  - PSMAfore biomarker analysis
  - Mevrometostat + Enzalutamide
  - **Metasases-directed therapy for mCRPC**

    - Mini Oral #22. Niazi. Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration resistant prostate cancer: A randomized phase II trial (GROUQ-PCS 9)
    - Case Based Session. # . Tang et al. World-wide oligometastatic prostate cancer metaanalysis leveraging individual patient data from randomized trials (WOLVERINE)

- Metastatic, hormone-sensitive prostate cancer
- Localized prostate cancer

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Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration resistant prostate cancer: A randomized phase II trial (GROUQ-PCS 9)

Tamim Niazi, Fred Saad MD, Rashmi Koul MD, Isabelle Thibault MD, Peter W. M. Chung MD, George Wakil MD, Michael Lock MD, Guila Delouya MD, Steven Tisseverasinghe MD, Boris Bahoric MD, Andrew Feifer MD, Venkata Ramana Agnihotram PhD, Theodoros Tsakiridis MD, Fabio L. Cury MD, Rafika Dahmane MD,, Nikhilesh Gajanan Patil MD, Scott Tyldesley MD

Clinical Trials.gov identifier: NCT02685397
This study was supported by Astellas Canada

Patient population
- 1L mCRPC
- 1-5 metastases
- Docetaxel allowed at mHSPC stage
- No prior NHAs
- Ongoing ADT
- ECOG 0–1

Stratification factors
- Site of distant metastases
- Number of mets <4 vs 4+

1:1

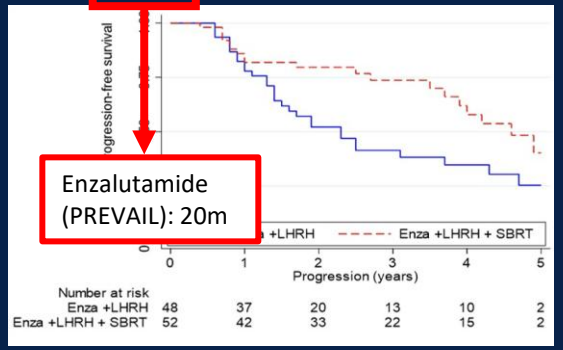
Enzalutamide 160 mg + Androgen Deprivation therapy
N=48

Enzalutamide 160 mg + Androgen Deprivation therapy + MDT (SBRT)
N= 52

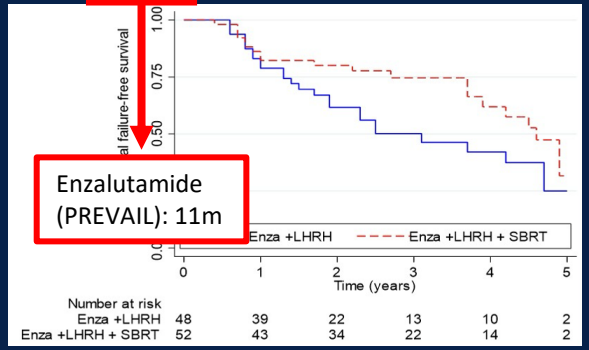
Primary endpoint
- Radiographic progression or death (rPFS) by investigator assessment

Key secondary endpoint
- Biochemical Progression Free survival or death (bPFS)
- Time to subsequent therapy
- Health-related quality of life
- Safety and tolerability
- Overall survival

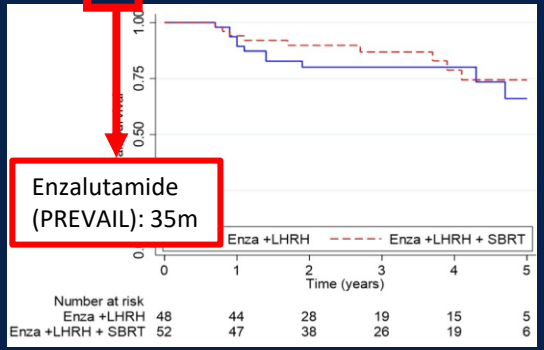
Radiographic progression-free survival
4.6 vs 2.3 yrs; HR 0.48; p=0.014



Biochemical progression-free survival
4.6 vs 3.1 yrs; HR 0.58; p=0.065



Overall survival
NR vs NR; HR 0.71; p=0.407



No additional toxicity: AEs G≥1: 83.3 vs 86.5% (p=0.781); G≥2: 43.8% vs 36.5%; p=0.542

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World-wide oligometastatic prostate cancer (omPC) meta-analysis leveraging individual patient data (IPD) from randomized trials (WOLVERINE): an analysis from the X-MET collaboration

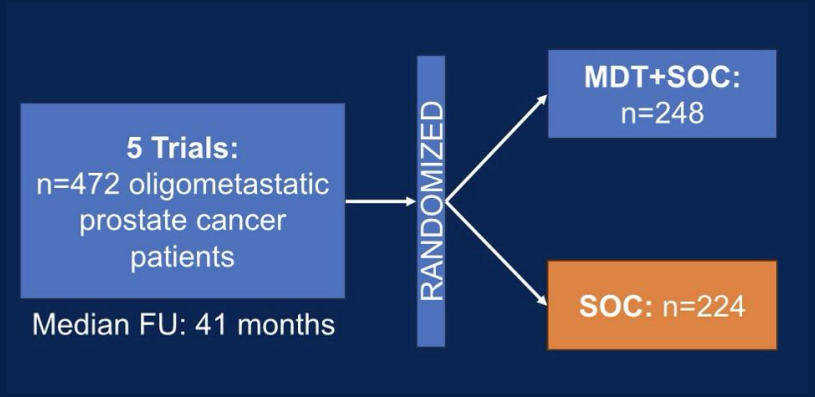
Chad Tang, Alex Sherry, Hyunsoo Hwang, Giulio Francolini, Lorenzo Livi, Phuoc Tran, Paul Corn, Ana Aparicio, Gabriele Simontacchi, Ana Kiess, Jarey Wang, Valerie Fonteyne, Renee Bultijnck, Robert Olson, Stephen Harrow, Ethan Ludmir, Pierre Blanchard, Ryan Sun, David Palma, Piet Ost

X-met collaboration

Trials with MDT + SoC vs Soc allone

Individual patient data pooled and the following endpoints harmonized across studies
- PFS, rPFS, CRPC-PFS, OS

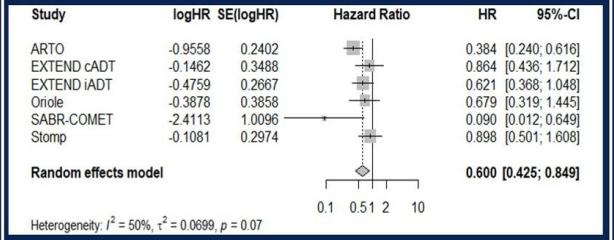
Two parallel analyses conducted:
- Meta-analysies with common and random effects. Models
- Cox regression using individual patients stratified by trial enrollment



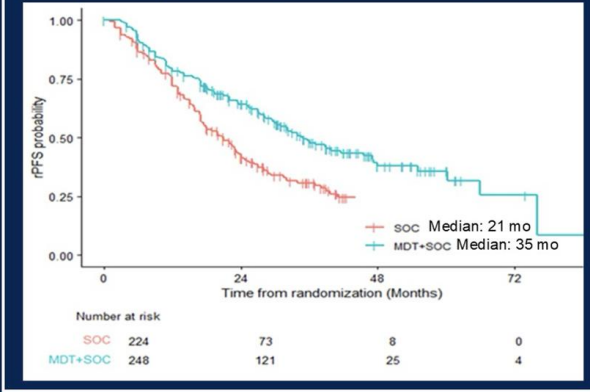
	SOC	MDT+SOC
2nd Generation ARPI	134 (60%)	125 (50%)
ADT Alone	40 (18%)	52 (21%)
Observation	50 (22%)	69 (28%)
PSA at enrollment (median)	1.9	1.9
Number of metastases (median)	2	2
CRPC = Yes	104 (46%)	95 (38%)
CRPC = No	120 (54%)	153 (62%)
Prior Primary Treated = No	37 (17%)	42 (17%)
Prior Primary Treated = Yes	185 (83%)	204 (82%)
Baseline Imaging = Conventional	79 (35%)	110 (44%)
Baseline Imaging = PET	145 (65%)	138 (56%)

Radiographic progression-free survival

Trial Level Analysis:
Random effects model P=0.004



Cox Regression (Stratified by Trial):
MDT (vs SOC) HR: 0.59 (95% CI: 0.46-0.76), P <0.001

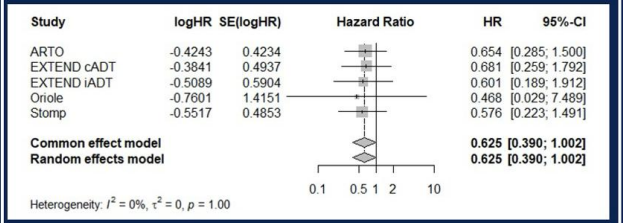


Overall survival

	Random-effects model: HR (95% CI)
PFS	0.44 (0.35-0.57), P<0.0001
rPFS	0.60 (0.43-0.85), P=0.0039
CRFS	0.58 (0.37-0.92), P=0.019
OS	0.63 (0.39-1.004), P=0.051

	Cox regression: HR (95% CI)
PFS	0.45 (0.35-0.58), P<0.0001
rPFS	0.59 (0.46-0.76), P<0.0001
CRFS	0.58 (0.37-0.91), P=0.020
OS	0.64 (0.40-1.01), P=0.057

Trial Level Analysis:
Random effects model P=0.051



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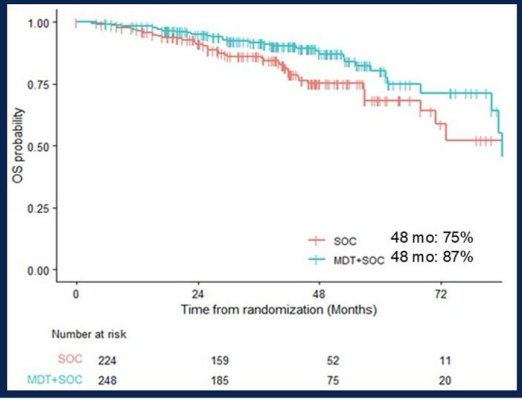


- Metastatic, castration-resistant prostate cancer

- **Metastatic, hormone-sensitive prostate cancer**
  - **Factors associated with outcome in ARPI-treated patients**

    - Oral. Abstract #20. Fisher et al. Which patients with metastatic hormone-sensitive prostate cancer (mHSPC) benefit more from androgen receptor pathway inhibitors (ARPIs)? STOPCAP metaanalyses of individual participant data (IPD)

- Localized prostate cancer

Treatment options in mHSPC

	Trial	Br Control	SG: HR (IC95%); p-valor
ADT + Docetaxel	CHAARTED	ADT	0,61 (0,47-0,8); p<0,001
	STAMPEDE	ADT	0,78 (0,66-0,93); p=0,006
ADT + Abiraterone	LATITUDE	ADT	0,66 (0,56-0,78); p<0,001
	STAMPEDE	ADT	0,61 (0,49-0,75); p<0,001
ADT + Apalutamide	TITAN	ADT	0,65 (0,53-0,79); p<0,001
ADT + Enzalutamide	ENZAMET	ADT + NSAA	0,67 (0,52-0,86); p=0,002
	ARCHES	ADT	0,66 (0,53-0,81); p<0,001
ADT + Docetaxel + Abiraterone	PEACE-1	ADT + Docetaxel	0,75 (0,59-0,95); p=0,017
ADT + Docetaxel + Darolutamide	ARASENS	ADT + Docetaxel	0,68 (0,57-0,80); p<0,001

Wide consensus that:

- ADT monotherapy is suboptimal (the vast majority of patients benefit from at least ADT + ARPi combos)

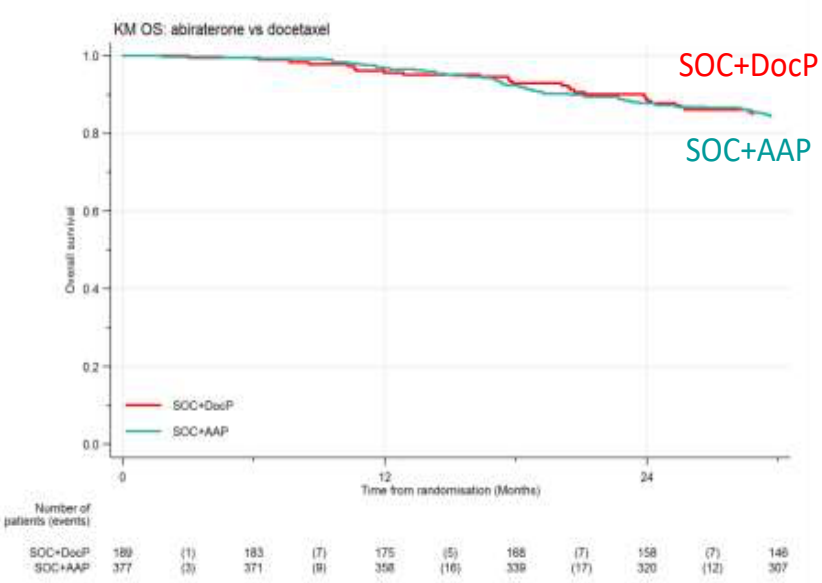
- ADT + Docetaxel is inadequate (triplet therapy is superior to ADT + Docetaxel)

No difference between Abi and Docetaxel in STAMPEDE

Who needs chemotherapy?

Generally, patients with **higher burden** (high volume, de novo) of disease and **worse prognosis** are selected for treatment with **chemotherapy**

Different studies have evaluated **molecular biomarkers** (RNA expression profiles, Rb1/PTEN/TP53 or SPOP mutations) with **prognostic value**



Can we define **predictive biomarkers** to **decide who needs** (and who can be spared of) **chemotherapy**?

Are there any patients that **do not benefit from doublet (ADT + ARPi)** therapy?

ASCO Genitourinary Cancers Symposium

MRC Clinical Trials Unit

UCL

STOPCAP M1

FUNDED BY PROSTATE CANCER UK

Which patients with metastatic hormone-sensitive prostate cancer (mHSPC) benefit more from androgen receptor pathway inhibitors (ARPIs)?

STOPCAP meta-analysis of individual participant data

David Fisher, C Vale, L Rydzewska, P Godolphin, N Agarwal, G Attard, K Chi, N Clarke, I Davis, K Fizazi, S Gillessen, G Gravis, N James, D Matheson, R Oldroyd, M Parmar, C Sweeney, B Tombal, I White, J Tierney

PRESENTED BY: David Fisher, MRC Clinical Trials Unit at UCL, London

Aims of current analysis:

- Do effects vary between classes of ARPI?
- Do ARPI effects vary by patient or disease characteristics?

Available: 7 trials; 7,778 patients (70%)

- 4 trials of androgen biosynthesis inhibitors; 4,685 patients (100%)
  STAMPEDE (abi), LATITUDE (abi), PEACE-1 (abi), SWOG 1216 (ort)*
- 3 trials of "amides" ± abiraterone; 3,093 patients (48%)
  ENZAMET (enz), TITAN (apa), STAMPEDE (abi + enza)

Design

- Pairwise meta-analysis of individual participant data (IPD) from completed trials

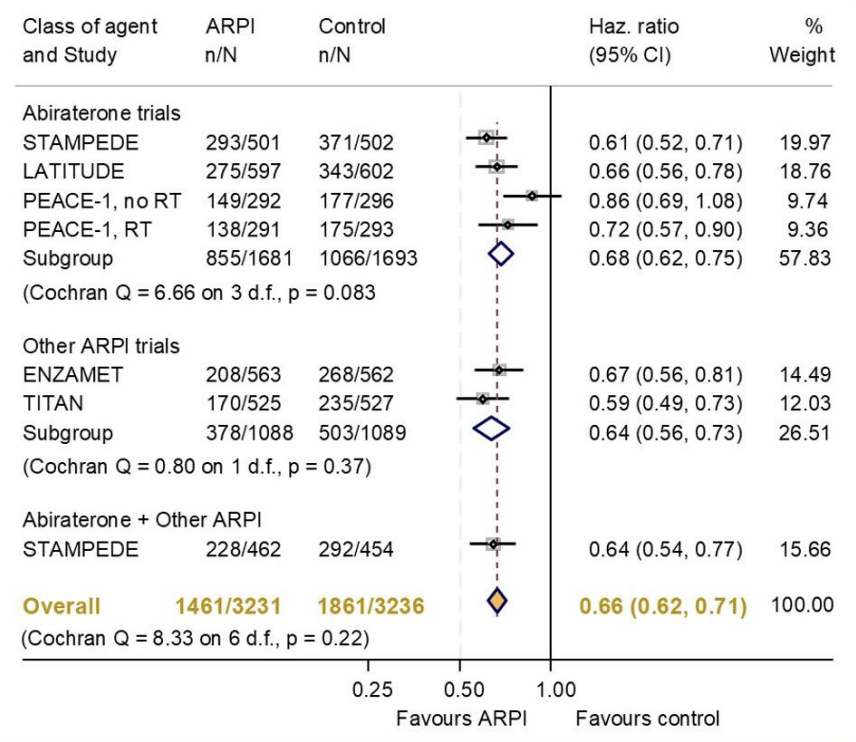
Outcomes

- Overall survival (OS): primary outcome for main effects
- Progression-free survival (PFS): primary outcome for subgroup analyses
  - To increase power, with OS as sensitivity
  - Defined as time to first clinical progression, radiological progression or death
- Prostate cancer specific survival (PCSS): sensitivity outcome

- ITT, two-stage, fixed-effect IPD* meta-analysis of hazard ratios (HRs)
  - With pre-specified sensitivity analyses
- Adjusted for core set of covariates
  - Age, PSA, performance status, Gleason, timing of diagnosis
- Adjusted for trial-adaptive changes or protocol modifications
  - Docetaxel as part of standard care
- 5-year absolute differences from HRs and appropriate baseline rates

Trial ID	Synchronous	High volume	Median age (IQR)	Docetaxel as part of SOC	cT4*	No. of participants	Follow-up (years)	Survival (years)
STAMPEDE (abi)	94%	56%*	67 (62-71)	0%	28%	1,003	8.0	3.8
LATITUDE (abi)	100%	94%	65 (60-70)	0%	27%	1,199	4.3	3.0
PEACE-1 (abi)	100%	57%	67 (60-72)	61%†	19%	1,172	6.0	4.6
ENZAMET (enz)	68%*	54%	69 (64-75)	45%†	14%	1,125	5.7	6.1
TITAN (apa)	86%*	63%	65 (60-70)	11%‡	19%	1,052	3.7	4.4
STAMPEDE (abi+enz)	93%	53%*	69 (63-74)	9%§	26%	916	6.0	4.3
SWOG 1216 (ort)	Unknown	Unknown	68 (62-74)	0%	Unknown	1,311	6.9	6.3

Effects of ARPIs on OS by class of agent



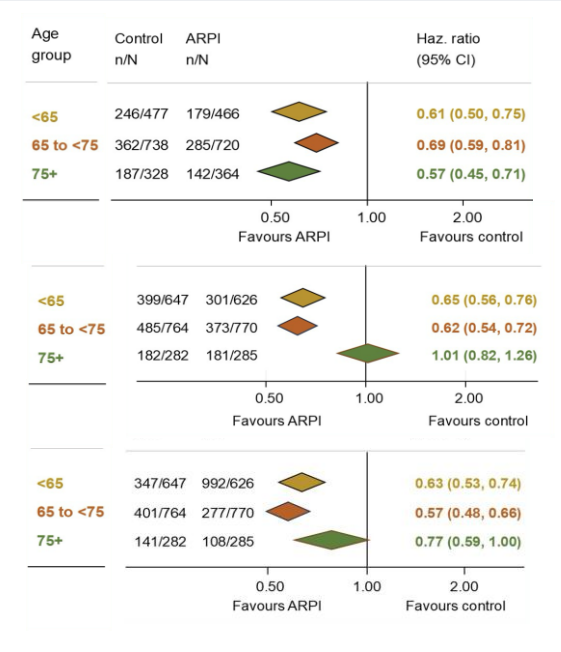
- Clear benefit of ARPIs on OS
  - HR = 0.66 (CI 0.62 to 0.71)
  - 13% absolute improvement at 5 years
- Clear benefit of ARPIs on PFS
  - HR = 0.51 (CI 0.48 to 0.55)
  - 21% absolute improvement at 5 years
- No clear difference by class of agent
  - Based on 48% “amide” data
- No clear difference in the effects of ARPIs on PFS by
  - **Volume** of metastases
  - **Timing** of metastatic diagnosis
  - Clinical T-stage
  - Gleason sum score
  - Nodal involvement
  - Location of metastases
  - WHO performance status
  - BMI at randomisation
- Similar results for sensitivity analysis

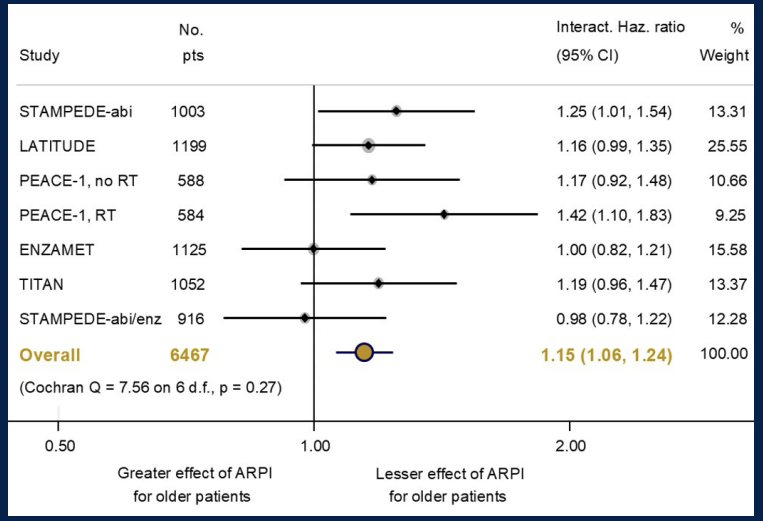
Effect of ARPIs by age subgroup

Amide trials (OS): Interaction HR 0.93; p=0.61

Abiraterone trials (OS): Interaction HR 1.56; p=0.001

Abiraterone trials (PCSS): Interaction HR 1.23; p=0.19





		PFS	OS	PCSS*
Younger age groups (<75)	Abiraterone trial data	~25%	~16%	~17%
	Amide (± abi) trial data	~27%	~18%	?
Oldest age group (75+)	Abiraterone trial data	~8%	~0%	~9%
	Amide (± abi) trial data	~27%	~19%	?

- Clear benefit of ARPIs on OS & PFS for majority of mHSPC patients
- For younger patients, clear benefit from all ARPIs
- For older patients, consider benefits/risks of abiraterone and “amides”
- First meta-analysis of individual participant data from ARPI trials

- Metastatic, castration-resistant prostate cancer

- Metastatic, hormone-sensitive prostate cancer
  - Factors associated with outcome in ARPI-treated patients

- **Localized prostate cancer / Active Surveillance**

  - Oral session. #309. Roy et al. Radical prostatectomy (RP) versus radiotherapy (RT) in high-risk prostate cancer (HR-PCa): Emulated randomized comparison with individual patient data (IPD) from two phase III randomized trials (RCTs)
  - Oral session. #308. Zhao et al. Gene signature predictor of dose-response to prostate radiation: Validation of PORTOS in phase III trials

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Radical Prostatectomy vs Radiotherapy in High-Risk Prostate Cancer: Individual Patient Data from two Phase III Randomized Trials

Soumyajit Roy, Yilun Sun, James Andrew Eastham, Martin Gleave, Himisha Beltran, Amar U. Kishan, Angela Y Jia, Nicholas G. Zaorsky, Jorge A. Garcia, Eric J. Small, Paul L. Nguyen, Gerhardt Attard, Rana R. McKay, Alton Oliver Sartor, Seth A. Rosenthal, Susan Halabi, Mack Roach III, Felix Y Feng, Michael J. Morris, Howard M. Sandler, Daniel E. Spratt

University Hospitals Seidman Cancer Center · RUSH · Memorial Sloan Kettering Cancer Center · Vancouver Prostate Centre · Dana-Farber Cancer Institute · UCLA Jonsson Comprehensive Cancer Center · NRG Oncology · CALGB · UC San Diego Moores Cancer Center · ICR The Institute of Cancer Research · Duke Cancer Institute · Cedars Sinai · UCSF · Mayo Clinic

PRESENTED BY: Soumyajit Roy, MBBS, MSc.

- **Primary objective:**
  - To compare the cumulative incidence of distant metastasis (DM) between treatment groups considering deaths as competing events.

CALGB 90203 (PUNCH)

High-risk Prostate Cancer

- cT1-T3a
- PSA ≤100 ng/mL
- Gleason score of 8-10
- Kattan nomogram predicted bPFS probability of <60% at 5-years

→ **RP w/ personalized post-op therapy**
23% received adjuvant RT
49% received salvage therapy.

→ **RP w/ personalized post-op therapy + 6 c of neoadjuvant docetaxel and ADT**
13% received adjuvant RT
39% received salvage therapy

Extended pelvic LN dissection used in both arms.

NRG/RTOG 0521

High-risk Prostate Cancer

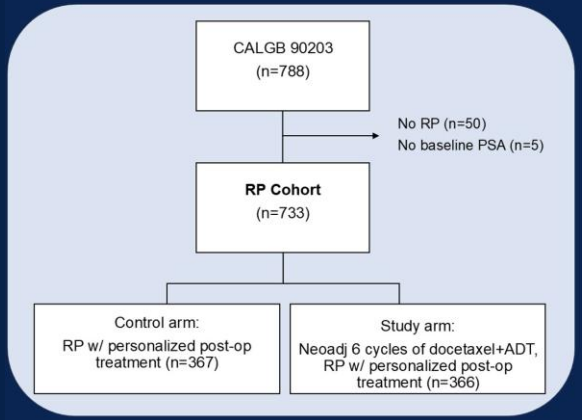
- GS 9-10
- GS 7-8 + PSA >20-150 ng/mL
- GS 8 + PSA <20 ng/mL + ≥cT2

→ **RT plus Long-term ADT**

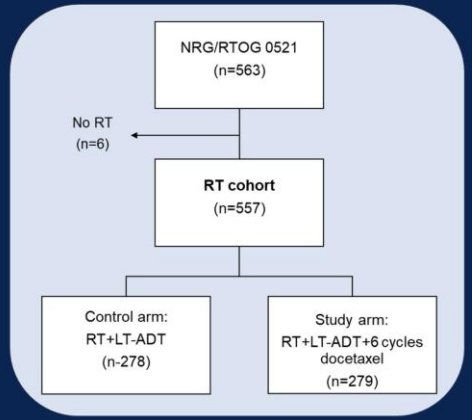
→ **RT plus Long-term + 6 c of adjuvant docetaxel**

RT: 72-75.6 Gy with nodal coverage
ADT: 24 months of GnRH agonist

Radical Prostatectomy Cohort

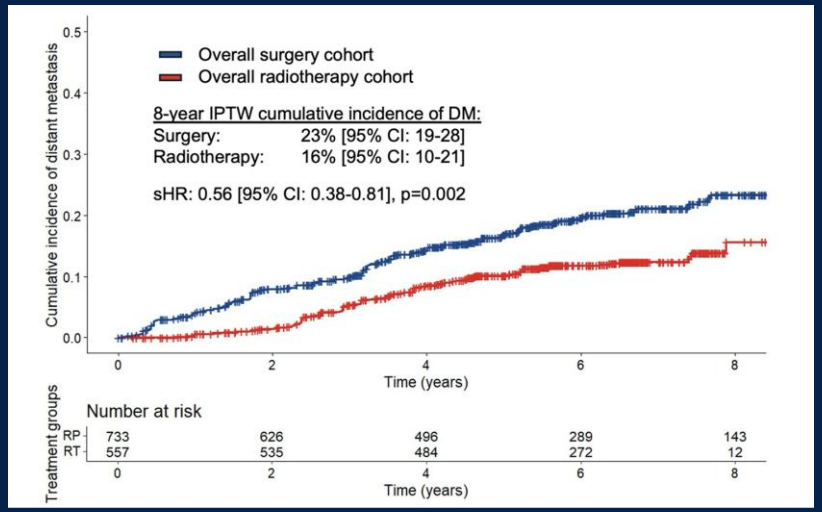


Radiotherapy Cohort

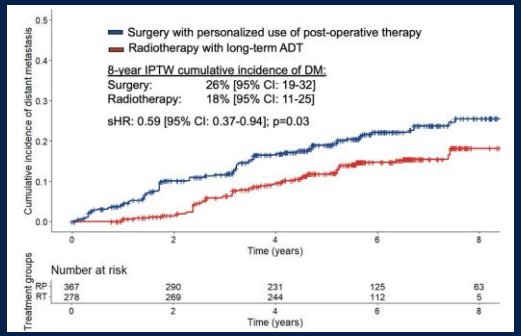


	Surgery-based treatment (n=733)	RT-based treatment (n=557)	P-value
Age			
Median (IQR)	63 (57 to 67)	66 (60 to 72)	<0.001
>70	69 (9%)	173 (31%)	
Biopsy Gleason score			
6-7	93 (13%)	89 (16%)	0.03
8	279 (38%)	176 (32%)	
9-10	361 (49%)	292 (52%)	
Clinical tumor stage			
T3-T4	127 (17%)	152 (27%)	<0.001
Baseline PSA			
Median (IQR)	10 (6.0 to 20)	15 (7.0 to 34)	<0.001
>20 ng/mL	187 (25%)	236 (43%)	
Risk Groups			
High (NCCN)	578 (79%)	379 (66%)	<0.001
Very High (STAMPEDE)	155 (21%)	178 (34%)	

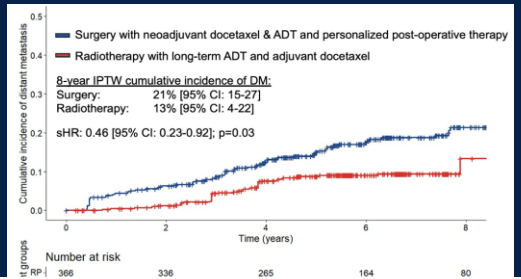
Primary objective: Overall Cohort



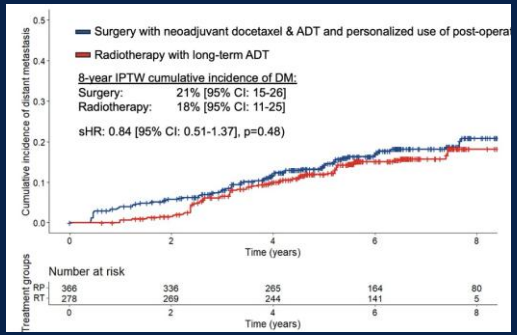
RT+LT-ADT vs RP+Personalized Post-op Rx



Docetaxel arm

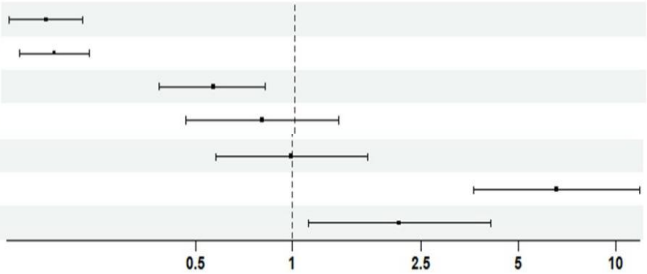


RT+LT-ADT vs Chemo +ADT +RP +Personalized Post-op Rx



Secondary endpoints

Endpoints	8-yr Incidence (RP)	8-yr Incidence (RT)	IPTW HR [95% CI]
Biochemical recurrence	0.72 (0.67-0.76]	0.30 [0.24-0.35]	0.17 [0.13-0.22]
Progression	0.77 [0.72-0.80]	0.33 [0.27-0.38]	0.18 [0.14-0.23]
Distant Metastasis (DM)	0.23 [0.19-0.28]	0.16 [0.10-0.21]	0.56 [0.38-0.81]
PCSM1 (Death after Progression)	0.15 (0.10-0.19)	0.11 (0.07-0.15)	0.79 (0.46-1.36)
PCSM2 (Death after DM)	0.10 [0.06-0.13]	0.08 [0.05-0.12]	0.99 [0.58-1.71]
OCM1 (Death without Progression)	0.01 [0.004-0.02]	0.11 [0.07-0.15]	6.57 [3.64-11.85]
OCM2 (Death without DM)	0.07 [0.03-0.10]	0.14 [0.09-0.18]	2.14 [1.12-4.10]

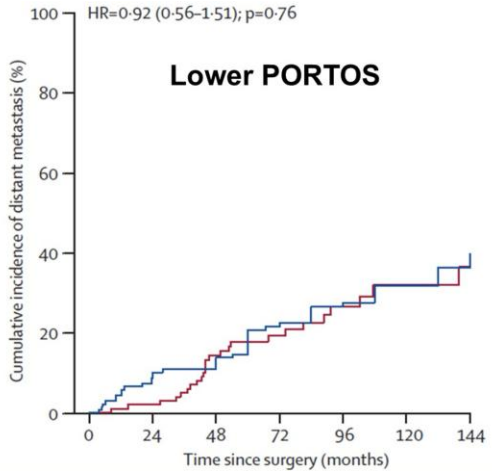


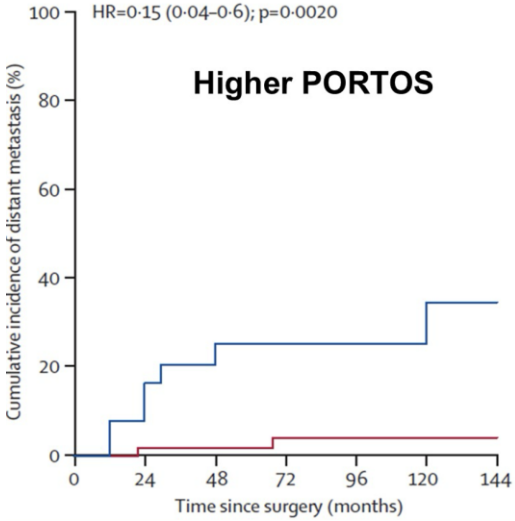
ASCO® Genitourinary Cancers Symposium

Gene signature predictor of dose-response to prostate radiation: Validation of PORTOS in phase III trials

Shuang (George) Zhao, Hyunnam Monica Ryu, James A. Proudfoot, Elai Davicioni, Jeff M. Michalski, Daniel E. Spratt, Stefanie Hayoz, Jeffry Simko, Howard M. Sandler, Alan Pollack, Matthew Parliament, Ian S. Dayes, Rohann Jonathan M. Correa, Theodore Karrison, William A. Hall, Daniel M. Aebersold, Felix Y. Feng, Pirus Ghadjar, Phuoc T. Tran, Alan Dal Pra

PRESENTED BY: Shuang (George) Zhao MD, University of Wisconsin





PORTOS: 24-gene prostate cancer RT gene expression score

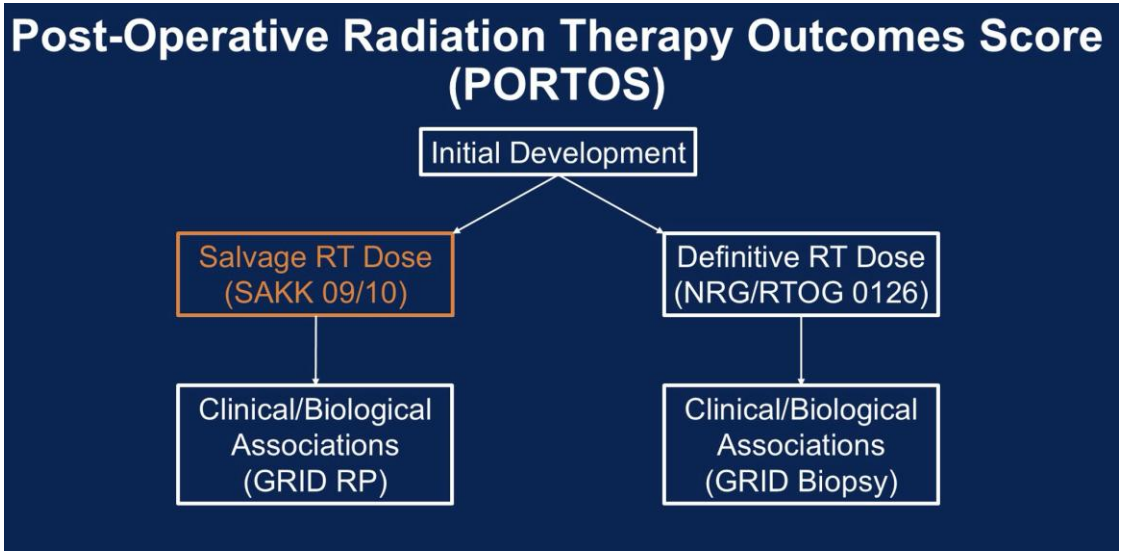
Developed (Zhao et al Lancet Oncol 20169 on retrospective cohort studies

High PORTOS score associated with benefit from postoperative radiotherapy

Validation in independent clinical trials:

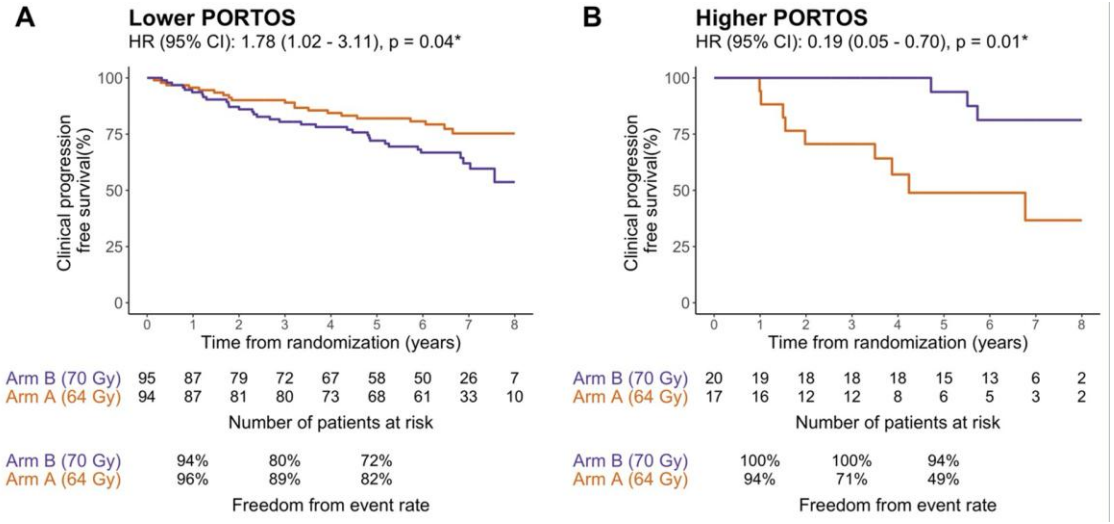
RTOG 0126 showed a benefit for RT dose escalation (DE) from 70.2Gy to 79.2Gy (primary RT)

SAKK 09/10 did not show a benefit from 64Gy to 70Gy (salvage RT)

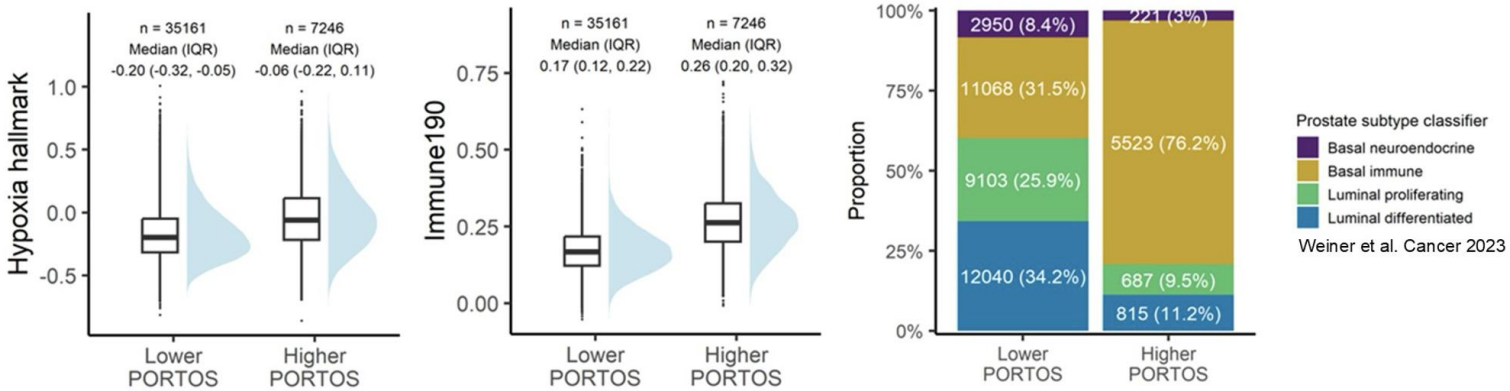


SAKK 09/10

Biochemically-recurrent prostate cancer patients. Salvage radiation 64Gy vs. 70Gy

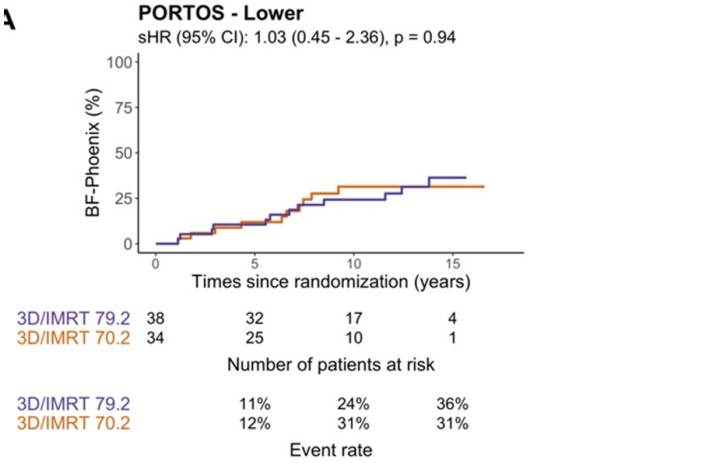


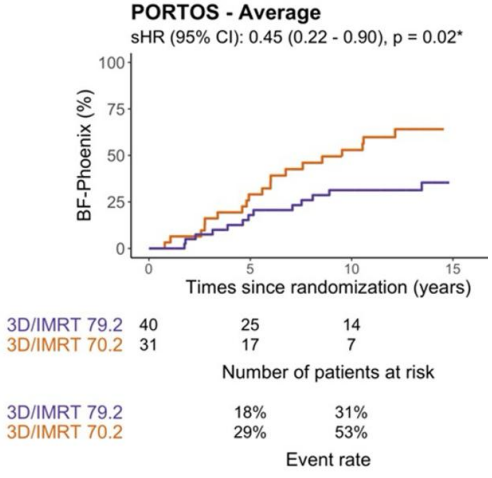
No association with clinico-pathological features
Associated with immune/hypoxia signatures

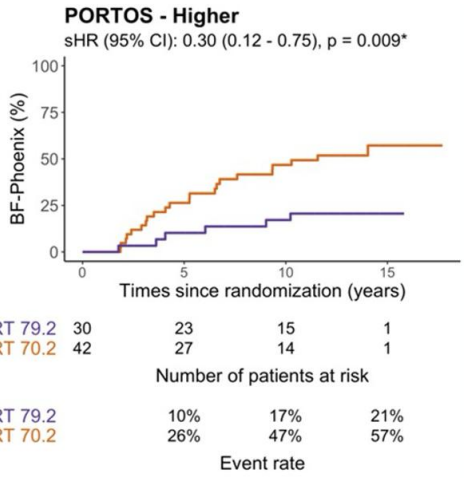


RTOG 0126

Intermediate-risk
prostate cancer patients
Definitive radiation
70.2Gy vs. 79.2Gy.







No association with clinico-pathological features
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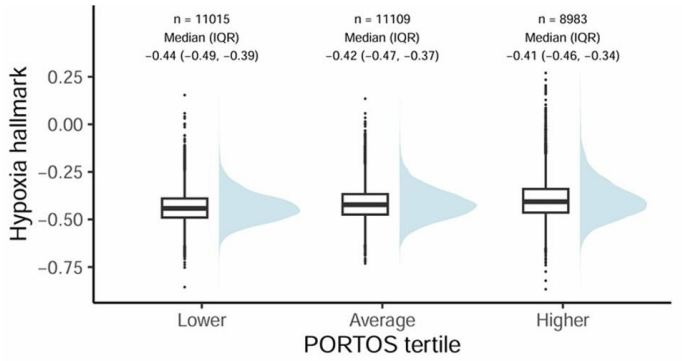
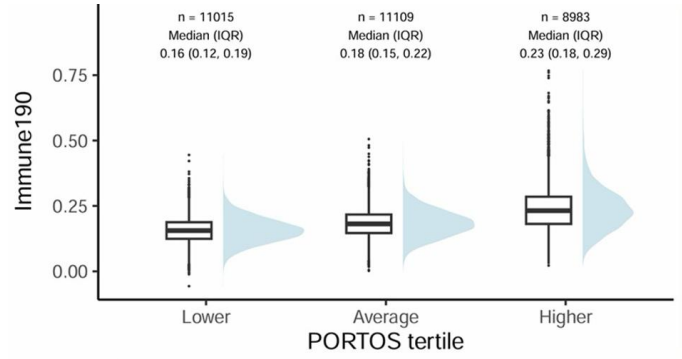




ASCO Genitourinary Cancers Symposium

A High Omega-3, Low Omega-6 Diet with Fish Oil for Men with Prostate Cancer on Active Surveillance: The CAPFISH-3 Randomized Clinical Trial

William J. Aronson, Tristan Grogan, Pei Liang, Patricia Jardack, Amana Liddell, Claudia Perez, Mikayla Lerman, David Elashoff, Jonathan W. Said, Pinchas Cohen, Leonard S. Marks, Susanne M. Henning

VA Greater Los Angeles Healthcare System, Los Angeles, CA; Department of Medicine Statistics Core, Department of Urology, Department of Pathology, University of California Los Angeles; Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA.

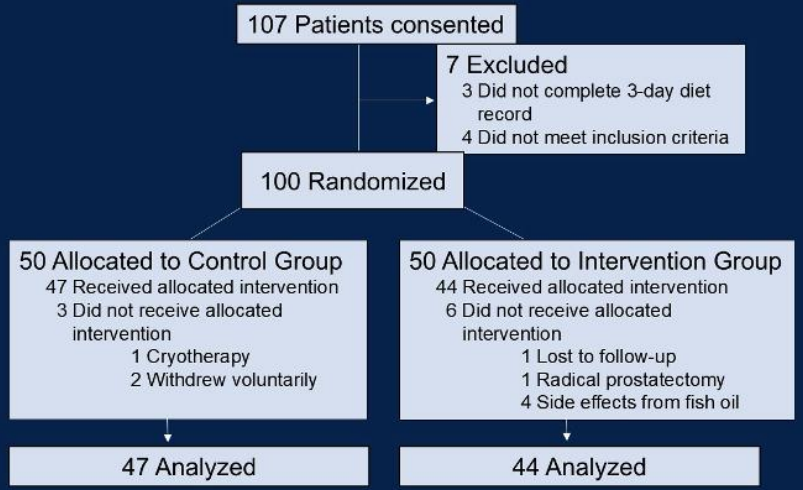
The influence of boosting gut health and phytochemical rich foods in men with prostate cancer

Prof Robert Thomas, Madeleine Williams, Dr Jeff Aldous, Prof Robert U. Newton, Dr A Mitra, Dr S Russel, Mr Z Fazili, Prof Stacey A. Kenfield

Bedford & Addenbrookes Cambridge University Hospitals. Bedford University and UCLH
Urology & Biostatistics, University of California, (UCSF), USA
Exercise Medicine Research Institute, Edith Cowan University, Australia

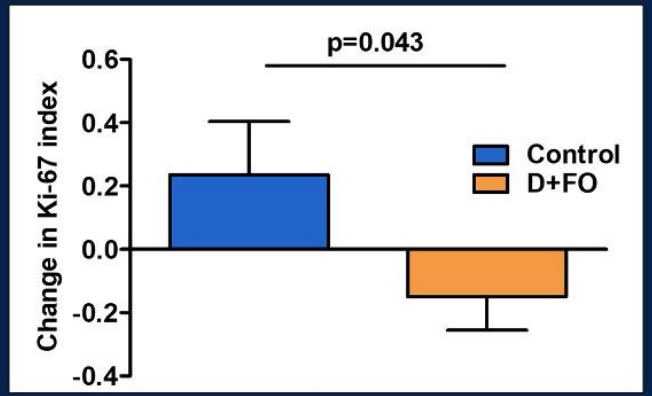
CAPFISH-3 Trial

- Single center, Phase II, randomized, open label, two-arm study in men on active surveillance for prostate cancer



- <30% of calories from fat with decreased consumption of foods high in omega-6 fatty acids such as corn oil, fried foods, highly processed foods and chips, and to increase intake of omega-3 rich foods (e.g. salmon, tuna)
- ω-6 to ω-3 fat intake ratio of less than 4:1
- EPA+DHA intake 2.2 g per day in fish oil capsules
- Control group instructed not to take fish oil

Primary Endpoint Ki-67 Index



Ki-67 index increased by 24% in the control group and decreased by 15% in Diet + FO group

- Reduced triglyceride levels
- Reduced macrophage colony stimulating factor levels
- No change in tumor volume, Grade Group, PSA, or Decipher score

The influence of boosting gut health and phytochemical rich foods in men with prostate cancer

220 men CaP surveillance PSA increasing

215 accepted → 3 withdrew pre randomisation

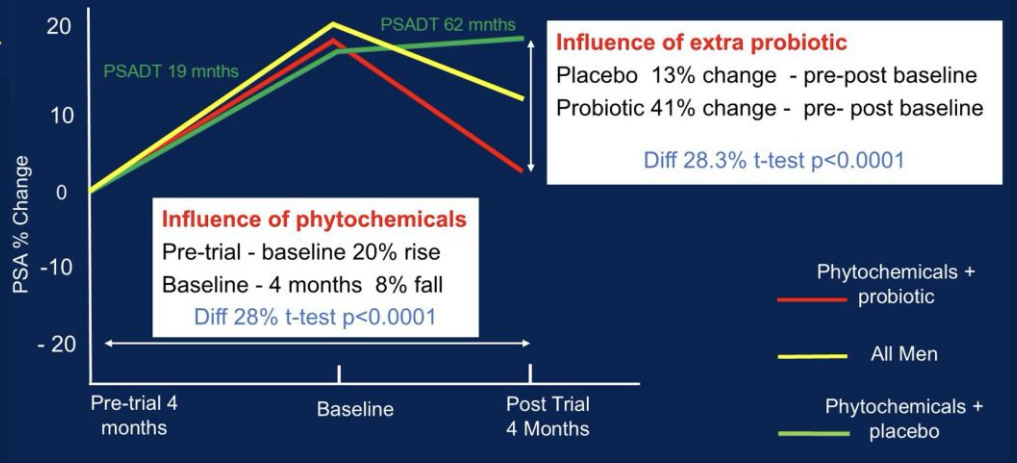
Randomisation 1:1

107 men

Blinded Probiotic

105 men

Blinded Placebo



Influence of extra probiotic

Placebo 13% change - pre-post baseline

Probiotic 41% change - pre- post baseline

Diff 28.3% t-test p<0.0001

Influence of phytochemicals

Pre-trial - baseline 20% rise

Baseline - 4 months 8% fall

Diff 28% t-test p<0.0001

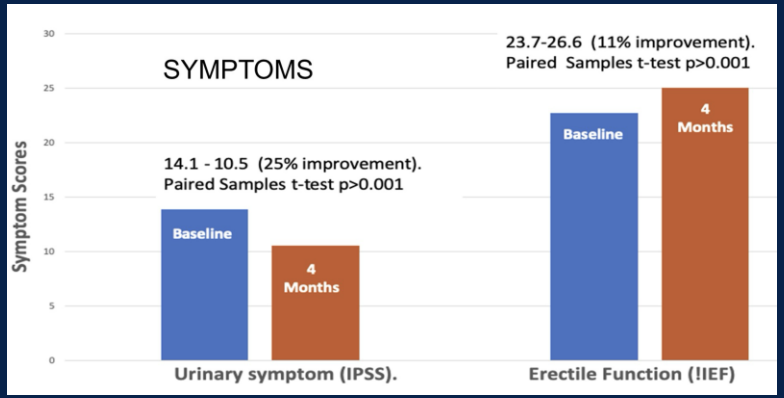
Demographics

- Histologically confirmed Ca Prostate,
- Cambridge Prognostic Group 1-2
- Managed with surveillance.
- No Androgen Deprivation Therapy

End points

- PSA dynamics (pre to baseline then 4 months post intervention between 2 groups)

- MRI changes (180 men)
- Urinary symptoms (IPSS)
- Erectile function (IIEF)



ASCO GU 2025 – What's new?

- Talazoparib + enzalutamide prolongs survival in an all-comer population. Benefit varies across molecular subgroups.
  - Adequately balance expected efficacy and toxicity for an individualized approach

- Lu-177-PSMA-617 + enzalutamide prolongs survival in 1st line mCRPC
  - Secondary analysis of a trial powered por PSA response
  - Signs of synergy between hormone therapy and radioligand therapy

- Other enzalutamide combinations (mevrometostat) may be relevant in the future

- Metastases directed-therapy increases rPFS in oligometastatic mCRPC
  - Supports a widely utilized practice in clinic

- Benefit of hormonal agents in mHSPC (abiraterone) may be lower for older patients
  - Should patients >75 years receive enzalutamide/apalutamide/darolutamide?

- Radiotherapy + ADT may provide superior MFS than surgery for high-risk localized prostate cancer
- Molecular signatures may identify which patients need increased RT dose

GONORTE
Grupo Oncológico

ACTUALIZACIONES TRAS EL CONGRESO AMERICANO DE ONCOLOGÍA CLÍNICA GU