mHSPC: Chemo-hormonal Therapy and Treatment Intensification

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Disclosures

Consultant: Astellas; AstraZeneca; BMS; Bayer; Caris Life Sciences Eisai; Exelixis; Ipsen; JNJ, Dendreon; Pfizer, Seattle Genetics, Guardant Health; Novartis; MJH; Medscape; UroToday

Contracted Research: AstraZeneca, Merck, BlueEarth Diagnostics, Merck, Exelixis
Caris Life Sciences, ESSA Pharma

Equity: Luminate

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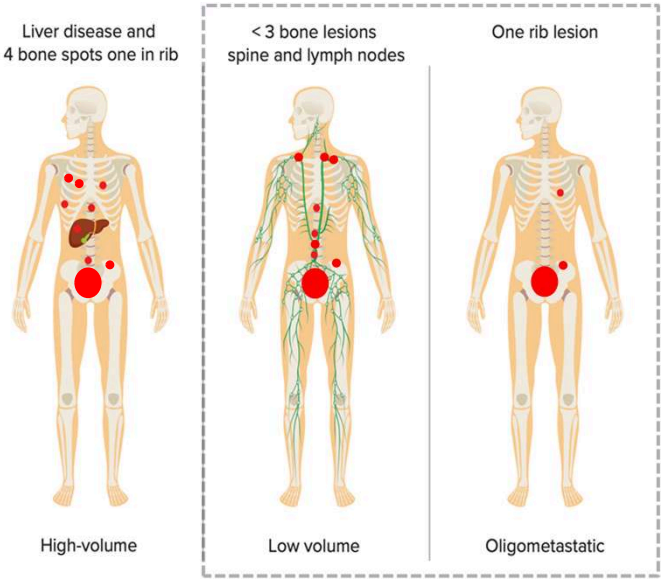
Metastatic Disease is Heterogenous

1. Newly diagnosed

- 5%-8%
- ↑ with PSMA PET

2. Recurrent

- More frequent > *de novo*
- ↑ with PSMA PET

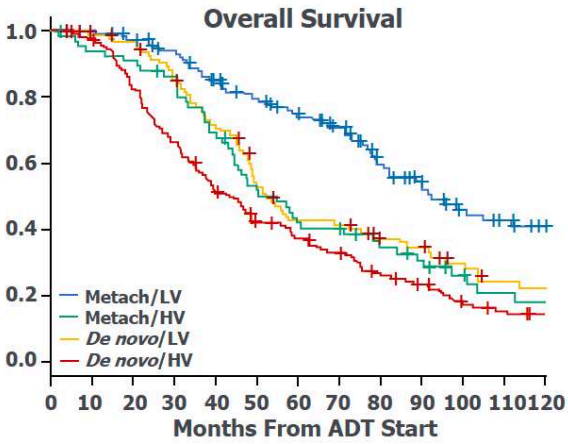


Barata P et al, Cancer 2019; Sorce et al, Prostate 2022; cancer.gov access 2023

Prognosis according to volume and presentation at diagnosis

High-volume de Novo Metastatic Disease Is Associated With the Poorest Prognosis

Groups	N (% events)	mOS, years (95% CI)
Metach/ Low Vol	125 (50)	7.7 (6.7, 10.6)
Metach/ High Vol	67 (75)	4.6 (3.7, 6.7)
De novo/ Low Vol	96 (70)	4.3 (4.0, 6.5)
De novo/ High vol	148 (84)	3.6 (3.1, 4.7)



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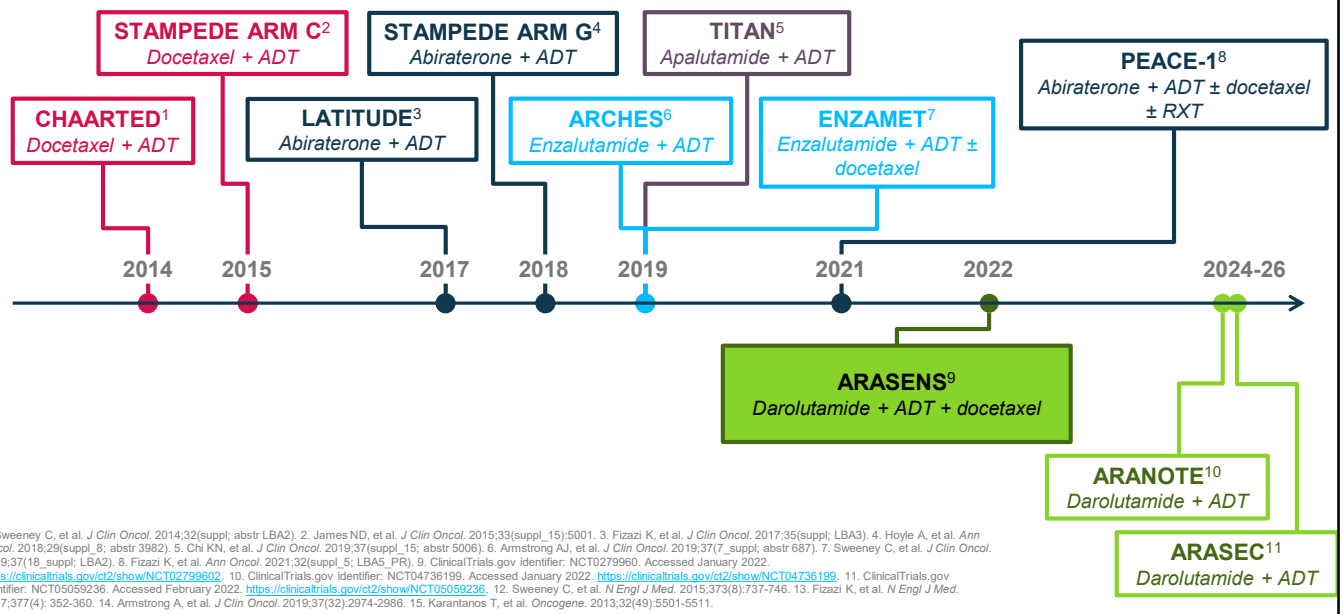
The Standard of Care in mHSPC



1. Sweeney C, et al. *J Clin Oncol*. 2014;32(suppl; abstr LBA2). 2. James ND, et al. *J Clin Oncol*. 2015;33(suppl_15):5001. 3. Fizazi K, et al. *J Clin Oncol*. 2017;35(suppl; LBA3). 4. Hoyle A, et al. *Ann Oncol*. 2018;29(suppl_8; abstr 3982). 5. Chi KN, et al. *J Clin Oncol*. 2019;37(suppl_15; abstr 5006). 6. Armstrong AJ, et al. *J Clin Oncol*. 2019;37(7_suppl; abstr 687). 7. Sweeney C, et al. *J Clin Oncol*. 2019;37(18_suppl; LBA2). 8. Fizazi K, et al. *Ann Oncol*. 2021;32(suppl_5; LBA5_PR). 9. ClinicalTrials.gov identifier: NCT0279960. Accessed January 2022. https://clinicaltrials.gov/ct2/show/NCT02799602. 10. ClinicalTrials.gov identifier: NCT04736199. Accessed January 2022. https://clinicaltrials.gov/ct2/show/NCT04736199. 11. ClinicalTrials.gov identifier: NCT05059236. Accessed February 2022. https://clinicaltrials.gov/ct2/show/NCT05059236. 12. Sweeney C, et al. *N Engl J Med*. 2015;373(8):737-746. 13. Fizazi K, et al. *N Engl J Med*. 2017;377(4): 352-360. 14. Armstrong A, et al. *J Clin Oncol*. 2019;37(32):2974-2986. 15. Karantanos T, et al. *Oncogene*. 2013;32(49):5501-5511.

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Summary of HR for OS in Phase 3 Trials Evaluating ARPIs in mHSPC

M1 HSPC	All M1	High Volume	Low Volume	M0 at First Diagnosis - Metachronous M1
LATITUDE – Abiraterone (All *de novo*; N=1,199)	**0.66** (0.58-0.78)	**0.62** (0.52-0.74)	**0.72** (0.47-1.10)	N/A
STAMPEDE – Abiraterone (>90% *de novo*; N=999)	**0.60** (0.49-0.71)	**0.54** (0.43-0.69)	**0.55** (0.41-0.76)	N/A
PEACE-1 – Abiraterone (60% conc docetaxel; N=1,173)	**0.82** (0.69-0.98)	**0.72** (0.55-0.95)	**0.83** (0.50-1.39)	N/A
ENZAMET – Enzalutamide (45% conc docetaxel; N=1,125)	**0.67** (0.52-0.86)	**0.53** (0.42-1.09)	**0.39** (0.21-0.71)	**0.56** (0.29-1.06)
TITAN – Apalutamide (10% prior docetaxel; N=1,052)	**0.65** (0.53-0.79)	**0.70** (0.56-0.88)	**0.52** (0.35-0.79)	**0.39** (0.22-0.69)
ARCHES – Enzalutamide (18% prior docetaxel; N=1,150)	**0.66** (0.53-0.81)	**0.66** (0.52-0.88)	**0.66** (0.43-1.03)	N/A
ARASENS – Darolutamide + Docetaxel (77% high vol; N=1,305)	**0.68** (0.57-0.80)	**0.69** (0.57-0.82)	**0.68** (0.41-1.13)	N/A
ARANOTE – Darolutamide (72.5% *de novo*; N=669)	**0.81** (0.59-1.12)	**0.80** (0.57-1.13)	**0.90** (0.38-2.13)	N/A

Fizazi K, et al. *J Clin Oncol*. 2019;37(7_suppl):141. Hoyle AP, et al. *Eur Urol*. 2019;76(6):719-728. James ND, et al. *Ann Oncol*. 2020;31(suppl_4):S509. Davis ID, et al. *N Engl J Med*. 2019;381(2):121-131. Chi KN, et al. *N Engl J Med*. 2019;381(1):13-24. Chi KN, et al. *J Clin Oncol*. 2021;39(6_suppl):11. Smith MR, et al. *N Engl J Med*. 2022;386(12):1132-1142. Fizazi K, et al. *Lancet*. 2022;399(10336):1695-1707. Saad F, et al. *J Clin Oncol*. 2024;42(36):4271-4281.

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Significance of PSA responses in mHSPC

Deep prostate-specific antigen response and overall survival in patients with metastatic castration-sensitive prostate cancer: A systematic review and meta-analysis.

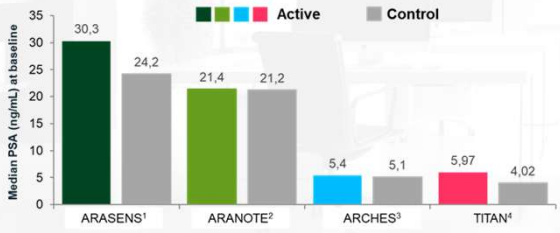
Authors: Syed Arsalan Ahmed Naqvi, Irbaz Bin Riaz, Manal Imran, Muhammad Daim Bin Zafar, Kunwer Sufyan Faisal, Zaryab Bin Riaz, Parminder Singh, and Alan Haruo Bryce | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 6_suppl • https://doi.org/10.1200/JCO.2023.41.6_suppl.195

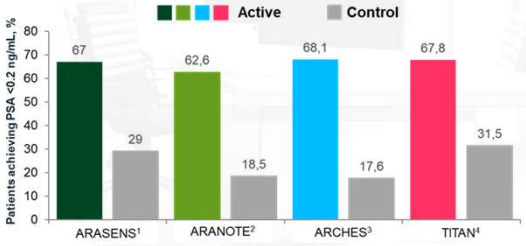
			Anticipated absolute effects	
Outcome	Participants (trials)	Hazard ratio (95% CrI)	Risk of death without deep PSA response within 8 months	Survival benefit with deep PSA response within 8 months
Overall survival	1980 (4 trials)	**0.41** (0.31 to 0.53)	347 deaths per 1,000	187 fewer deaths per 1,000; (223 fewer to 145 fewer)

Meta-analysis from: CHAARTED, LATITUDE , TITAN, PEACE1 and ARASENS

Median baseline PSA



Proportion of Patients With Undetectable PSA (<0.2 ng/mL) at Any Time



1. Smith MR, et al. N Engl J Med. 2022;386:1132–42. 2. Saad F, et al. J Clin Onol. 2024;42:4271–81. 3. Armstrong AJ, et al. J Clin Oncol. 2019;37:2974–86. 4. Chowdhury S, et al. Ann Oncol. 2023;34:477–85.

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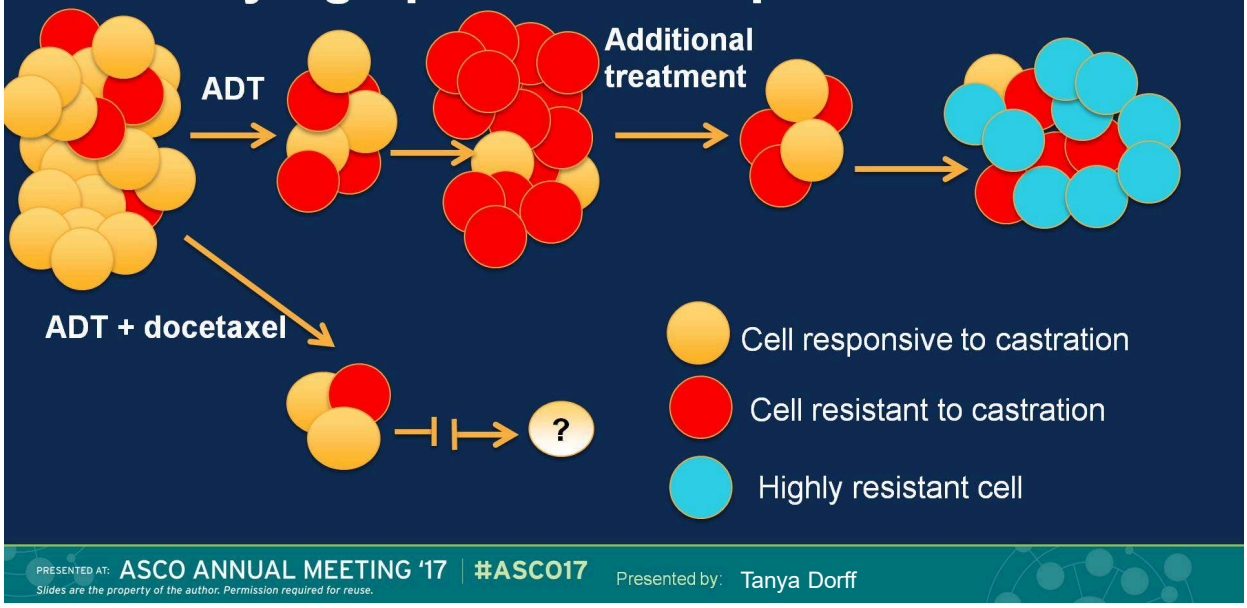
Intensifying up-front tx for prostate CA



PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: Tanya Dorff

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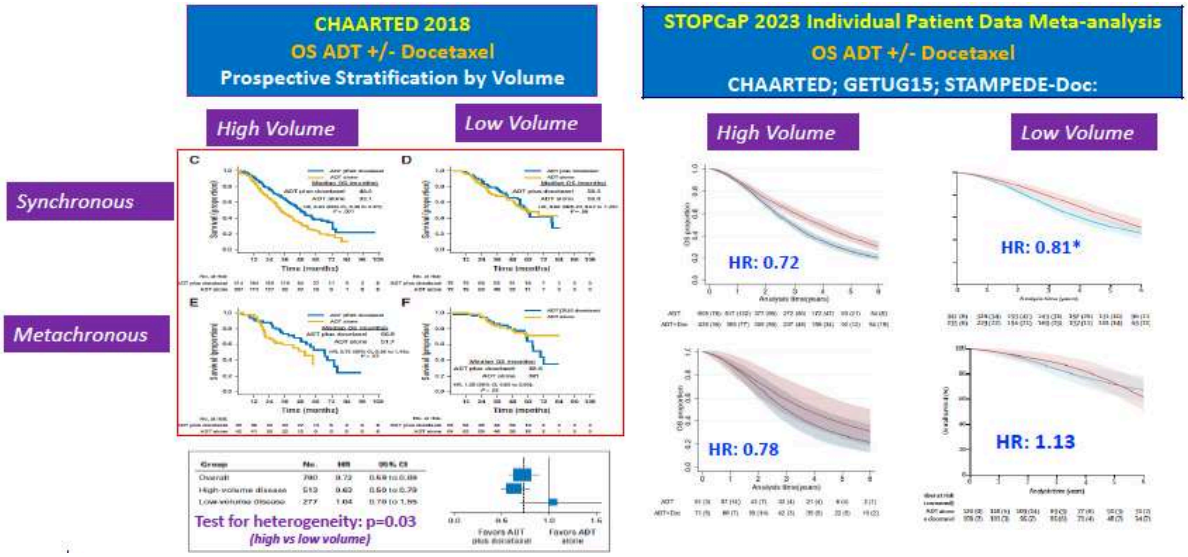
Clinical Factors predictive for Docetaxel Benefit: Volume



Kyriakopoulos et al. J Clin Oncol 2018; Vale et al. ASCO 2022

CHAARTED and GETUG-AFU15: Pooled Analysis

Median and 95% CI overall survival (in months) in the overall population and prespecified subgroups

		Overall population	HV	LV	*p* value [a]	Upfront	PRLT
		N = 790	*N* = 513	*N* = 277		*N* = 575	*N* = 214
CHAARTED	ADT + D	57.6	51.2	63.5		52	67.4
		(52; 63.9)	(45.2; 58.1)	(58.3; 78.5)		(45.5, 58.1)	(59, 74.3)
	ADT alone	47.2	34.4	NR		39.5	NR
		(41.8; 52.8)	(30.1; 42.1)	(59.8; NR)		(32.4; 45.2)	(57.6; NR)
		N = 385	*N* = 183	*N* = 202		*N* = 272	*N* = 108
GETUG-AFU15	ADT + D	62.1	39.8	NR		52.6	NR
		(49.5; 73.7)	(28; 53.4)	(69.5; NR)		(43.3; 66.8)	(69.5; NR)
	ADT alone	48.6	35.1	83.4		41.5	69.8
		(40.9; 60.6)	(29.9; 43.6)	(61.8; NR)		(36.3; 54.5)	(62.2; NR)
	Pooled average HR (95% CI), *p* value [c]	0.79	0.68	1.03	0.017	0.76	0.9
		(0.67; 0.93)	(0.56; 0.82)	(0.77; 1.38)		(0.63; 0.92)	(0.61; 1.33)
		0.004	<0.001	0.8		0.004	0.6
	p value [d]	0.07	0.3	>0.9		0.1	0.7

ADT = androgen deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio; HV = high volume; LV = low volume; NR = not reported; PRLT = prior local treatment.

Gravis et al, Eur Urol 2018

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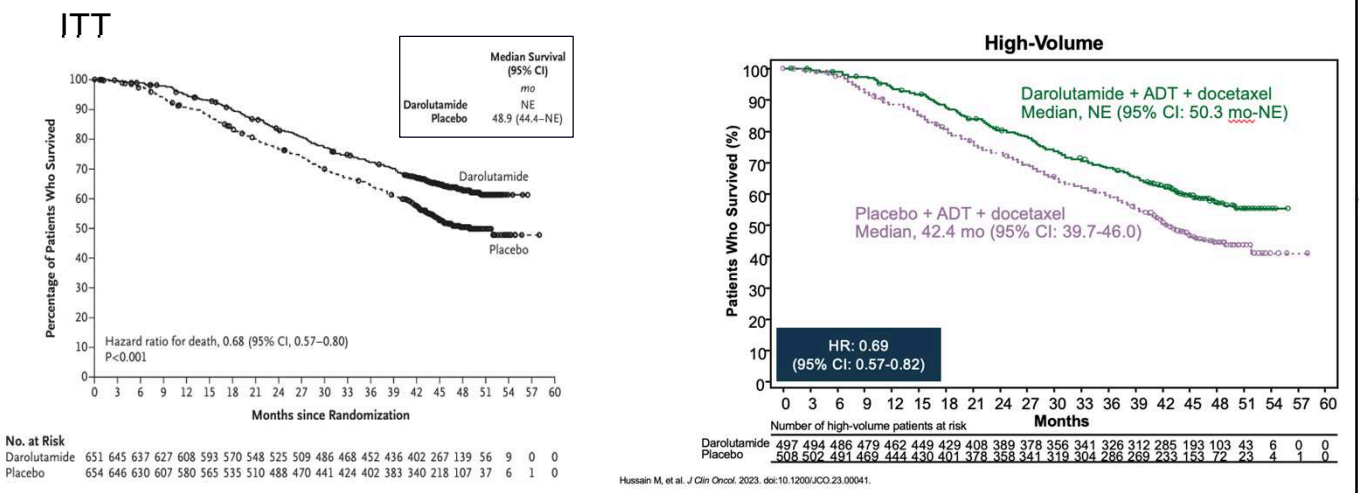
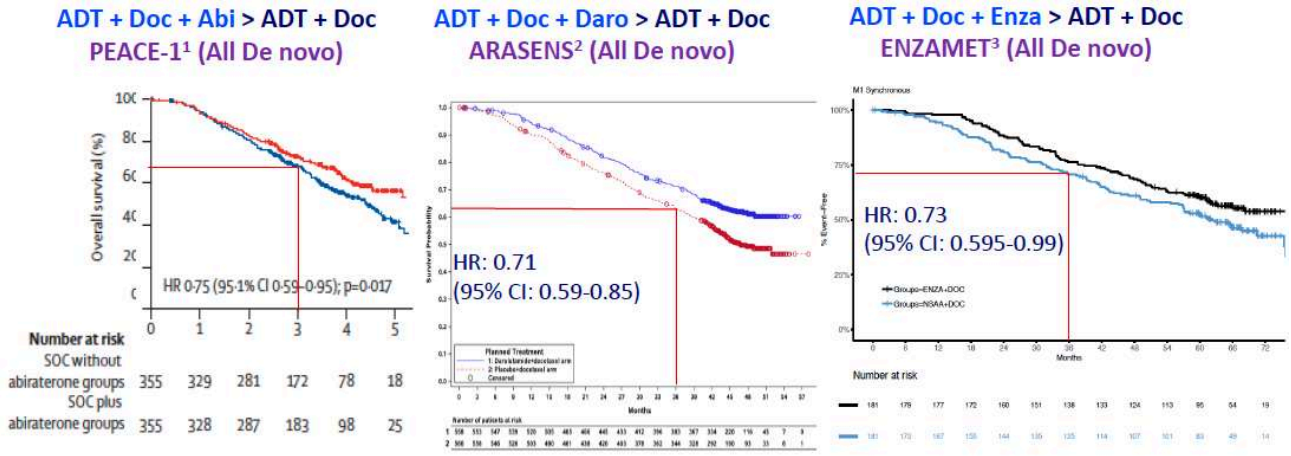
ARASENS Doc +- Daro (77% High-Volume / 86% *de novo*) OS



Hussain M, et al. *J Clin Oncol*. 2023. doi:10.1200/JCO.23.00041.

Adding an ARPI to Docetaxel in Synchronous mHSPC Consistently Improves OS



Fizazi Et al. Lancet 2022; Smith et al. NEJM 2022; Sweeney et al .Lancet Oncol 2023

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Who needs docetaxel?

STAMPEDE docetaxel and abiraterone phase 3 trials

Metastatic prostate cancer
≥ 1 metastases on bone / CT scan

High-risk localised (adjuvant)
Local lymph node positive or if negative,
≥ 2 high risk features:

T3/T4, PSA ≥40ng/ml, Gleason sum 8-10

3909 directly-randomised patients → ADT +/- docetaxel/docetaxel + zoledronic acid

3909 directly-randomised patients → ADT +/- ABI

Aim: To link tumour multi-gene expression signatures to 14-year prospective overall survival follow-up

95% synchronous M1

STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (MRC-PR08, NCT00268476) www.stampedetrial.org
STRATOSPHERE (STratification for RAtional Treatment-Oncomarker Pairings of STAMPEDE patients starting long-term Hormone treatment) protocol overseen by the STAMPEDE trial management groups and biological research group

James N *et al.* Lancet. 2016
Attard G *et al.* Lancet Oncol 2023

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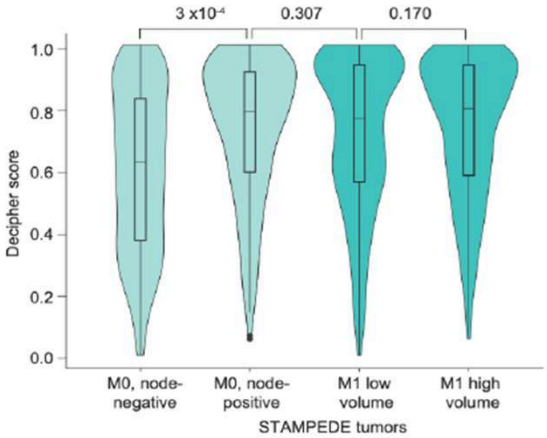
Can we use molecular data to identify pts? Decipher as the example

What is the Decipher classifier?

- 22 mRNA features[1]
- Designed to identify biological state associated with metastases
- Prognostic in localised disease[2]
- Associates with enrichment of cell cycle proliferation pathways



1. Erho N *et al.* PLOS one. 2013; 2. Nguyen P *et al.* Int J Radiat Oncol Biol Phys. 2023

M0, non-metastatic
M1 metastatic

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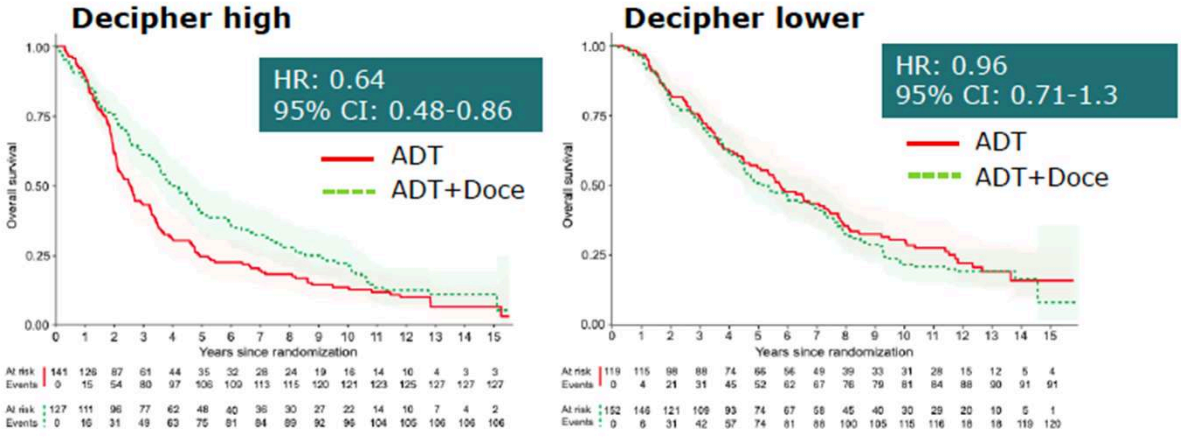
Decipher score predicts docetaxel efficacy in metastatic PC



High Decipher score identifies patients more likely to benefit from docetaxel
Biomarker-treatment interaction effect p value= 0.039*

No significant interaction effect demonstrated in non-metastatic disease

Kaplan-Meier estimates with 95% CI in lighter shade.
Decipher score dichotomized around median of metastatic cohort in combined docetaxel and abiraterone trials

BARCELONA 2024 ESMO congress

Emily Grist MBBS, MRCP, PhD

Interaction test from multivariable model adjusted for Gleason score, disease burden, age, pre-ADT PSA, WHO PS, nodal stage, tumor stage, NSAID/aspirin use, and metastatic volume.

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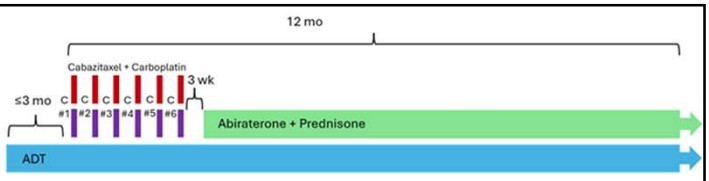
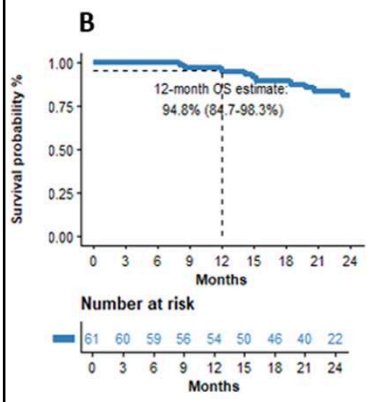
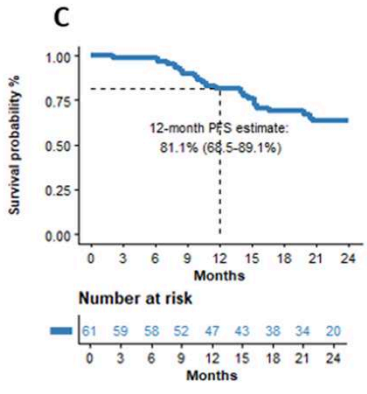
CASCARA Phase 2 trial
More Chemo than Docetaxel?



N=61 pts





Severity	Grade 1-2	Grade 3-4
Blood and lymphatic system disorders	19 (31.1%)	3 (4.9%)
Anemia	19 (31.1%)	3 (4.9%)
Febrile neutropenia	0	1 (1.6%)
Gastrointestinal disorders	32 (52.5%)	2 (3.3%)
Constipation	7 (11.5%)	0
Diarrhea	15 (24.6%)	0
Nausea	24 (39.3%)	1 (1.6%)
Vomiting	9 (14.8%)	2 (3.3%)
General disorders	32 (52.5%)	2 (3.3%)
Fatigue	32 (52.5%)	2 (3.3%)
Musculoskeletal and connective tissue disorders	8 (13.1%)	0
Muscle spasms	8 (13.1%)	0
Nervous system disorders	8 (13.1%)	0
Peripheral sensory neuropathy	8 (13.1%)	0
Skin and subcutaneous disorders	8 (13.1%)	0
Alopecia	8 (13.1%)	0
Vascular disorders	12 (19.7%)	0
Hot flash	12 (19.7%)	0
Special Considerations		**N (%)**
Number of Subjects with a Grade 3-5 TEAE		26 (43%)
Number of Subjects with a TEAE that caused a Drug Interruption/Hold		9 (15%)
Number of Subjects with a TEAE that caused a Dose Reduction		4 (6.6%)
Number of Subjects with a TEAE that caused Drug Discontinuation		6 (9.8%)

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Antonarakis, CCR 2026

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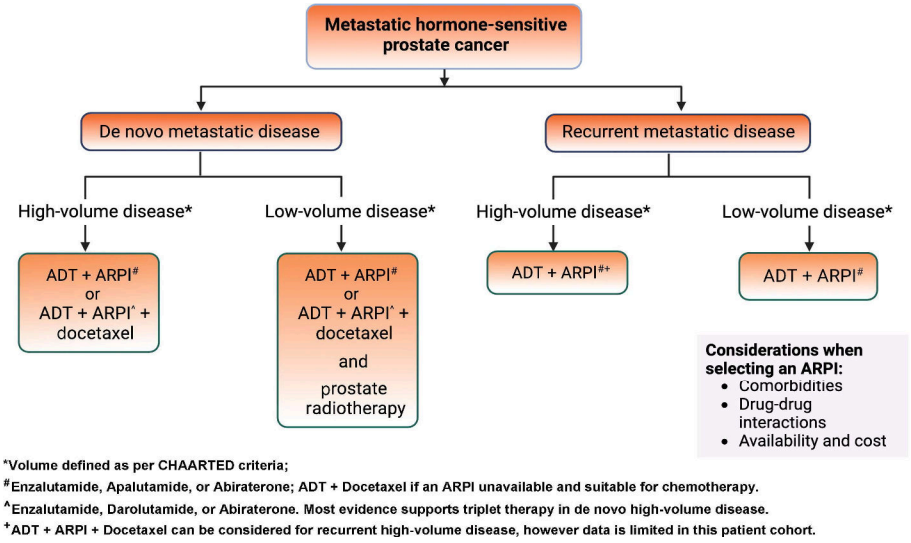
Treatment Intensification Strategies in mHSPC



*Volume defined as per CHAARTED criteria;
#Enzalutamide, Apalutamide, or Abiraterone; ADT + Docetaxel if an ARPI unavailable and suitable for chemotherapy.
^Enzalutamide, Darolutamide, or Abiraterone. Most evidence supports triplet therapy in de novo high-volume disease.
+ADT + ARPI + Docetaxel can be considered for recurrent high-volume disease, however data is limited in this patient cohort.

CCTG-PR26: Phase 3 TRIPLE-SWITCH

KEY ELIGIBILITY
- mCSPC (any volume/risk)
- Androgen Deprivation 6-12 months
- AR Pathway Inhibitor* >/= 4 months *(any of Abiraterone acetate, Enzalutamide, Apalutamide, or Darolutamide)*
- PSA ≥ 0.2 at enrolment
- Docetaxel naïve / eligible
- No evidence of progression by PSA, radiographic, or clinical since ADT

mCSPC
ADT 6-12 mo
ARPI* ≥ 4 mo
PSA ≥ 0.2

ctDNA at registration

RANDOMIZE 1:1

Arm A: Docetaxel 75mg/m² IV q3wk x6 + ADT + ARPI

Arm B: Standard ADT + ARPI

ctDNA C2, post C6, PD

PRIMARY ENDPOINT:
- Overall Survival

SECONDARY ENDPOINTS:
- Time to CRPC, PSA 50/90/<0.2/<0.02
- ctDNA

STRATIFICATION:
- PSA 0.2-4 vs >4
- ARPI class
- Liver metastases
- De novo vs Recurrent

SAMPLE SIZE:
- n=830, target HR 0.75

Study Chairs: Michael Ong (CCTG) and Alexandra Sokolova (SWOG)

CIHR IRSC | Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer | SWOG Cancer Research Network

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A032302 – Phase 3 "ASPIRE" Trial

Key Eligibility Criteria

All high volume or de novo low volume mCSPC

ADT+/-ARSI ≤120 days prior to registration

ECOG PS 0 -2

Candidate for docetaxel

NGS results available

n=1200
1:1

- ADT + Apalutamide + Docetaxel
- ADT + Apalutamide

Treatment until disease progression/ withdrawal and long-term follow-up for survival

Stratification
- TSG alteration 0 vs 1 vs 2+
- Volume of disease

TSG (tumor suppressor gene) altered will be defined as any copy number loss or deleterious mutation in one or more of the TSG (TP53, PTEN and RB1) **on tissue testing from any CLIA based assay.**

Primary Endpoint
- Overall survival

Secondary Endpoints
- rPFS
- Time to castration-resistant prostate cancer
- PSA response at 6 months and relation to rPFS and OS
- Safety and tolerability

Exploratory Endpoints
- Prognostic and predictive capability of Artera AI score
- Prognostic capability of Decipher score
- PSMA PET scan

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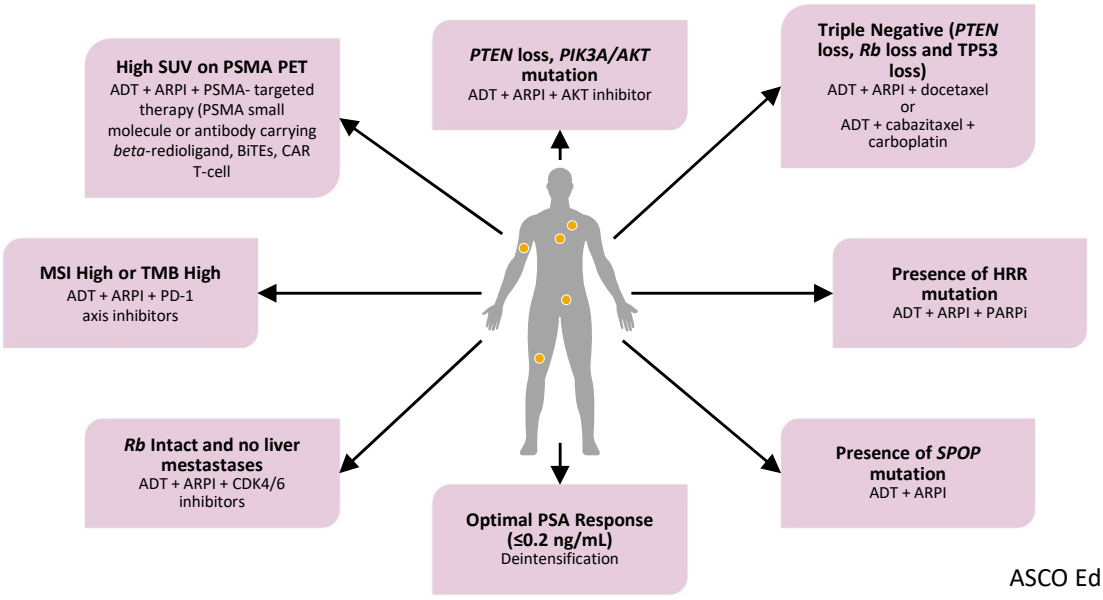
Personalizing Treatment Intensification in mHSPC



ASCO Ed Book, 2022

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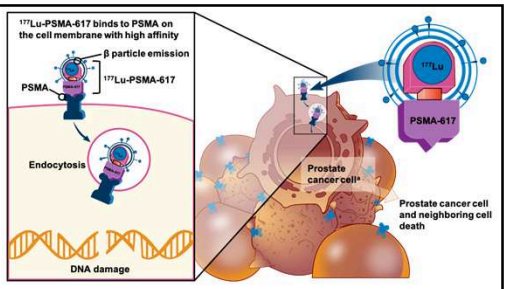
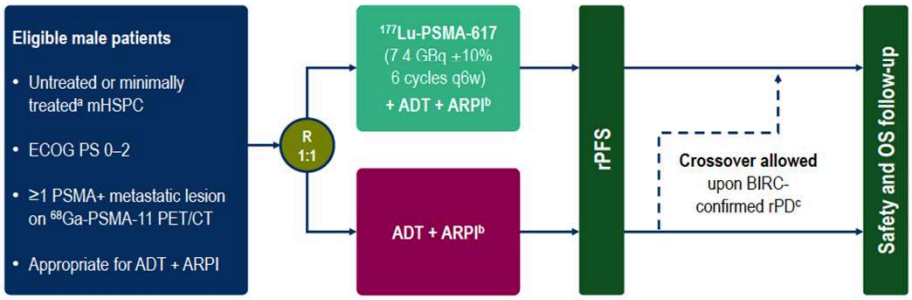
PSMAddition (mHSPC): ^{177}Lu-PSMA-617 with SOC vs SOC alone





Stratification factors
- Disease volume (high/low) – per CHAARTED criteria[1]
- Age ≥ 70 years (yes/no)
- Previous or planned treatment of primary tumour by radiation or prostatectomy (yes/no)

Follow-up periods
- rPFS: until event in all patients
- Safety: 30 days then 24 and 48 weeks after treatment discontinuation
- OS: every 90 days after last contact

1. https://www.clinicaltrials.gov/study/NCT04720157. 2. Tagawa S et al. ASCO 2023. Abstract TPS5116.

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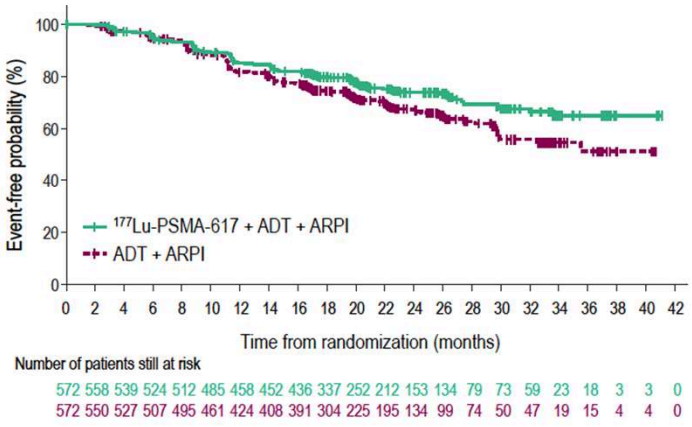
rPFS by BIRC – the primary endpoint was met

Data cut-off: 13 January 2025

PSMA Addition



	177Lu-PSMA-617 + ADT + ARPI (N = 572)	ADT + ARPI (N = 572)
Events – n (%) rPD Death without rPD	139 (24.3) 112 (19.6) 27 (4.7)	172 (30.1) 152 (26.6) 20 (3.5)
HR (95% CI)	0.72 (0.58, 0.90)	
p value	0.002[a]	
Median rPFS (95% CI) – months	NR (NE, NE)	NR (29.7, NE)

Immature OS = HR 0.84 (0.63-1.13)

[a] Significance threshold at rPFS IA2: 0.009 (one-sided; stratified log-rank test); information fraction, 74.4%
CI, confidence interval; IA, interim analysis; NE, not estimable; NR, not reached

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HRR Genes Play an Important Role in Repairing Double-Strand DNA Damage

DNA damage, including double-strand breaks, is a constantly occurring event[1,2]

DNA double-strand breaks

REPAIR PATHWAYS

- NHEJ: Low fidelity: Nonhomologous end joining (NHEJ)
- HRR: High fidelity: HRR

HRR genes include[2,3]:
ATM
BRCA1
BRCA2
CDK12
FANCA
PALB2

Impairment of genes involved in the HRR pathway can affect a cell's ability to accurately repair DNA double-strand breaks[1,2,4]

ATM, ataxia-telangiectasia mutated; *BRCA1*, breast cancer susceptibility gene 1; *BRCA2* , breast cancer susceptibility gene 2; *CDK12*, cyclin-dependent kinase 12; *FANCA*, Fanconi anemia, complementation group A; HRR, homologous recombination repair; *PALB2*, partner and localizer of BRCA2.

1. den Brok WD, et al. *JCO Precis Oncol*. 2017;1:1-13. 2. Lozano R, et al. *Br J Cancer*. 2021;124(3):552-563. 3. Shore N, et al. *Future Oncol*. 2021;17(22):2907-2921. 4. Wagener-Ryczek S, et al. *J Pers Med*. 2021;11(7):612.

HRR+ Pts Have More Aggressive Disease

	Cohort A (N=191)	Cohort B (N=217)	Cohort C (N=52)	p-value Cohort A vs. Cohort B
Age at diagnosis median (range)	63 (45 - 87)	63 (44-89)	60 (43-93)	
Race/Ethnicity				
Non-Hispanic White	143 (74.9%)	145 (66.8%)	42 (80.8%)	0.27
Non-Hispanic Black	32 (16.8%)	40 (18.4%)	6 (11.5%)	
Hispanic	5 (2.6%)	12 (5.5%)	2 (3.8%)	
Non-Hispanic Asian	4 (2.1%)	5 (2.3%)	0 (0%)	
Other	7 (3.7%)	15 (6.9%)	2 (3.8%)	
Gleason Score				0.09
6	15 (7.9%)	5 (2.3%)	1 (1.9%)	
7	40 (20.9%)	46 (21.2%)	11 (21.2%)	
8-10	114 (59.7%)	131 (60.4%)	36 (69.2%)	
Unknown	22 (11.5%)	35 (16.1%)	4 (7.7%)	
PSA at diagnosis median (IQR)	18.2 (7.0 - 151.4)	20.7 (8.1 - 126.7)	23.7 (6.2 - 46.2)	0.22
Prior prostatectomy or definitive radiation	98 (51.3%)	123 (56.7%)	36 (69.2%)	0.32
De novo metastatic disease	86 (45.0%)	87 (40.1%)	18 (34.6%)	0.37
Visceral disease	45 (23.5%)	35 (16.1)	6 (11.5%)	--

HRR+ Pts treated with PARPi or Platinum-based chemo:

Younger Patients
++ newly diagnosed metastatic disease
+ Higer Gleason Score
+ visceral disease

Cohort A: BRCA1/2
Cohort B: ATM, CDK12, CHEK1, CHEK2, FANCL
Cohort C: RAD51B/C/D, RAD54L2, BARD1, GEN1, PALB2, FANCA, BRIP1

PROMISE consortium

University Hospitals Seidman Cancer Center | School of Medicine Case Western Reserve University | Graham et al, ASCO 2022; JCO PO 2024 (*in press*) | Pedro C. Barata, MD MSc FACP | @PBarataMD

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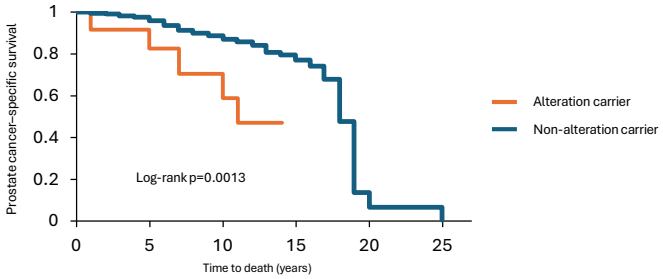
Impact of different *HRR* germline alterations on survival in prostate cancer: *BRCA1/2* and *ATM*[1]

- Patients with *BRCA1/2* and *ATM* germline alterations had a significantly shorter survival time when initially diagnosed with localized prostate cancer (p=0.0013) as well as with an initial diagnosis of metastatic prostate cancer (p=0.00038)

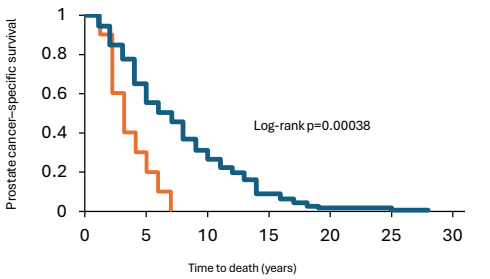
Survival in patients: *HRR* alteration (*BRCA* and *ATM*) carriers versus noncarriers

Initially diagnosed with localized disease (n=674)



HRR status	Median survival (years)	95% CI
Alteration carrier	11.0	NR
Non-alteration carrier	18.0	17.2, 18.8

Initially diagnosed with metastatic disease (n=122)



HRR status	Median survival (years)	95% CI
Alteration carrier	3.0	1.5, 4.5
Non-alteration carrier	6.0	4.5, 7.5

CI, confidence interval; HRR, homologous recombination repair; NR, not reported

1. Na R et al. Eur Urol 2017;71:740–7

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Expanding Reach of Combination Approaches Earlier in Disease

Phase 3 AMPLITUDE: Niraparib + AAP in mHSPC[1]

Key Eligibility Criteria
- Adult patients with prostate adenocarcinoma and deleterious germline or somatic HRR gene alteration[a]
- ADT started ≥14 d prior to randomization and planned to continue through treatment phase

N = 788

R (1:1)

- **Niraparib** 200 mg and **abiraterone acetate** 1,000 mg (in dual-action formulation) + **prednisone** 5 mg daily — **n = 394**
- **Abiraterone acetate** 1,000 mg + **prednisone** 5 mg daily — **n = 394**

- **Primary endpoint:** investigator-assessed radiographic PFS
- **Secondary endpoints:** OS, symptomatic PFS, time to subsequent therapy

Phase 3 TALAPRO-3: Talazoparib + Enzalutamide in mHSPC[2]

Key Eligibility Criteria
- Adult patients with metastatic prostate adenocarcinoma and confirmed DDR gene alteration[a]
- Ongoing ADT for participants who have not undergone bilateral orchiectomy
- ECOG PS 0-1

N = ~550

Stratification
- Setting (de novo vs relapsed)
- Disease volume (high vs low)[b]
- Mutational status (*BRCA* vs non-*BRCA*)

R (1:1)

- **Talazoparib** 0.5 mg/d (0.35 mg/d if moderate renal impairment) PO + **enzalutamide** 160 mg/d PO
- **Placebo** + **enzalutamide** 160 mg/d PO

Remain on blinded treatment

Follow-Up
- Safety: through 28 d after last dose of study treatment
- Long term: every 8 wk through wk 57, then every 12 wk until radiographic progression

- **Primary endpoint:** radiologic PFS
- **Secondary endpoints:** OS, objective response and DOR in soft-tissue disease, time to PFS response, time to PSA progression

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Graham et al, ASCO 2022; JCO PO 2024 (*in press*)

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AMPLITUDE: Randomized, Double-Blind, Placebo-Controlled Trial in HRRm mCSPC

First and final rPFS analysis and first interim analysis of time to symptomatic progression and overall survival. Median follow-up: 30.8 months

Key inclusion criteria:
- mCSPC[a]
- Alteration in ≥1 HRR eligible gene: *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*[b]
- ECOG PS 0-2

Key exclusion criteria:
- Any prior
  - PARPi
  - ARPI other than AAP

Prior allowed treatments in mCSPC:
- ADT ≤6 months
- Docetaxel ≤6 cycles[c]
- AAP ≤45 days
- Palliative RT

Randomized 1:1 (N=696)

Nira (200 mg QD) + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

PBO + **AAP** (1000 mg QD + 5 mg QD) + **ADT** (n=348)

Primary end point
- rPFS by investigator review

Key secondary end points
- Time to symptomatic progression
- OS
- Safety

Stratification factors:
- *BRCA2* vs *CDK12* vs all other alterations
- Prior docetaxel (yes vs no)
- Disease volume (high vs low)

Clinical data cutoff: January 7, 2025

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[a]Patients with lymph node–only disease are not eligible. [b]HRR gene panel was fixed prior to trial initiation based on MAGNITUDE trial and external data from the published literature. [c]Last dose ≤3 months prior to randomization.
ECOG PS, Eastern Cooperative Oncology Group performance status; Nira, niraparib; OS, overall survival; PBO, placebo; RT, radiotherapy; QD, once daily.

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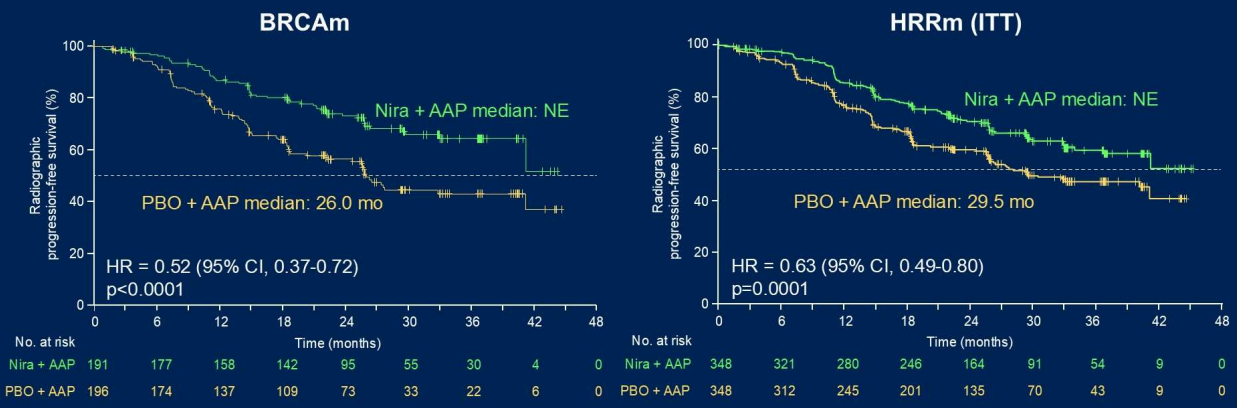
Primary End Point: Radiographic Progression-Free Survival



AMPLITUDE met the primary end point: Nira + AAP significantly reduced the risk of radiographic progression[a] or death by 48% in BRCAm group and by 37% in HRRm population

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[a]rPFS by investigator review; rPFS improvement by blinded independent central review was as large: HR = 0.51 (95% CI, 0.37-0.72) for BRCAm group and 0.61 (95% CI, 0.47-0.79) for HRRm group.
NE, not estimable.

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Pfizer Press release | Prescription Medicines | Medicines

TALZENNA Plus XTANDI Significantly Improves Radiographic Progression-Free Survival in Metastatic Prostate Cancer

Thursday, March 19, 2026 - 06:45am | 17 min read

- *Primary endpoint met in Phase 3 TALAPRO-3 study demonstrating a statistically significant and clinically meaningful reduction in risk of disease progression or death in HRR gene-mutated metastatic hormone sensitive prostate cancer*
- *Consistent rPFS efficacy benefit was observed in patients whose tumors harbored BRCA and non-BRCA HRR gene alterations*
- *Interim analysis showed a strong trend toward improvement in overall survival*
- *These results will be discussed with global health authorities to potentially expand TALZENNA indication in this earlier stage disease*

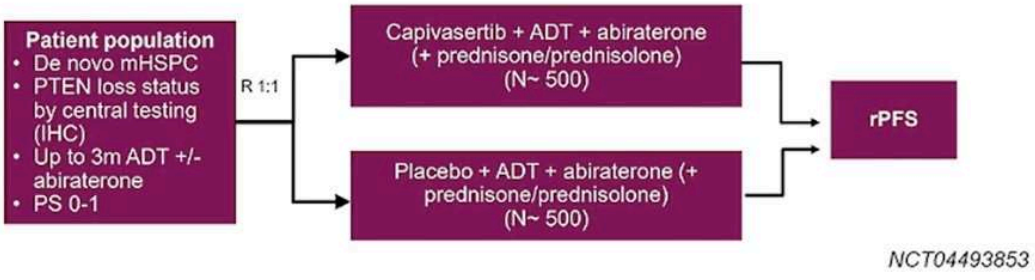
www.pfizer.com/news/press-release

BERLIN 2025 ESMO congress

Biomarker selection: PTEN-loss

CAPItello-281 Clinical Study Design

Estimations:
~5500 first screening part for biomarker status.
~1000 men expected to have PTEN deficiency



NCT04493853

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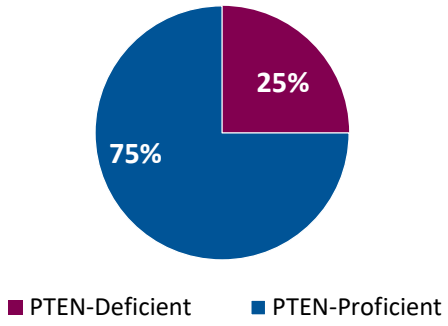
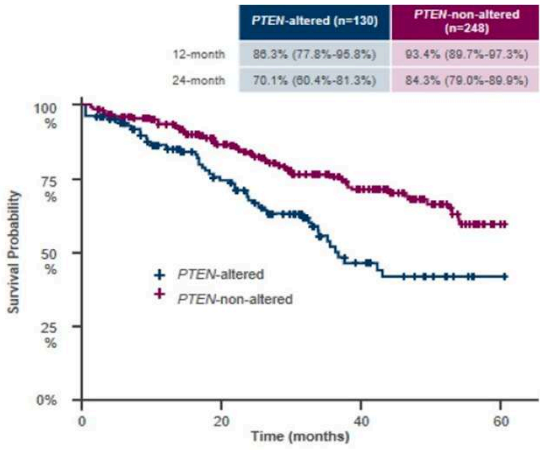
PTEN-Deficiency Is Common in mHSPC and Outcomes on ADT-Based Therapy Are Poor

39,000 cases per year PTEN-Deficiency is present in 25% of patients with mHSPC

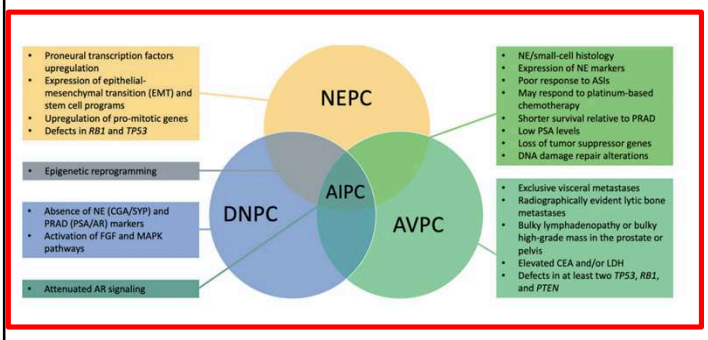


Patients with PTEN-deficient tumors have inferior outcomes on ARPI + ADT-based therapy*

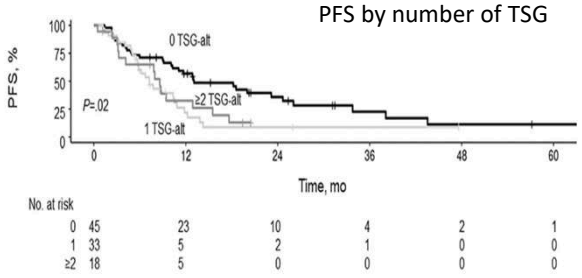


* Real-World OS data in patients with mHSCP receiving ARPI + ADT stratified by PTEN-status

mHSPC with Tumor Suppressor genes (*TP53, Rb1, PTEN*)



PFS by number of TSG



- 17% with 2/3 (AVPC) in mHSPC cohort (N=97 pts)

Characteristic	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
TSG-alt (vs TSG-normal)	2.37 (1.42–3.96)	<0.001	1.94 (0.98–3.86)	0.06
Treatment with ADT + D (vs ADT + A)	1.36 (0.81–2.28)	0.20	1.80 (0.84–3.83)	0.13
Prior treatment (vs none)				
Surgery	1.16 (0.48–2.77)	0.70	0.90 (0.28–2.89)	0.90
RT	0.40 (0.13–1.22)	0.11	0.76 (0.15–3.91)	0.70
High disease volume (vs low)	1.82 (0.99–3.33)	0.05	0.98 (0.41–2.32)	>0.90
Mets at diagnosis (vs none)	0.34 (0.15–0.76)	0.009	1.18 (0.41–3.45)	0.80

ADT + A androgen deprivation therapy plus abiraterone acetate, *ADT + D* androgen deprivation therapy plus docetaxel, *HR* hazard ratio, *Mets* metastases, *OS* overall survival, *PFS* progression-free survival, *RT* radiotherapy, *TSG-alt* tumor suppressor gene alteration.

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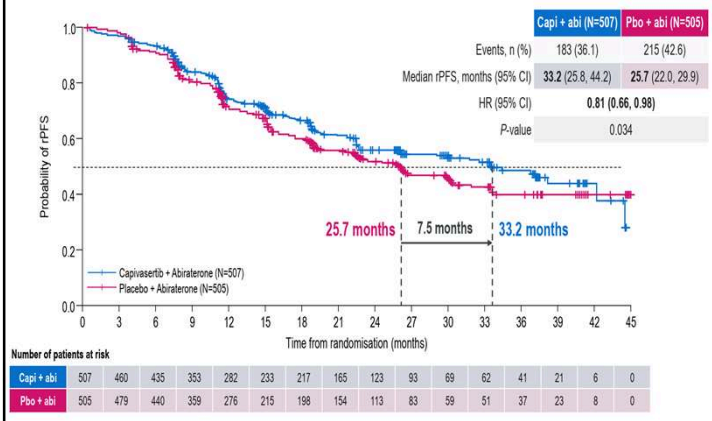
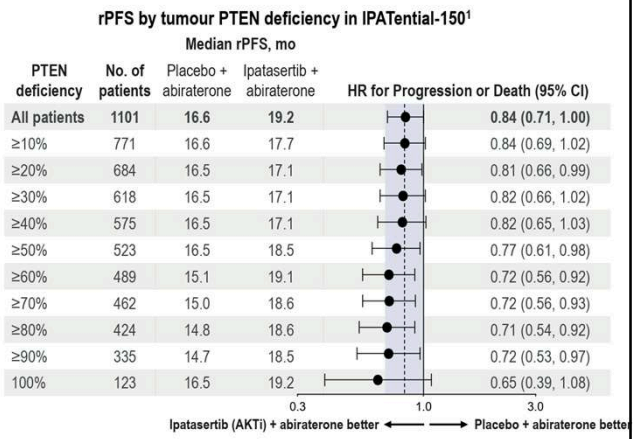
CAPitello-281: *PTEN* Story





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Barata's Take Home Messages

- Treatment Intensification is SOC for patients with mHSPC;
- Triplet therapy should be strongly considered for selected patients, particularly those with synchronous, high-volume disease
- mHSPC is biologically heterogeneous; clinical factors, disease burden, genomics, and PSA response can help personalize treatment intensity
- Patients who do not achieve an optimal PSA nadir may warrant reassessment of treatment strategy and consideration of additional therapy
- Genomic testing should be considered early, as it identifies patients for potentially actionable alterations

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Thank you!

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