Updates in Hormone Sensitive Prostate Cancer

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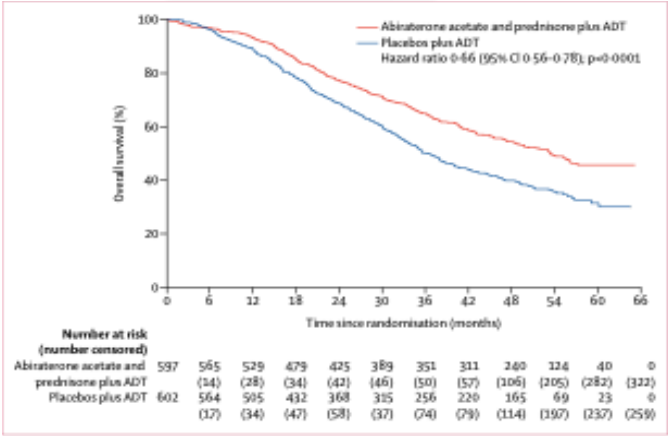
ADT + ARPI in HSPC

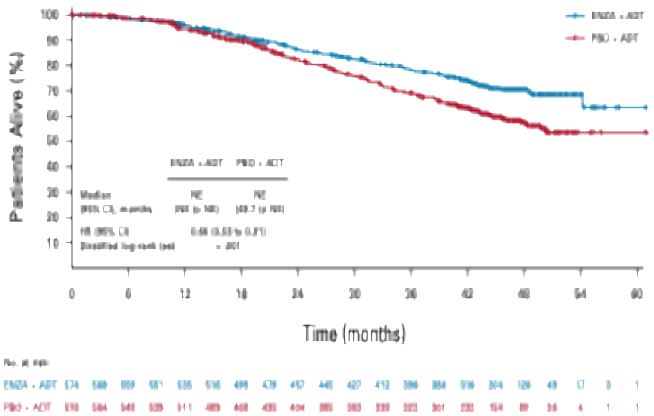
LATITUDE



- Metastatic disease on conventional imaging
- ≥2/3 high-risk factors: *Gleason ≥8, ≥3 lesions on bone scan, and visceral metastases*

Fizazi et al. Lancer 2019

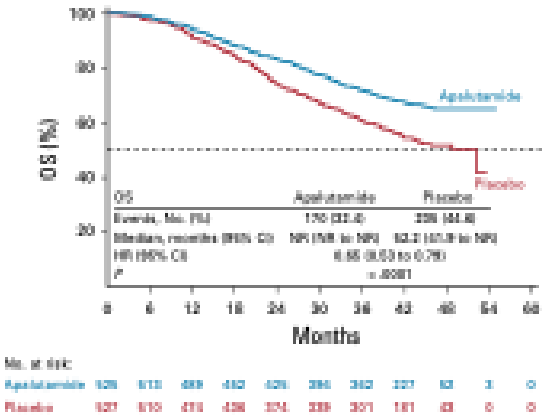
ARCHES



- Metastatic disease on conventional imaging
- Docetaxel permitted (18% received)

Armstrong et al. JCO 2022

TITAN



- Metastatic disease on conventional imaging
- Docetaxel permitted

Chi et al. JCO 2021

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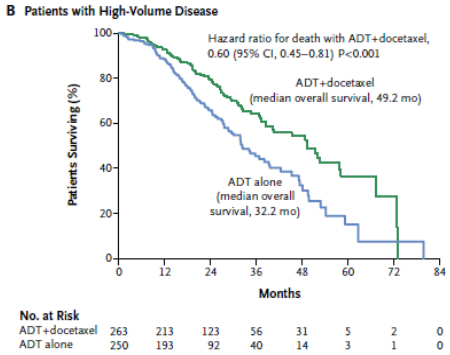
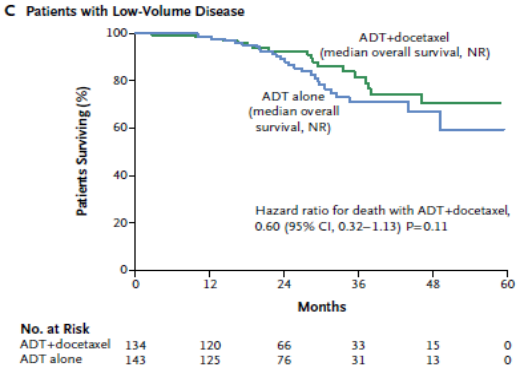
Early docetaxel improved OS: Long term OS from CHAARTED trial



- Docetaxel improved OS on long term follow up
- **Benefit most prominent in *de novo and* high-volume disease**



Subgroup	ADT+ D	ADT alone	HR[4] (95% CI; p-value)
	OS rate[3] (95% CI)		
Overall	34.9% (30.0-39.8)	28.9% (24.3-33.5)	0.77 (0.65-0.92; p=0.004)
Synchronous[1] HV	28.5% (22.2-35.1)	15.4% (10.7-20.8)	0.67 (0.53-0.84; p=0.0005)
Synchronous[1] LV	44.6% (32.9-55.6)	40.9% (29.6-51.9)	0.77 (0.51-1.18; p=0.23)
Metach[2] HV	37.1% (23.6-50.6)	19.8% (9.3-33.1)	0.84 (0.49-1.46; p=0.54)
Metach[2] LV	43.4% (30.1-55.9)	64.2% (50.9-74.8)	1.65 (0.95-2.87; p=0.07)
HV	30.2% (24.4-36.1)	16.0% (11.7-21.0)	0.67 (0.55-0.82; p<0.0001)

1: Synchronous: no prior local therapy; 2: Metach: relapse after prior local therapy; 3: Estimated using the Kaplan-Meier method; 4: ADT+D vs. ADT alone using Cox's proportional hazards models, stratified by baseline stratification factors
LV: Low volume; HV: High volume; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval

Sweeney et al. NEJM 2015; Tripathi et al. ASCO 2022

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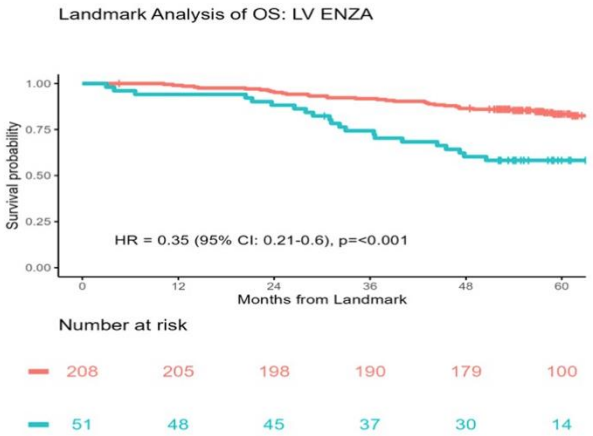
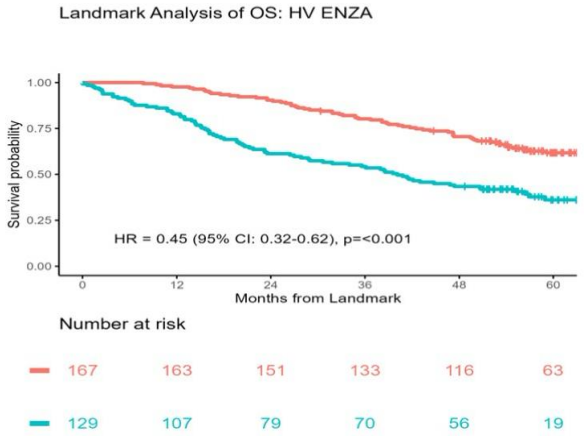
PSA nadir is prognostic in both ARPI and docetaxel treated patients!

Disease Volume	TS + NSAA PSA ≤0.2ng/mL	TS + NSAA PSA > 0.2ng/mL	TS + ENZA PSA ≤ 0.2ng/mL	TS + ENZA PSA >0.2ng/mL
High Volume				
% (No/Total No)	38 (110/290)	62 (180/290)	56 (167/296)	44 (129/296)
% 5 yr OS (95% CI)	66 (58, 76)	33 (26, 41)	62 (55, 70)	36 (28, 46)
Low Volume				
% (No/Total No)	62 (160/259)	38 (99/259)	80 (208/259)	20 (51/259)
% 5 yr OS (95% CI)	75 (68, 82)	42 (33, 54)	83 (78, 89)	58 (46, 74)





	ADT+ docetaxel # Death/N	ADT+ docetaxel Median OS (95% CI; months)	ADT+ docetaxel p-value[5]	ADT Alone # Death/N	ADT Alone Median OS (95% CI; months)	ADT Alone p-value[5]
Overall Population						
6-month PSA <0.2	66/127	**100.3 (70.4, NA[4])**	**<0.0001**	**35/77**	**116.8 (87.3, 141.5)**	**<0.0001**
6-month PSA ≥0.2	203/256	45.4 (39.2, 51.6)		246/301	31.8 (26.3, 38.1)	

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McLaughlin et al. ASCO 2024

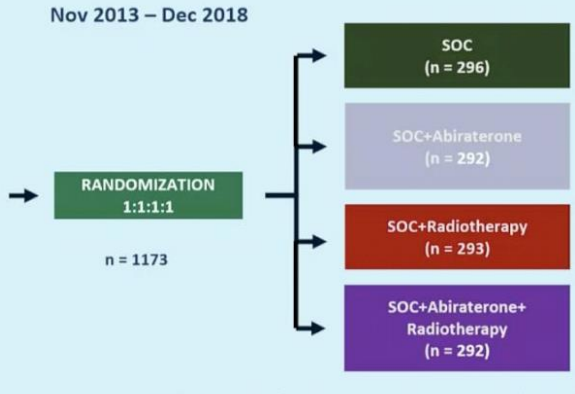
ADT + docetaxel +/- abiraterone

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

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

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



ECOG PS, Eastern Cooperative Oncology Group performanc

	Overall population (n=1172)		ADT with docetaxel population (n=710)*	
	SOC plus abiraterone groups (with or without radiotherapy; n=583)	SOC without abiraterone groups (with or without radiotherapy; n=589)	SOC plus abiraterone groups (with or without radiotherapy; n=355)	SOC without abiraterone groups (with or without radiotherapy; n=355)
Assigned to receive radiotherapy	291 (50%)	293 (50%)	178 (50%)	177 (50%)
Metastatic burden§				
High burden	331 (57%)	336 (57%)	224 (63%)	232 (65%)
Low burden	252 (43%)	253 (43%)	131 (37%)	123 (35%)

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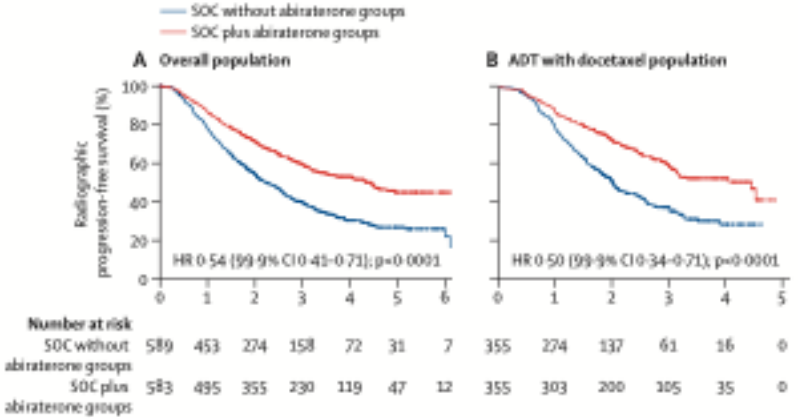
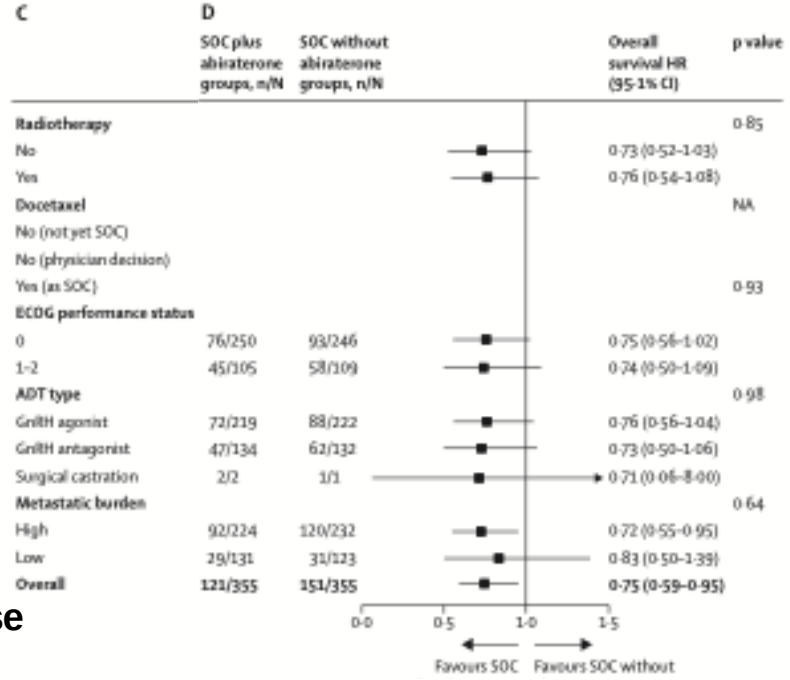
Fizazi et al. Lancet 2022

ADT + docetaxel +/- abiraterone



ADT + docetaxel + abiraterone > ADT + docetaxel

Greater benefit in patients with high-volume disease



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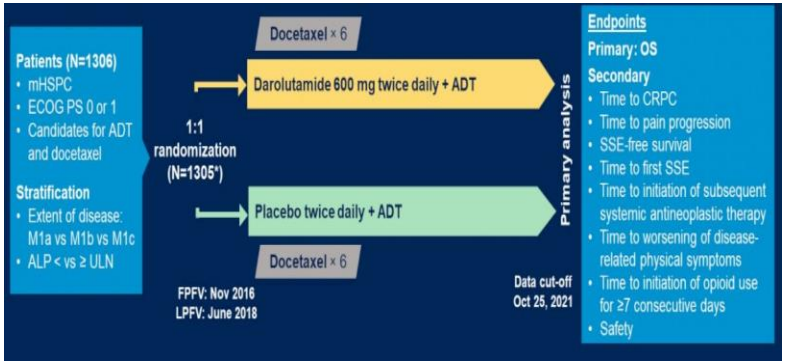
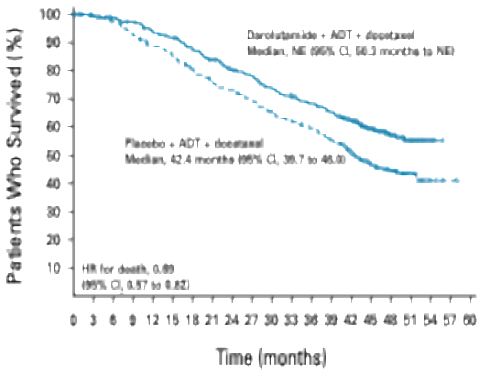
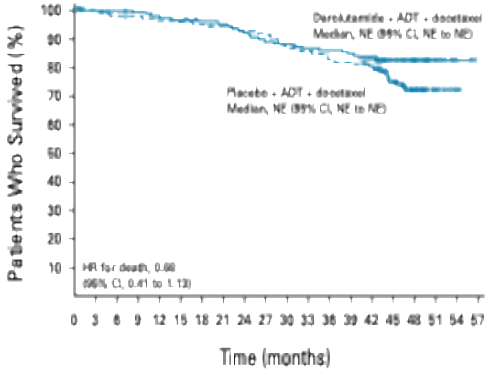
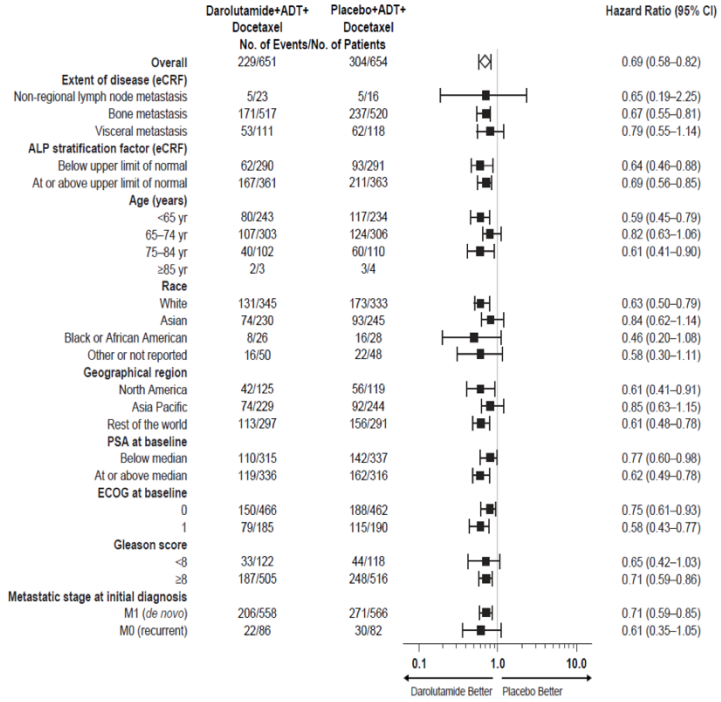
Fizazi et al. Lancet 2022

ADT + docetaxel + darolutamide









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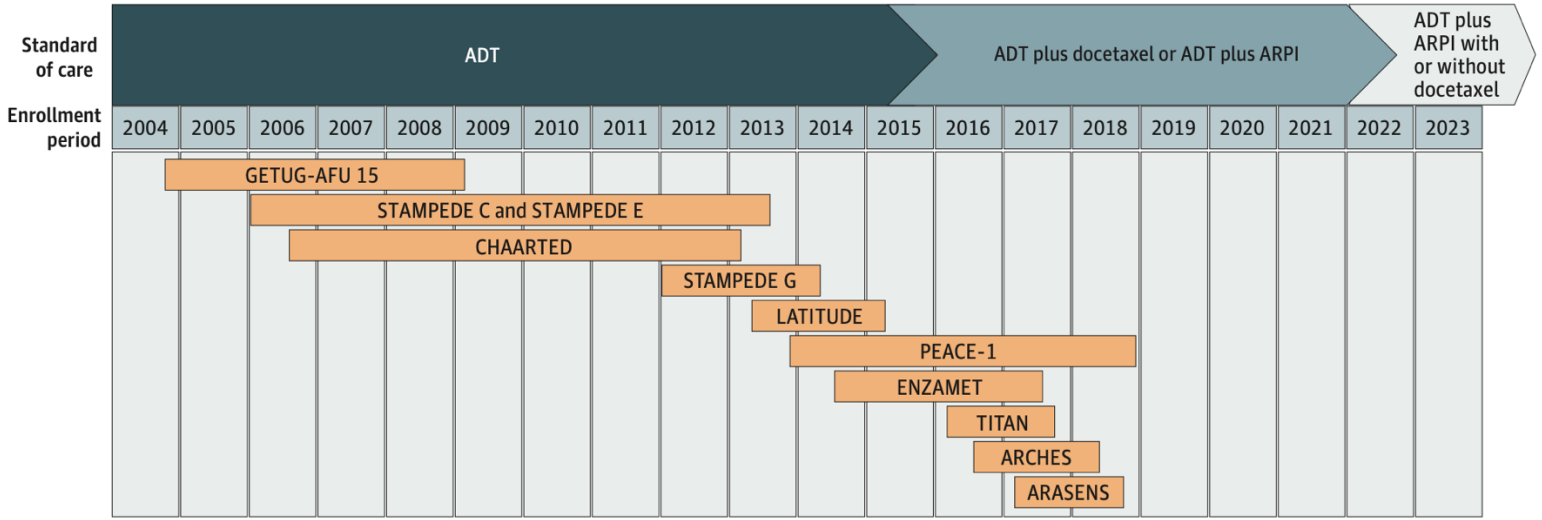
Hussain et al. JCO 2023

Evolution of SOC in HSPC



Studies were designed largely when ADT+ docetaxel was SOC
ARPI now most commonly used in HSPC

Is ADT + docetaxel + ARPI > ADT+ARPI ??

Benefit of triplet therapy most prominent in high volume subset

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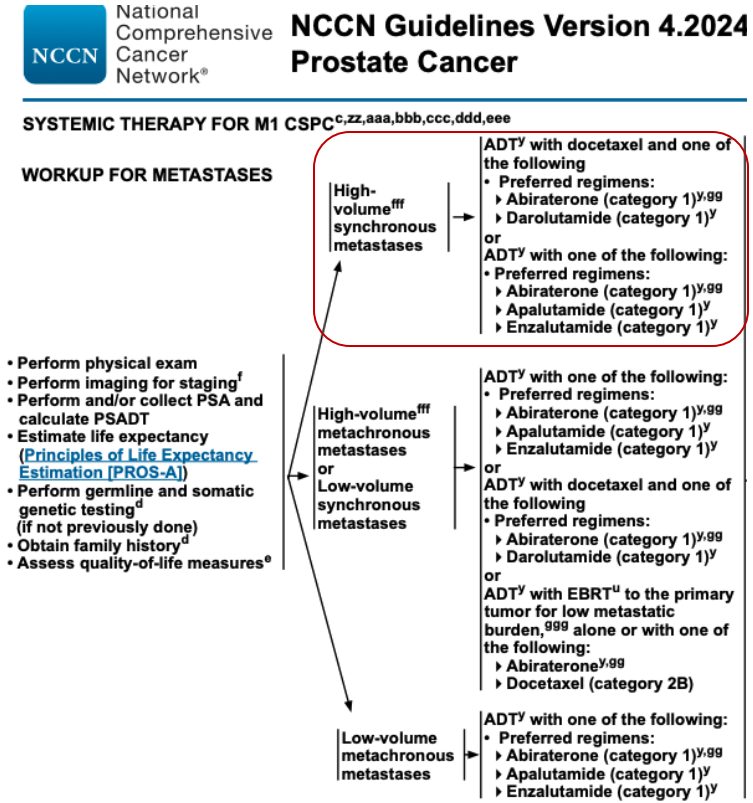
Hussain et al. JAMA 2024

Limitation of current data…



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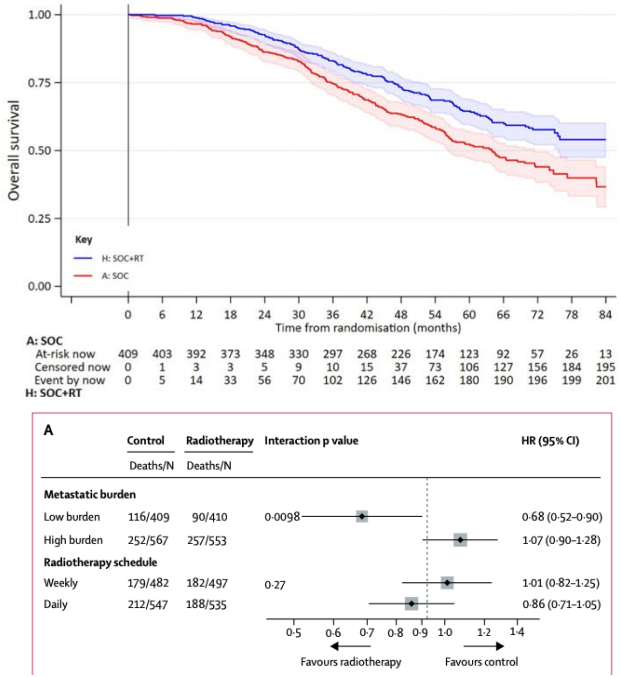
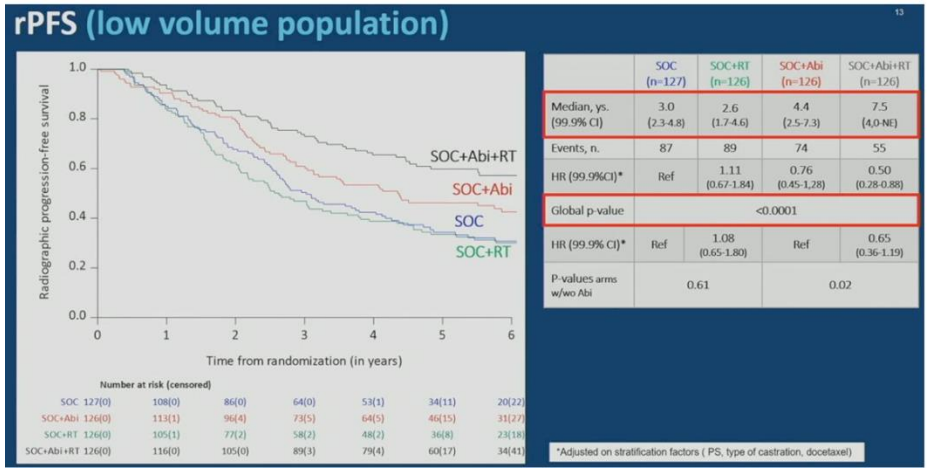
Local therapy in HSPC

STAMPEDE RT cohort



Radiation to primary improved OS in low volume disease subset

PEACE-1



No improvement in OS or PFS low volume disease overall, but some potential benefit in Abiraterone treated patients

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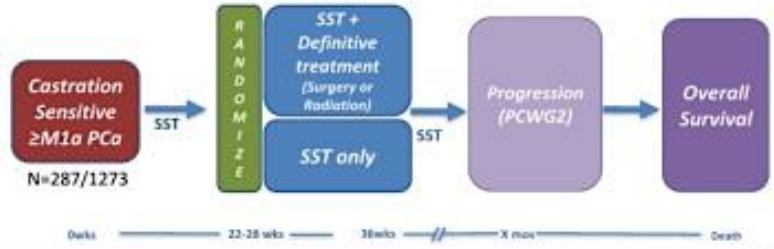
Bossi et al. ASCO 2023; Parker et al. Lancet 2018

Randomized, Phase III Trial of Standard Systemic Therapy (SST) or SST Plus Definitive Treatment of the Primary Tumor in Metastatic Prostate Cancer (S1802)



PI: Brian F Chapin, MD
SWOG : Dan Lin, David Quinn, Ana Aparicio, Cathy Tangen, Nicholas Vogelzang, Ian Thompson

Supported by: NCTN

Southwest Oncology Group
A National Cancer Research Group

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Can biomarker selection inform intensification in HSPC?

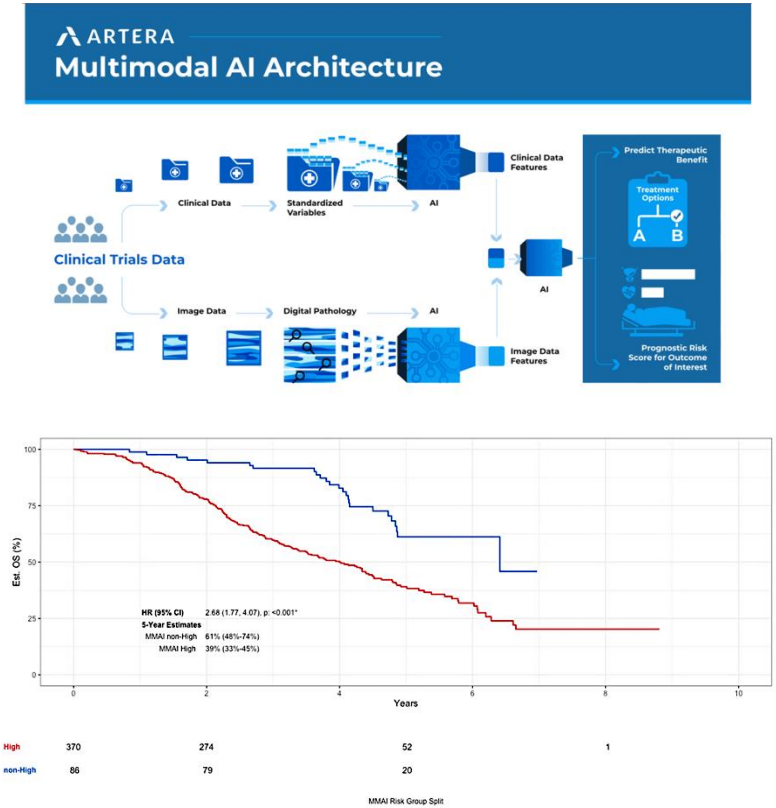

Table 1. Demographics and clinical characteristics by split arm.

Variable	Overall	DPEP N = 456	Non-DPEP N = 334
Arm			
ADT + docetaxel	397 (50%)	235 (52%)	162 (49%)
ADT alone	393 (50%)	221 (48%)	172 (51%)
Age			
Median (IQR)	63.0 (57.0, 69.0)	63.0 (56.0, 69.0)	63.0 (58.0, 69.0)
Race			
White	674 (85%)	401 (88%)	273 (82%)
African American	76 (9.6%)	37 (8.1%)	39 (12%)
Other / Unknown	40 (5.1%)	18 (4.0%)	22 (6.6%)
CHAARTED Clinical Subgroups			
LV-M	81 (13%)	57 (14%)	24 (11%)
HV-M	44 (7.1%)	29 (7.4%)	15 (6.6%)
LV-S	99 (16%)	66 (17%)	33 (14%)
HV-S	398 (64%)	242 (61%)	156 (68%)
(Missing)	168	62	106
PSA at Enrollment (ng/mL)			
Median (IQR)	11.7 (1.8, 67.5)	10.6 (1.9, 66.4)	12.9 (1.8, 68.5)
(Missing)	1	0	1

Abbreviations: DPEP, digital pathology evaluable population; ADT, androgen deprivation therapy; LV, low volume; HV high volume; S, synchronous; M, metachronous; PSA, prostate specific antigen (includes men on ADT prior to enrollment)

Table 2. Multivariable Cox proportional hazards model with Wald test p-values.

Endpoint	Variable	MVA† HR (95% CI)	P value
OS	MMAI-High vs. non-High	1.77 (1.10-2.84)	0.02
	ADT + Docetaxel vs. ADT	0.86 (0.65-1.12)	0.26
	HV-M vs. LV-M	2.60 (1.34-5.05)	0.005
	LV-S vs. LV-M	1.33 (0.71-2.48)	0.37
	HV-S vs. LV-M	2.49 (1.48-4.18)	<0.001

†Controlled for MMAI, treatment, and disease volume (high vs low) + synchronous (S) vs metachronous (M) disease.

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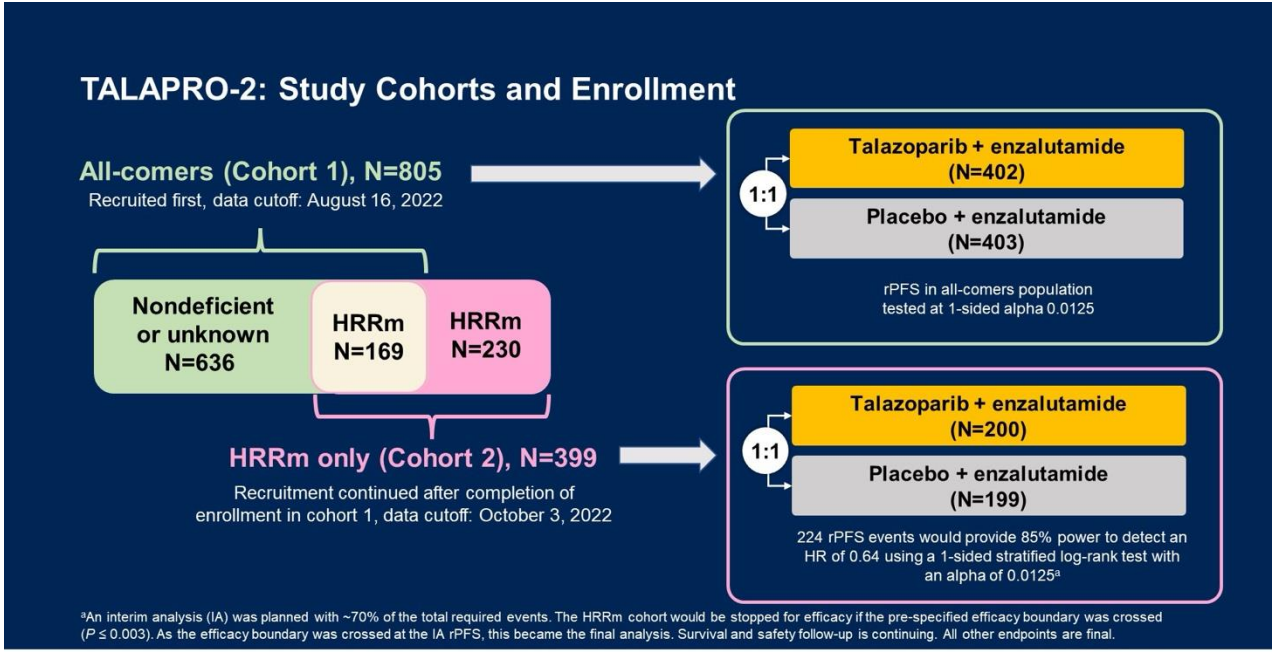
Markowski et al. ASCO 2024

Novel agents for treatment intensification in mHSPC: PARP inhibitors



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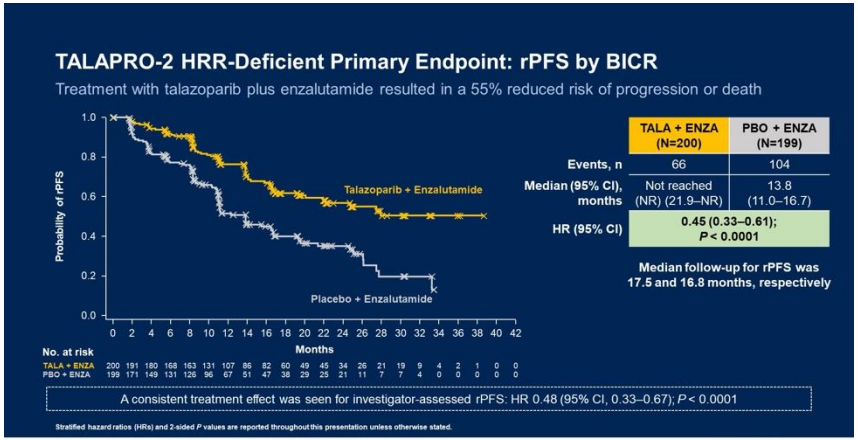

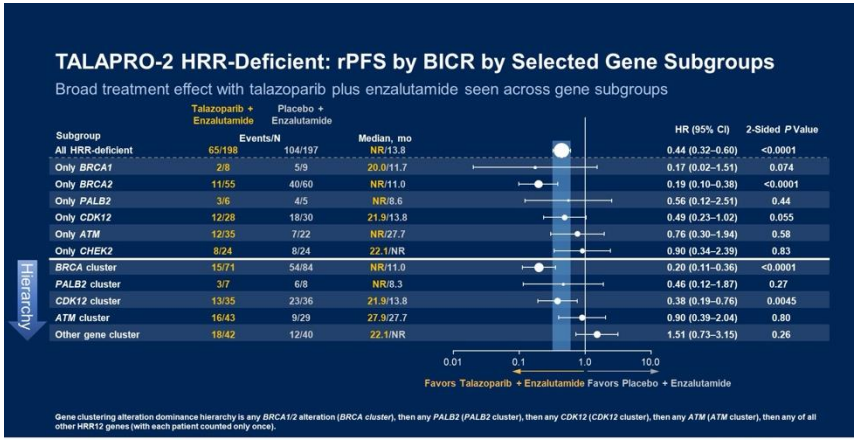

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Novel agents for treatment intensification in mHSPC: PARP inhibitors

Name/Sponsor	ARTA	PARP inhibitor	Design
AMPLITUDE	Abiraterone	Niraparib	Randomized, HRR+ (788)
TALAPRO-3	Enzalutamide	Talazoparib	Randomized HRR+ (550)
City of Hope PCF	**Abiraterone**	**Talazoparib**	**Single arm, Unselected (70)**

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Novel agents for treatment intensification in mHSPC: radioligand Rx

VISION study design

Eligibility
- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted SOC planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Adequate major organ and bone marrow function
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

~87% of patients scanned met the VISION imaging criteria for PSMA-positive mCRPC

2:1

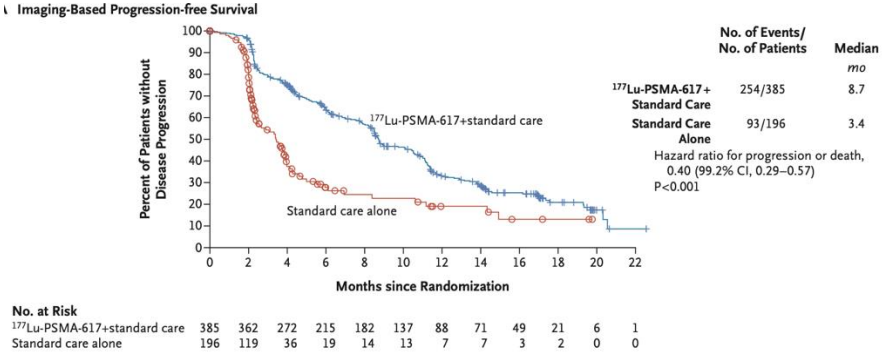
- **Protocol-permitted SOC + ^{177}Lu-PSMA-617**: 7.4 GBq (200 mCi) every 6 weeks, 4 cycles, increasable to 6 cycles
- **Protocol-permitted SOC alone**

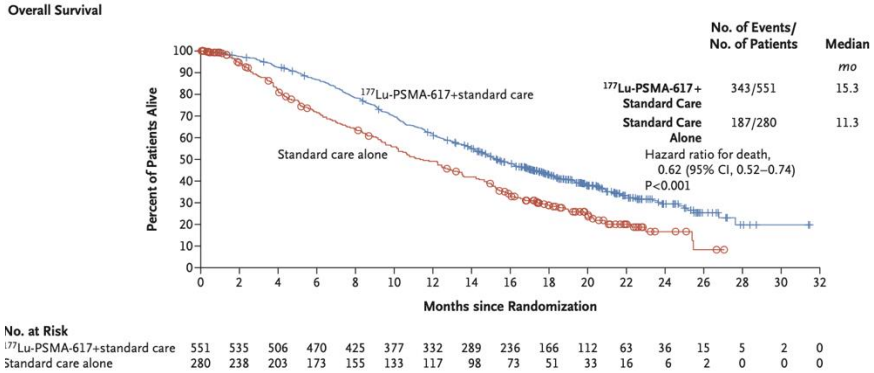
Treatment → Follow-up → Final analysis

Alternate primary endpoints
- Radiographic progression-free survival
- Overall survival

Key secondary endpoints
- Time to first symptomatic skeletal event
- RECIST v1.1 overall response rate
- RECIST v1.1 disease control rate

Other secondary endpoints
- Safety and tolerability
- Biomarkers including PSA
- Health-related quality of life and pain
  - FACT-P
  - Brief Pain Inventory – Short Form
  - EQ-5D-5L





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Sartor et al. NEJM 2021

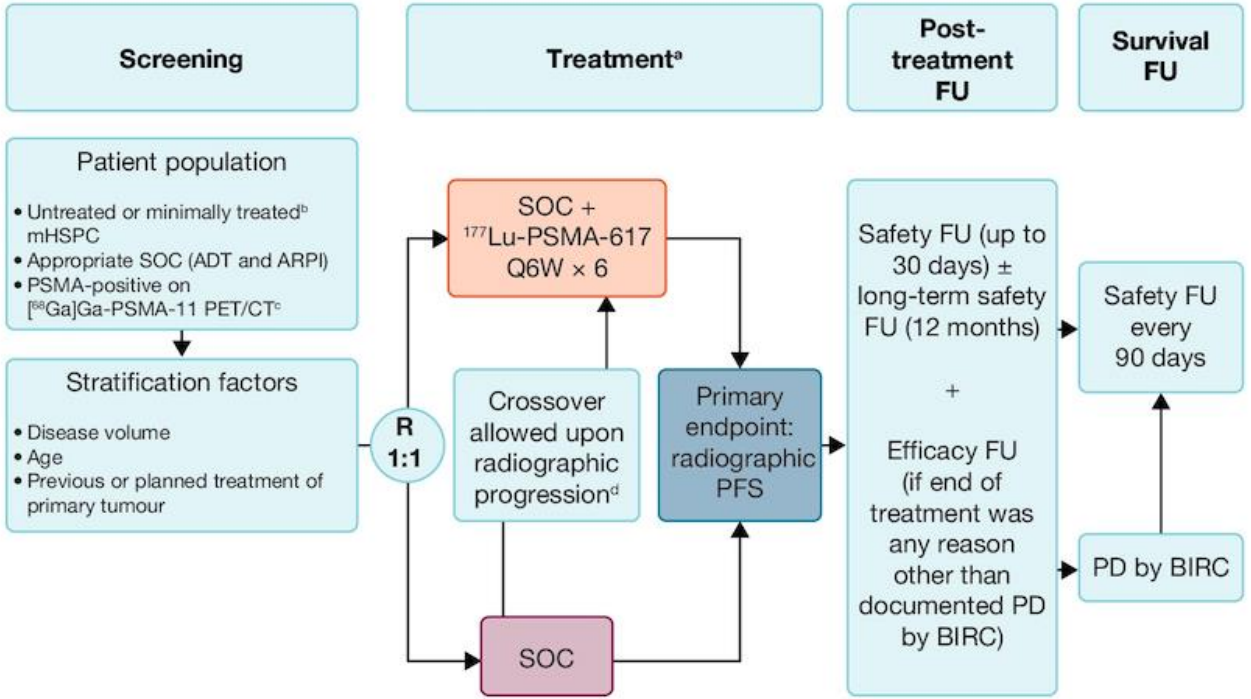
Novel agents for treatment intensification in mHSPC: radioligand Rx

Abstract #TPS210

Presenting author: Dr. A. Oliver Sartor
E-mail: osartor@tulane.edu

PSMAddition: a phase 3 trial to compare treatment with ^{177}Lu-PSMA-617 plus standard of care (SOC) versus SOC alone in patients with metastatic hormone-sensitive prostate cancer

A. Oliver Sartor,[1] Scott T. Tagawa,[2] Fred Saad,[3] Johann S. de Bono,[4] Felix Y. Feng,[5] Karim Fizazi,[6] Olga Sakharova,[7] Michael J. Morris[8]



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Sartor et al. GU ASCO 2022

Too much of a great thing??

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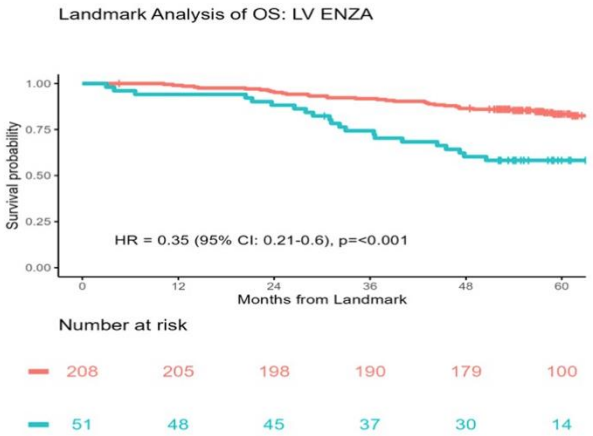

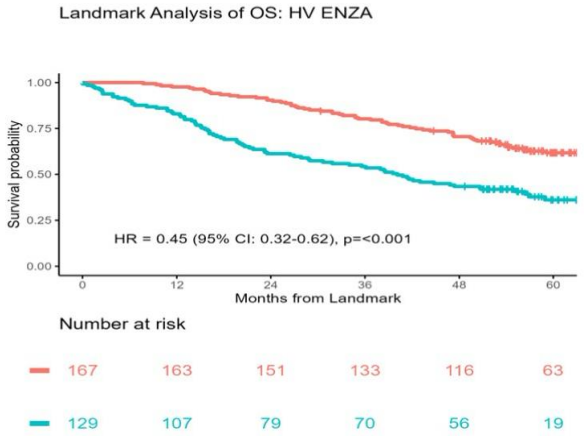

	ADT+ docetaxel # Death/N	ADT+ docetaxel Median OS (95% CI; months)	ADT+ docetaxel p-value[5]	ADT Alone # Death/N	ADT Alone Median OS (95% CI; months)	ADT Alone p-value[5]
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McLaughlin et al. ASCO 2024

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Authors: Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N., Celestia S. Higano, M.D., E. David Crawford, M.D., Glenn Liu, M.D., George Wilding, M.D., +13, and Ian M. Thompson, Jr., M.D. Author Info & Affiliations

Published April 4, 2013 | **N Engl J Med 2013;368:1314-1325** | **DOI: 10.1056/NEJMoa1212299** | **VOL. 368 NO. 14**

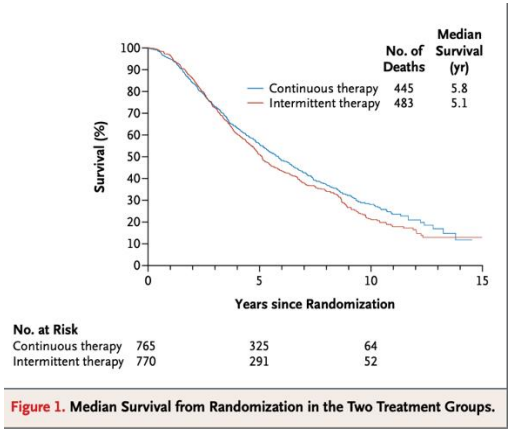

Figure 1. Median Survival from Randomization in the Two Treatment Groups.

Intermittent therapy was not non-inferior to continuous ADT

Selected for all patients, not based on response

Can response-adapted selection and ARPI integration provide opportunity for de-escalation?

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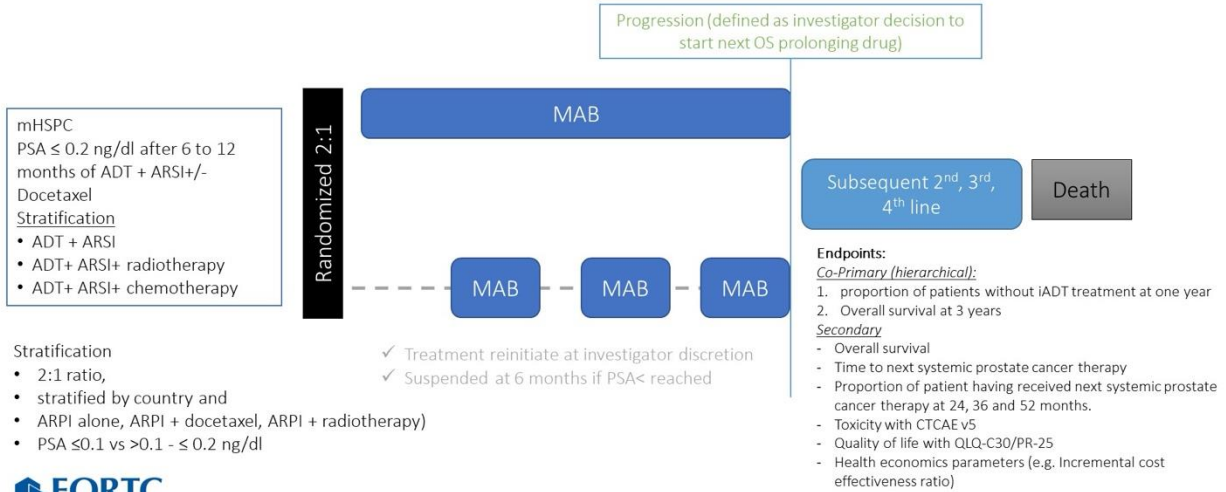
DE-ESCALATE (EORTC 2238, PEACE-6)

Intermittent Androgen Deprivation Therapy in the era of AR pathway inhibitors: a phase 3 pragmatic randomized trial



EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

mHSPC: metastatic hormone sensitive prostate cancer; PSA90%: decrease in PSA from baseline by 90%); MAB: Maximum androgen blockade

PI: Dr Bertand Tombal

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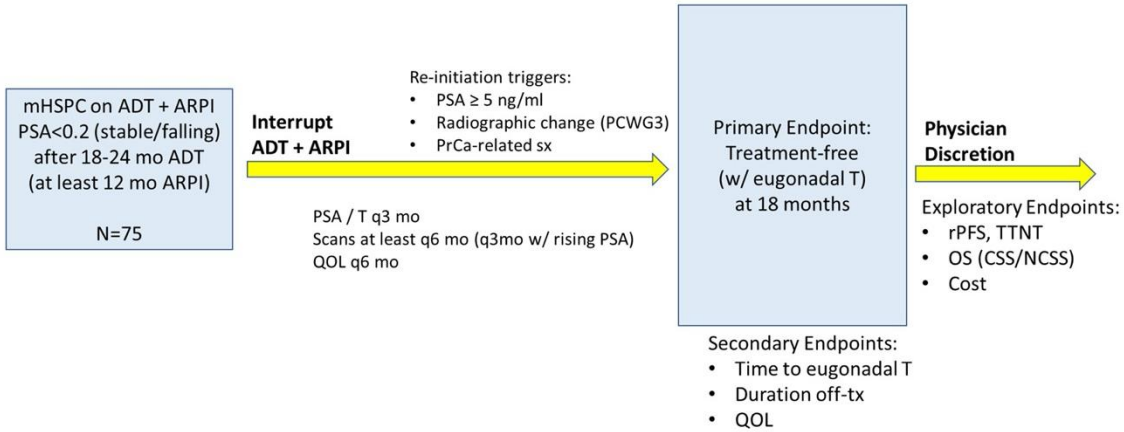
A-DREAM

A Phase 2 Trial of ADT Interruption in Patients Responding Exceptionally to AR-pathway Inhibitor In mHSPC



PI: Dr Atish Choudhury

Conclusions

- Intensification remains SOC for most eligible patients with mHSPC
- Doublet appropriate for most patients, greatest benefit of docetaxel-based triplet in *de novo* high volume patients
- Newer agents could change the combination of doublet/triplets and bring in biology driven combinations
- Need to also identify strategies for safe de-escalation of therapy in durable long-term responders to balance cost, toxicity, and QOL

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Thank you!

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