Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Triplet Therapy

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Disclosures:

Consultant or Advisory Board Member:
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METASTATIC PROSTATE CANCER

- Advanced prostate cancer has an ↑ incidence and is a continuum of multiple disease states
- De-novo (synchronous) metastatic prostate cancer is a global problem
  - Accounts for 50% of prostate-related mortality
- Intensification of treatment with multitargeted strategy → meaningful improvements in overall survival (OS)
- Androgen deprivation therapy (ADT) plus androgen receptor pathway inhibitor (ARPI) is currently the most used approach
- Triplet therapy (ADT + ARPI + Docetaxel) is the most effective therapy

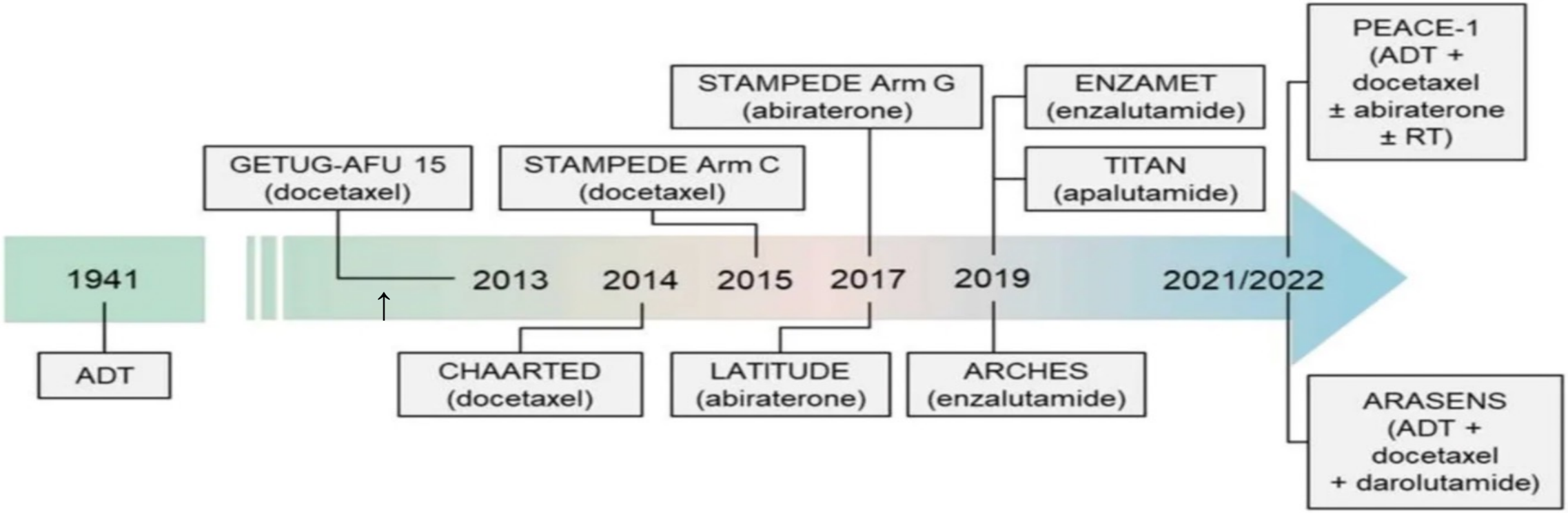
ADT alone age

Doublet age

ADT+Docetaxel
or
ADT+ARPI

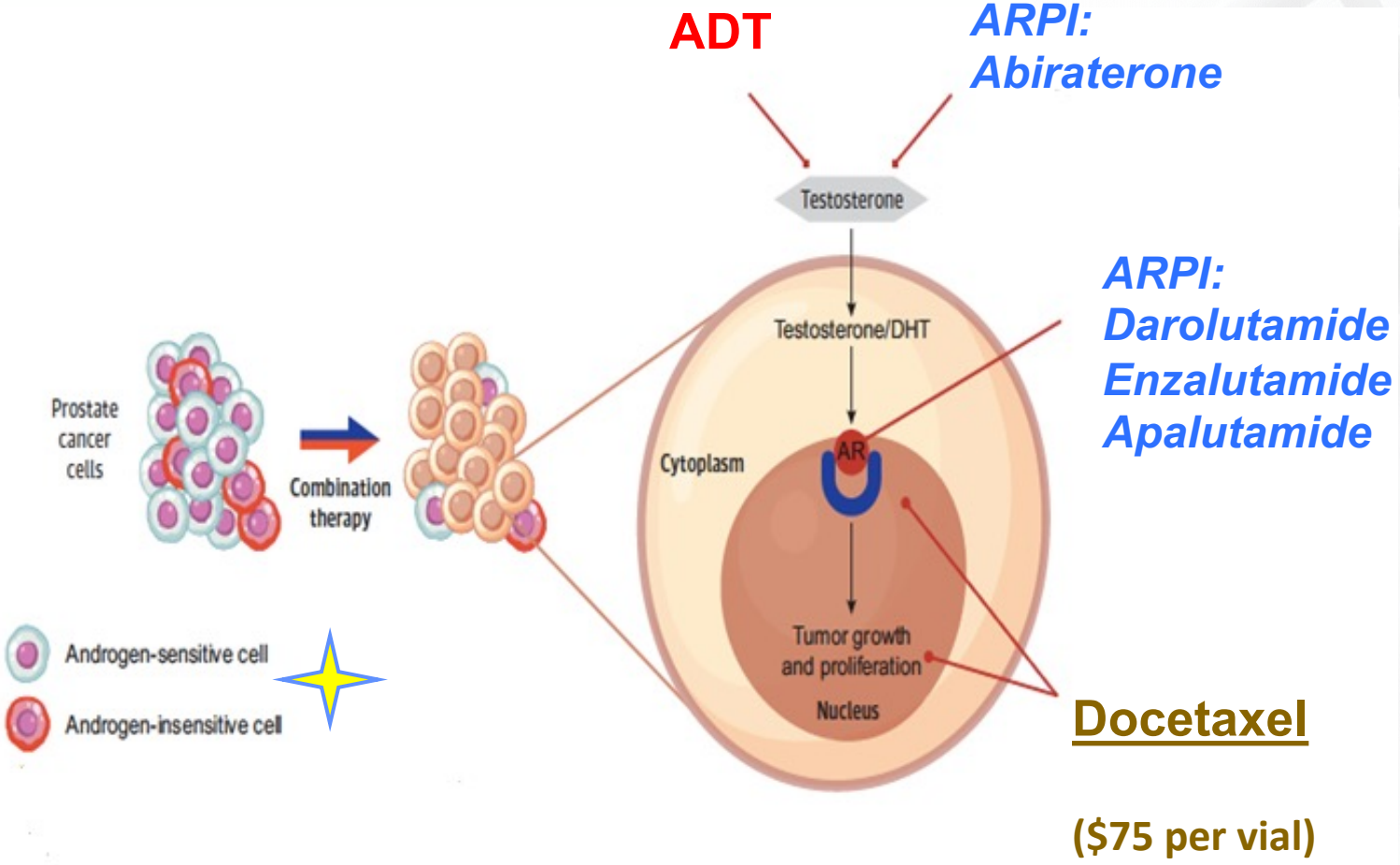
Triplet age

ADT+
Docetaxel+
ARPI



Early treatment intensification → ↑ Overall survival outcomes

TRIPLET THERAPY OFFERS COMPREHENSIVE DISEASE CONTROL



- **Multitargeting of malignancy**
- **Treats AR-dependent and AR-independent cells**
- **Offers chemotherapy earlier in the course of the disease.**
- **Targets early disease resistance through non-overlapping mechanisms of action**

Hussain, M., Fizazi, K., Shore, N. D., Heidegger, I., Smith, M. R., Tombal, B., & Saad, F. (2024). Metastatic Hormone-Sensitive Prostate Cancer and Combination Treatment Outcomes: A Review. *JAMA oncology*.

LANDMARK PHASE III TRIALS SUPPORTING TRIPLET THERAPY

PEACE-1 (2013-2018)

Key eligibility criteria
- mHSPC (synchronous)
- Distant mets by ≥ 1 lesion on bone scan and/or CT
- ECOG PS 0-2

Stratification
- ECOG PS (0 vs 1-2)
- Metastatic sites
- Types of castration (orchiectomy vs LHRH agonist vs LHRH antagonist)
- Docetaxel (yes vs no)

1:1:1:1 Randomization

- SOC (n=296)
- SOC+ Abiraterone (n=292)
- SOC+ RT (n=293)
- SOC + Abiraterone + RT (n=292)

PEACE-1 protocol was amended in 2015 to allow docetaxel use based on CHAARTED data. SOC ADT+Docetaxel became mandatory in 2017

ARASENS (2016-2018)

Key eligibility criteria
- mHSPC (synchronous +metachronous)
- ECOG PS 0-1
- Candidate for ADT and Docetaxel

Stratification
- Extent of disease (M1a-M1c)
- AlkP level

1:1 Randomization

- ADT + Docetaxel+ placebo (n=655)
- ADT+ Docetaxel+ Darolutamide 500mg BID (n=651)

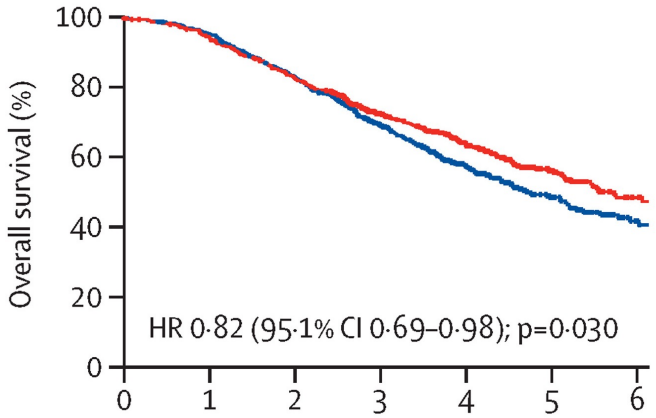
Data from other trials like ENZAMET (ADT+Enzalutamide+Docetaxel vs ADT + Enzalutamide) are exploratory and not powered.

Fazazi et al., Lancet, 2022. Smith et al., NEJM, 2022

PEACE-1

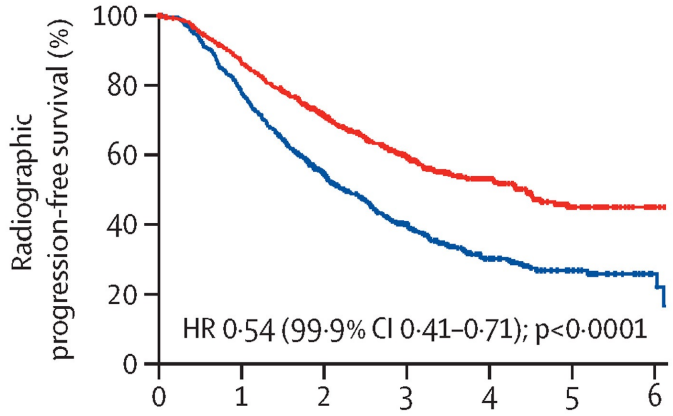
ADT + Docetaxel + Abiraterone > ADT + Docetaxel

Overall Survival



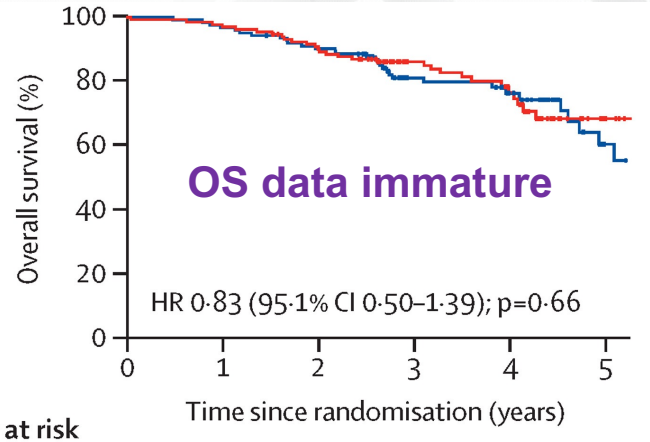
Number at risk							
SOC without abiraterone groups	589	556	480	334	207	101	37
SOC plus abiraterone groups	583	541	470	340	230	111	47

Radiographic PFS

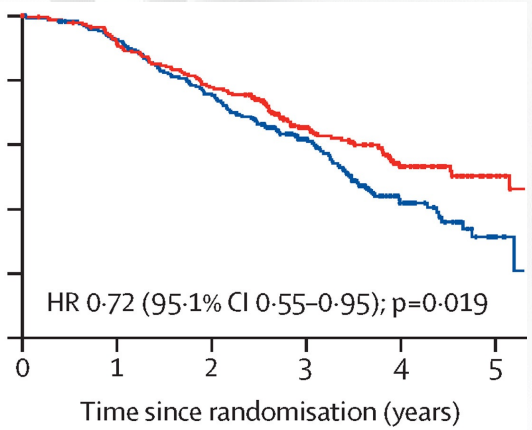


Number at risk							
SOC without abiraterone groups	589	453	274	158	72	31	7
SOC plus abiraterone groups	583	495	355	230	119	47	12

Low-volume



High-volume



Number at risk							
SOC without abiraterone groups	123	119	110	71	39	12	
SOC plus abiraterone groups	131	127	116	80	41	9	
	232	210	171	101	39	6	
	224	201	171	103	57	16	

Median OS of 61 months: longest ever reported

For discussion:

CHAARTED OS (ADT+Doce): 48 m

LATITUTE OS (ADT + Abi): 50 m

ARASENS

ADT + Docetaxel + Darolutamide

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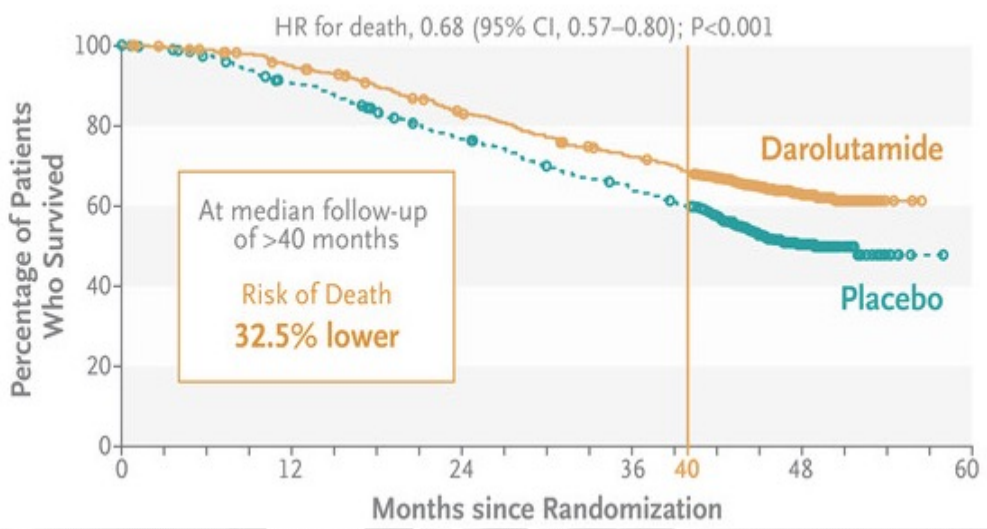
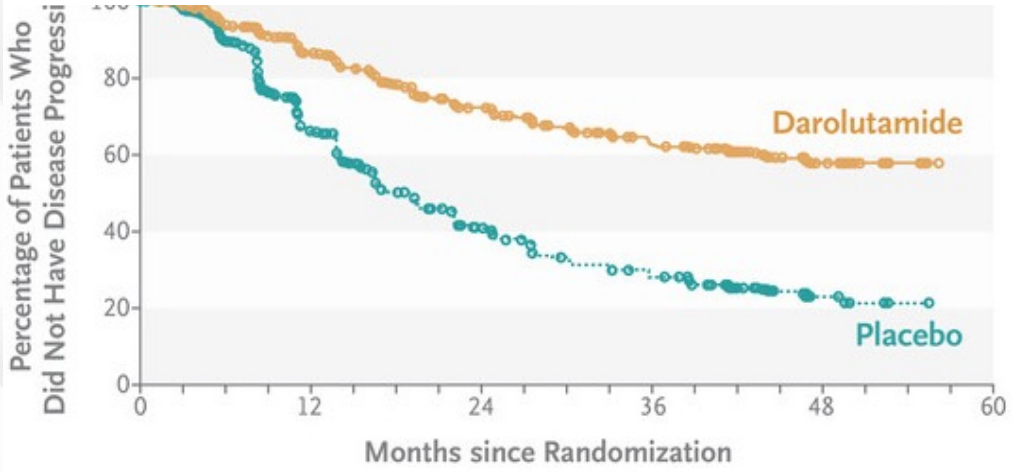
ADT + Docetaxel + Placebo

Overall Survival



Time to Castration-Resistant Prostate Cancer



OS benefit

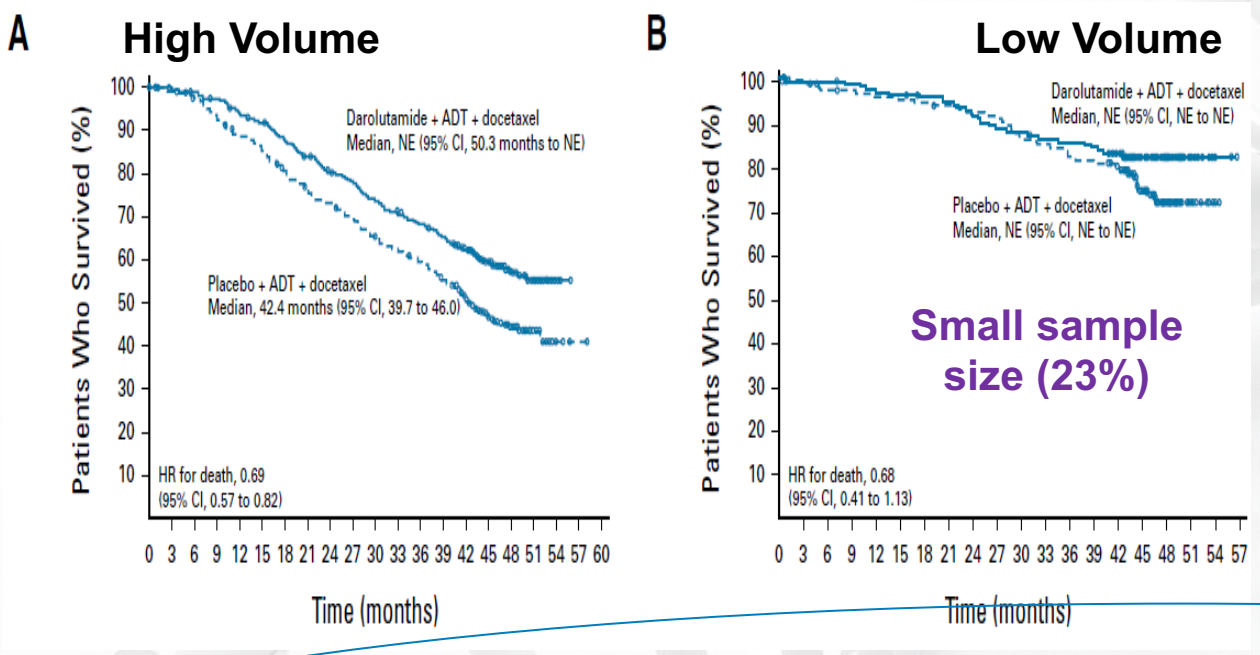
Median OS not reached

Consistent across prespecified subgroups

- De novo HR 0.71 (95% CI 0.59-0.85)
- Recurrent HR 0.61 (95% CI 0.35-1.05) *small subgroup*

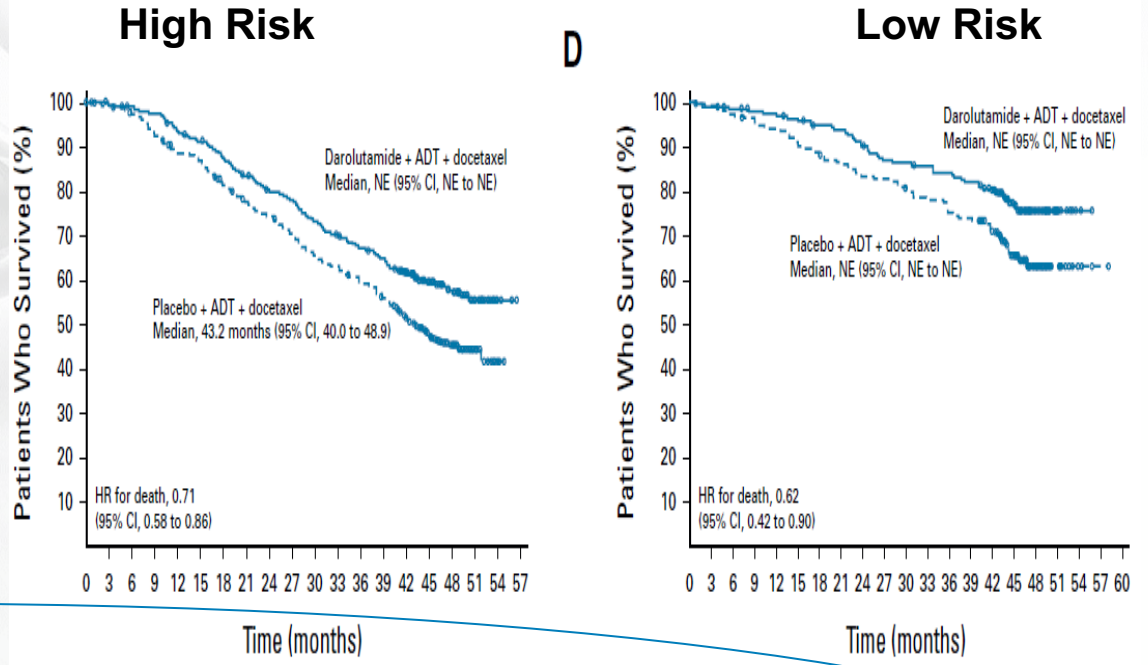
ARASENS: ADT+ Docetaxel + Darolutamide benefit is consistent across subgroups

CHAARTED Criteria



Low volume	≤ 3 bone metastases
High volume	**≥ 4 bone metastases** including >1 outside vertebral column or pelvis or visceral metastasis

LATITUDE Criteria

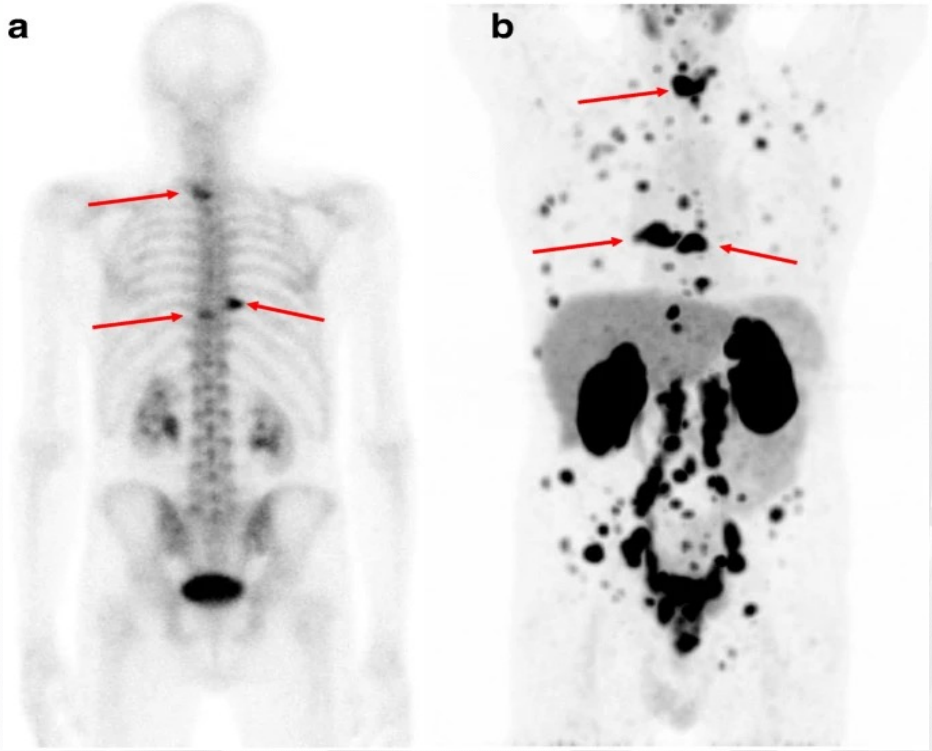


Low Risk	Not high risk
High Risk	≥ 2 of the following high-risk features: Gleason ≥8, ≥3 bone lesions, or measurable visceral mets

Hussain M, et al. Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial. J Clin Oncol. 2023 Jul 10;41(20):3595-3607

LIMITATIONS OF CURRENT VOLUME AND RISK CRITERIA

- **Relies on conventional imaging, not PET PSMA scan**



Conventional bone scan

PET PSMA scan

Low-risk per CHAARTED criteria

- **Volume status is not necessarily reflective of disease biology (early vs late presentation)**
- **Does not account for the presence of any AR-independent clones (benefit from docetaxel)**

→ **Missed chance for early treatment intensification with ADT+Docetaxel+APRI in first-line mHSPC setting**

Lower cumulative toxicities, symptoms, & disease burden before disease progression

only ≈ 50% receive 2nd-line therapies, many too frail to receive docetaxel in mHRPC

Zacho, Helle D., et al. *EJNMMI, 2020*, Feith A, Kim Adv Ther. 2022

ADVERSE EVENTS ARE SIMILAR W/ TRIPLETS

PEACE-1

Severe (Grade ≥3) AEs in ≥5% of Either Group, n (%)	Abiraterone + Doce + ADT* (n = 347)	Doce + ADT* (n = 350)
Hypertension	76 (22)	45 (13)
Neutropenia	34 (10)	32 (9)
Hepatotoxicity	20 (6)	2 (1)
Febrile neutropenia	18 (5)	19 (5)
Gamma-glutamyl transferase increase	17 (5)	14 (4)
Erectile dysfunction	7 (2)	5 (1)
Blood alkaline phosphatase increase	15 (4)	12 (3)

ARASENS

Grade 3/4 AEs in ≥2% of Patients, n (%)	Darolutamide + Doce + ADT (n = 652)	Placebo + Doce + ADT (n = 650)
Neutropenia	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

Predictable, well-characterized, and usually manageable

THE CONTROL ARM ISSUE

PEACE-1

ADT + Docetaxel + Abiraterone

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ADT + Docetaxel

ADT + Abiraterone?

ARASENS

ADT + Docetaxel + Darolutamide

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ADT + Docetaxel + Placebo

ADT + Darolutamide?

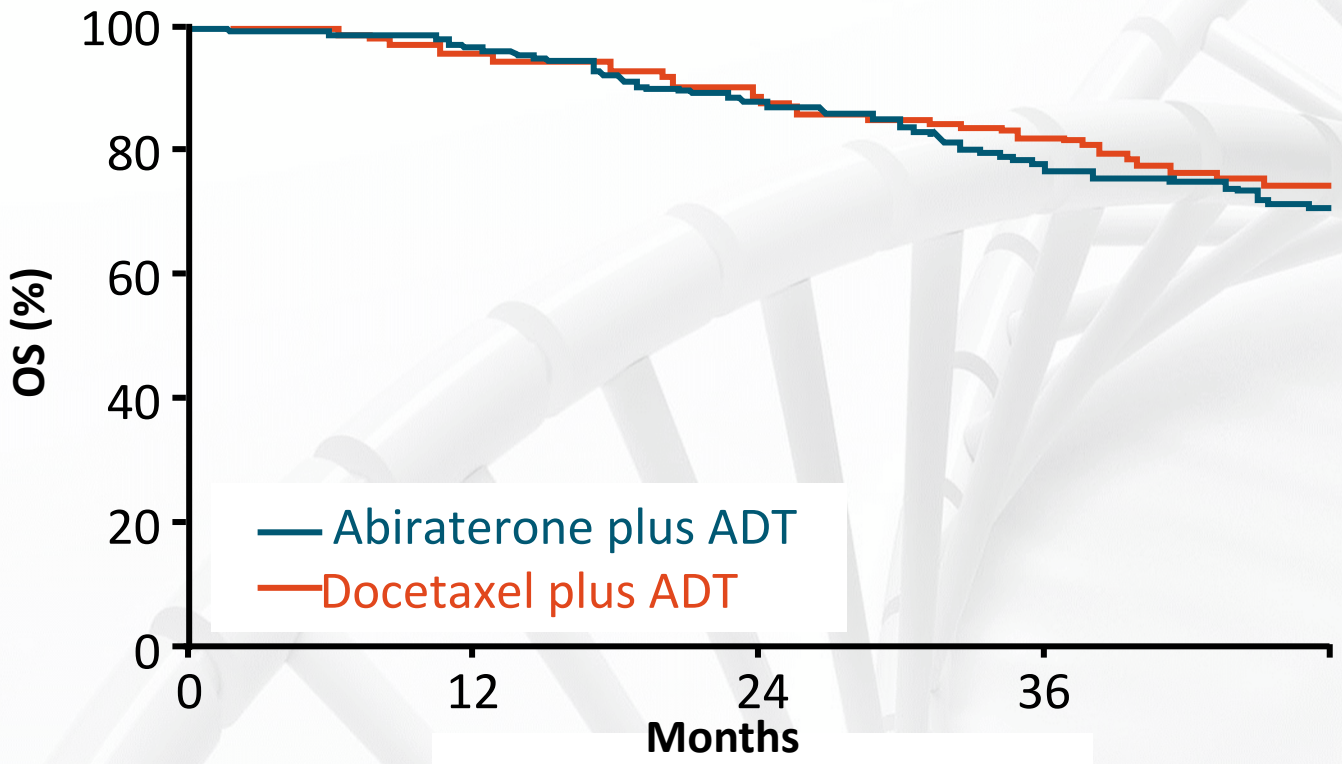
ADT–ARPI vs ADT-docetaxel: no dedicated randomized comparison in mHSCP

Systematic review and network meta-analysis by Wallis et al. → no statistically significant difference in OS between ADT-Abi and ADT-Docetaxel (HR: 0.84, 95% CI: 0.67-1.06).

Wallis CJD et al., Eur Urology, 2018

Limited evidence on superior OS for ADT+ARPI vs ADT+Docetaxel

OVERALL SURVIVAL IN STAMPEDE (multi-arm)



Only direct, randomized data available (not formally powered)

QOL of ADT-Abi vs ADT-docetaxel over 2 years by Rush et al.

- **Missed predefined value for clinical significance**
- **Decrease in QOL in ADT-Docetaxel was *transient***

ADT plus docetaxel control arm:

Appropriate for PEACE-1 + ARASENS

Not necessarily inferior to an ADT-ARPI control arm

Sydes. Ann Oncol. 2018; Rush et al., JCO 2022

TAKE HOME MESSAGES

- **PEACE-1 and ARASENS provide Level 1 evidence on OS improvement with triplet therapy in mHSPC over doublet therapy**

- **Early treatment intensification with triplets provides the greatest improvement in OS to date (over 5 years!) in de-novo prostate cancer and allows ↓ acquired resistance**

- **Triplet therapy is mostly well-tolerated: adverse events are predictable, well-characterized, and usually manageable. The duration of chemotherapy is finite (4.5 months, 6 cycles)**

- **No "one-size-fits-all" approach in the continuum of mHSPC disease states: no current validated molecular markers to guide Tx choice.**

- **Patients with mHSPC who are docetaxel-fit→ Give the most effective treatment available (triplet therapy) based on current evidence**

Thank you

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