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Novel Triplet with Darolutamide Improves OS for mHSPC

BACKGROUND

Despite recent progress in systemic treatment, metastatic, hormone-sensitive prostate cancer (mHSPC) has poor outcomes with an overall survival of 30% at 5 years.[1] Triplet therapy provides another option to improve overall survival in this complex population.

CLINICAL QUESTION:

Does a combination of **darolutamide**, **androgen-deprivation therapy (ADT)**, and **docetaxel** improve survival among patients mHSPC?

1.Oing & Bristow, 2023

METHODS

Study design was a phase 3, international, randomized, double-blind, placebo-controlled trial. Primary end point was overall survival.

STUDY POPULATION **1305 PATIENTS**

651 Darolutamide +ADT + docetaxel

654 Placebo + ADT + docetaxel

MEDIAN AGE 67 years old

0 25 50 75 100

Patient demographics and disease characteristics	Darolutamide + ADT + docetaxel (n = 651)	Placebo + ADT + docetaxel (n = 654)
Gleason score ≥8 at initial diagnosis, n (%)	**505** (77.6)	**516** (78.9)
High volume disease at baseline, n (%)[2]	**497** (76.3)	**508** (77.6)
Metastasis stage at screening, n (%): M1c, visceral metastasis with or without lymph-node or bone metastases	**111** (17.1)	**118** (18.0)
Metastasis stage at initial diagnosis, n (%): M1, distant metastasis	**558** (85.7)	**566** (86.5)
ECOG performance status score, n (%)	**0: 466** (71.6) **1: 185** (28.4)	**0: 462** (70.6) **1: 190** (29.1)
Serum PSA level, median (range), ng/mL	**30.3** (0.0-9219.0)	**24.2** (0.0-11,947.0)

Differences between baseline demographics/disease characteristics of triplet combination therapy groups in ARASENS and PEACE-1[3] trials:

Patient demographics and disease characteristics	ARASENS trial (n = 1305)	PEACE-1 trial (n = 710*)
Treatment arms	1. ADT + docetaxel (n = 654) 2. ADT + docetaxel + darolutamide (n = 651)	1. ADT + docetaxel (n = 355) 2. ADT + docetaxel + abiraterone acetate and prednisone (AAP) (n = 355)
High volume disease at baseline, n (%)	**1005** (77.0)[2]	**456** (64.2)
Metastasis stage at screening, n (%): M1c, visceral metastasis with or without lymph-node or bone metastases	**229** (17.5)	**88** (12.3)
Metastasis stage at initial diagnosis, n (%): M1, distant metastasis	**1124** (86.1)	**710** (100)

*ADT with docetaxel subgroups in PEACE-1 trial

RESULTS

PRIMARY ENDPOINT

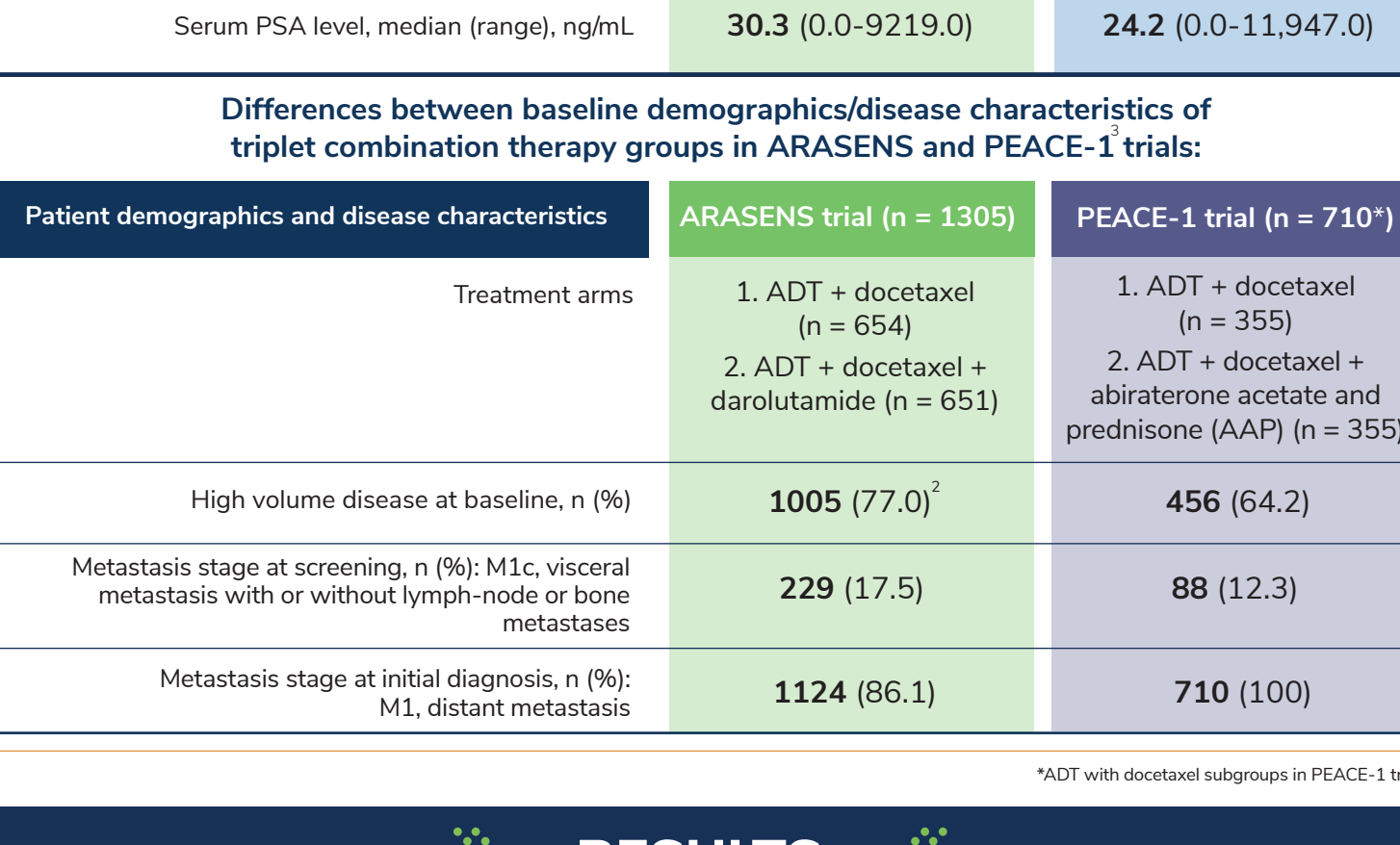
32.5% reduction in the risk of death with an absolute survival benefit of 12.3% at 4 years

- hazard ratio (HR), 0.68; 95% confidence interval (CI), 0.57 to 0.80; P<0.001

PRIMARY ANALYSIS

Overall survival by subgroup (hazard ratio [95% CI])

- Visceral metastatis: HR, 0.79 (95% CI, 0.55 to 1.14)
- Metastatic stage at initial diagnosis:
  - M1 (de novo): HR, 0.71 (95% CI, 0.59 to 0.85)
  - M0 (recurrent): HR, 0.61 (95% CI, 0.35 to 1.05)
- High volume disease: HR, 0.69 (95% CI, 0.57 to 0.82)[2]



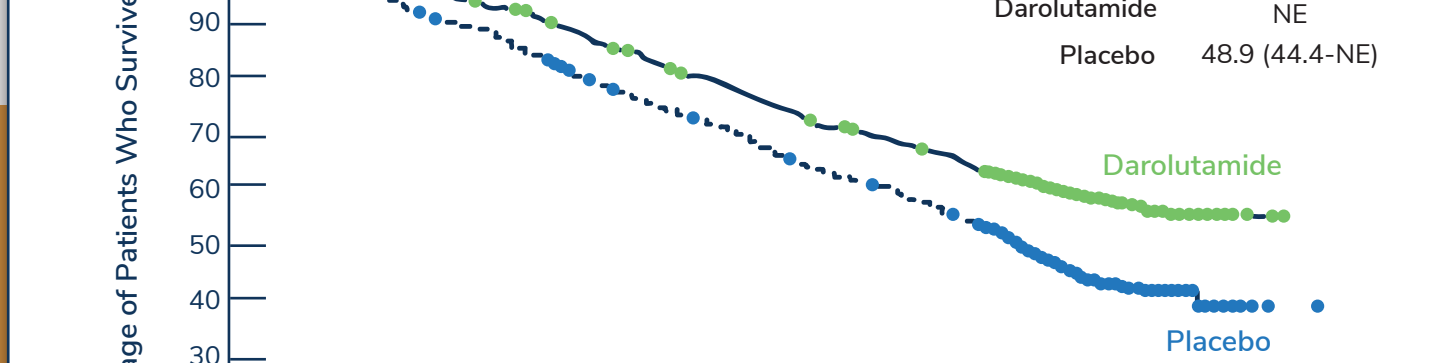
RESULTS

Primary analysis: Secondary efficacy endpoints
Key secondary endpoints, including time to mCRPC [mets], time to pain progression, time to symptomatic skeletal event (SSE), and time to subsequent antineoplastic therapy, **all favoured the addition of darolutamide to ADT plus docetaxel.**

Secondary analysis: Efficacy & safety by disease volume and risk subgroup[2]
Triplet combination therapy with darolutamide, ADT and docetaxel improved overall survival (OS) in patients with high-volume, high-risk and low-risk mHSPC. OS results in the smaller low-volume disease subgroup were non-significant (HR, 0.68; 95% CI, 0.41 to 1.13).

Safety profile/Adverse events

Adverse events (AEs) were similar between treatment groups. Most common AEs occurred more frequently during treatment overlap with doxacetal and included many known docetaxel-related toxicities. AEs of special interest for patients receiving androgen-receptor pathway inhibitors, rash and hypertension were more frequently reported with darolutamide than with placebo:



2. Hussain et al, 2023, 3. Fizazi et al, 2022

WHAT THIS STUDY ADDS

- **Provides evidence for survival benefit of darolutamide** in treatment-naive metastatic prostate cancer with consistent benefit in high volume population
- Adds to growing literature on feasibility and **safety of upfront triplet therapy**
- Whether all patients with low volume disease need treatment intensification beyond ADT and androgen receptor axis-targeted (ARAT) agents requires further exploration

REFERENCES: (1) Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): A Multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. The Lancet. 2022;399(10336):1695-1707. doi:10.1016/s0140-6736(22)00367-1. (2) Hussain M, Tombal B, Saad F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer (mHSPC) by disease volume and risk subgroups in the phase III ARASENS trial. Journal of Clinical Oncology. 2023;41(20):3595-3607. doi:10.1200/jco.23.00041. (3) Oing C, Bristow RG. Systemic treatment of metastatic hormone-sensitive prostate cancer—upfront triplet versus Doublet combination therapy. ESMO Open. 2023;8(2):101194. doi:10.1016/j.esmoop.2023.101194. (4) Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. New England Journal of Medicine. 2022;386(12):1132-1142. doi:10.1056/nejmoa21191

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