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Darolutamide plus ADT in mHSPC: ARASEC

US prospective, open-label phase 2 study with an external control arm

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Disclosures

Study sponsorship

- ARASEC (NCT05059236): Bayer
- CHAARTED (NCT00309985): ECOG-ACRIN Cancer Research Group and National Cancer Institute National Clinical Trials Network
- ARANOTE (NCT04736199): Bayer and Orion

Dr. McKay's disclosures

- Consulting fees from Astellas/Medivation, Ambrx, Arcus, ArteraAI, AstraZeneca, AVEO, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb, Calithera, Caris, Daiichi Sankyo, Dendreon, Eisai, Exelixis, GSK, Johnson & Johnson, Lilly, Merck, Myovant, Neomorph, Nimbus, Novartis, Pfizer, Precede, Sanofi, Seagen, Sorrento Therapeutics, Telix, and Tempus
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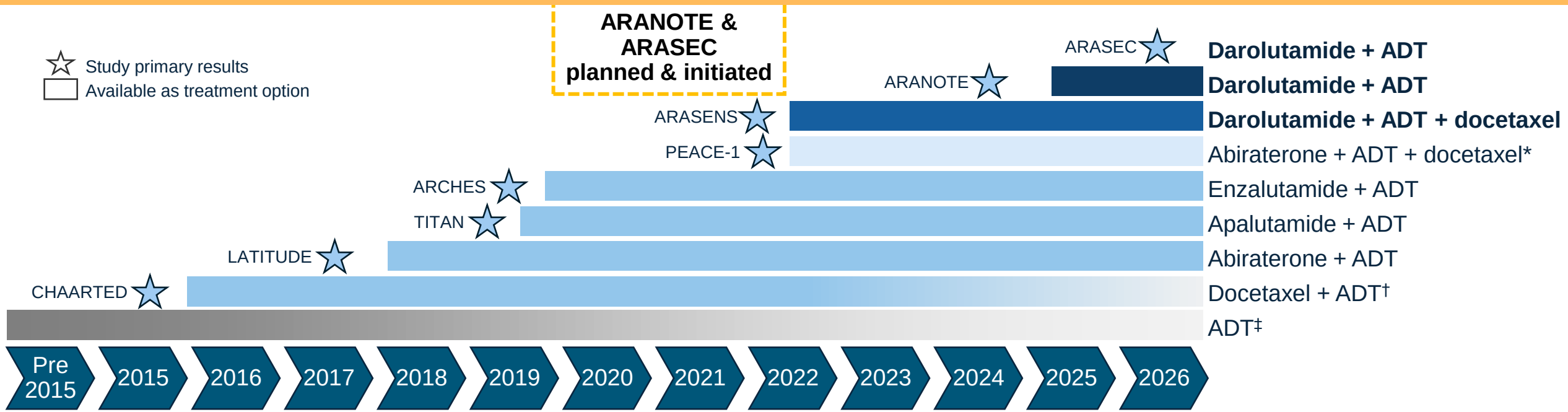
Why was ARASEC needed?

By 2020, combination therapy was the recommended standard of care for mHSPC[1]
Data on darolutamide + ADT in mHSPC were requested by clinicians and patients
An ADT control arm was not possible in the USA because ADT was no longer standard of care



*Not licensed indication.
†No longer recommended as doublet regimen.
‡Not recommended as monotherapy in most patients.
1. Lowrance WT, et al. *J Urol* 2021;205:14-21.

ARASEC is a US open-label study comparing a prospectively enrolled darolutamide arm versus the ADT arm from CHAARTED[1]

Patients
- Histologically or cytologically confirmed adenocarcinoma
- Radiographic evidence of metastatic disease*
- ECOG performance status 0, 1, or 2†

Open-label darolutamide 600 mg BID + ADT‡ (N=223)

ADT control arm from CHAARTED§ (N=393)

1:1 matching

Primary endpoint
- PFS¶

Secondary endpoints
- OS
- Time to mCRPC**
- Radiographic PFS††
- PSA <0.2 ng/mL response rate
- Safety (darolutamide arm only)

- Inclusion and exclusion criteria aligned with the CHAARTED enrollment criteria
- The schedule of assessments followed the CHAARTED schedule
- The PFS endpoint definition matched the CHAARTED definition§

*Metastatic prostate cancer documented by positive bone scan or metastatic lesions on computed tomography or magnetic resonance imaging (per investigator's discretion).
†Participants with ECOG performance status 2 were eligible only if the decline in performance status was due to metastatic prostate cancer.
‡ADT (with or without first-generation antiandrogen) started no earlier than 120 days before enrollment.
§Data were obtained from the National Cancer Institute's NCTN/NCORP data archive.
¶PFS is defined per CHAARTED as PSA progression OR clinical progression (increasing symptomatic bone metastases *or* radiographic progression [RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases] *or* clinical deterioration due to cancer per investigator's opinion) OR death.
**mCRPC is defined as for PFS without the death component.
††Imaging assessments in ARASEC were performed as described in CHAARTED; regular imaging was not mandatory, with assessments in both arms according to local standard of care.
1. McKay RR, et al. *Future Oncol* 2025;21:1365–1375.

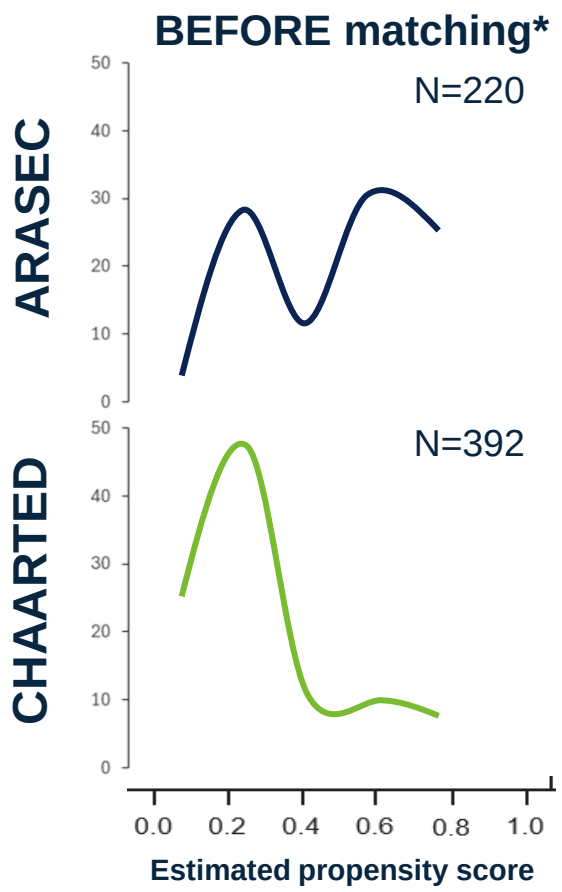
ARASEC and CHAARTED patients were matched 1:1 using propensity scores[1]

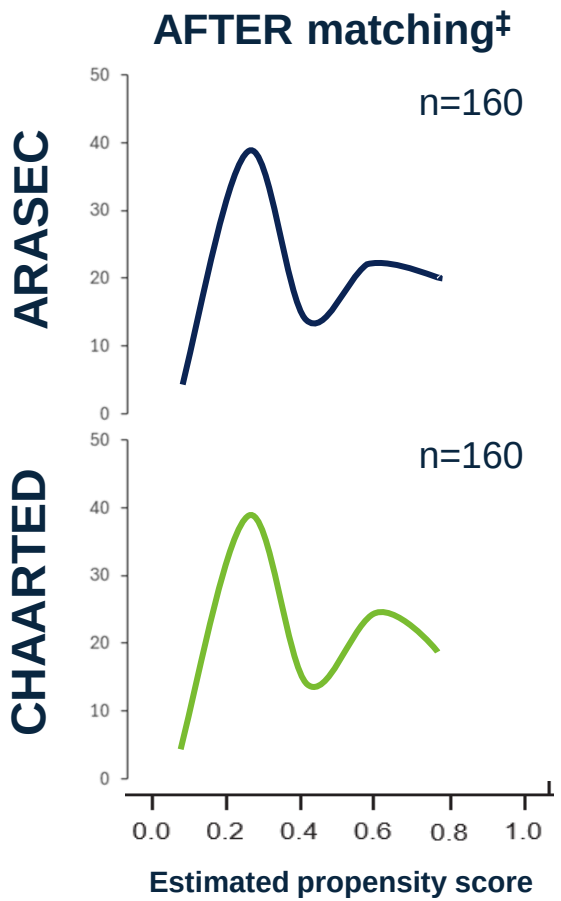
Distribution of propensity scores

Based on:

- **Age** (<68 vs ≥68 years)
- **ECOG performance status** (0 vs >0)
- **Extent of disease** (high volume with visceral metastases vs high volume without visceral metastases vs low volume)
- **Prior local therapy** (yes vs no, as a proxy for recurrent vs *de novo* disease)
- **Gleason score** (<8 vs ≥8 vs unknown)
- **Baseline PSA level** (≤10 vs >10 ng/mL)

Propensity score matching†



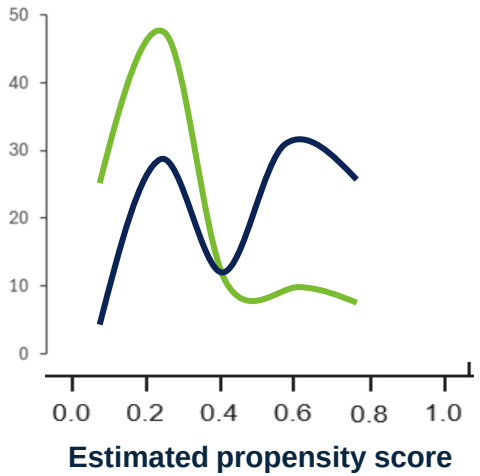


*In ARASEC, two patients were excluded from matching for missing extent of disease and one patient for missing extent of disease and PSA; in CHAARTED, one patient was excluded for missing prior local therapy and PSA.
†Using the greedy nearest-neighbor method without replacement and a caliper of 0.1.
‡Assuming a one-sided alpha of 0.025, power of 90%, and hypothetical enrollment ratio of 1:1 between the investigational and external control arms, approximately 160 patients/arm and 161 PFS events across the two arms were required to detect a HR of 0.60 in median PFS.

1. McKay RR, et al. *Future Oncol* 2025;21:1365–1375.

Matching ensured that patients with similar scores were compared

BEFORE matching*



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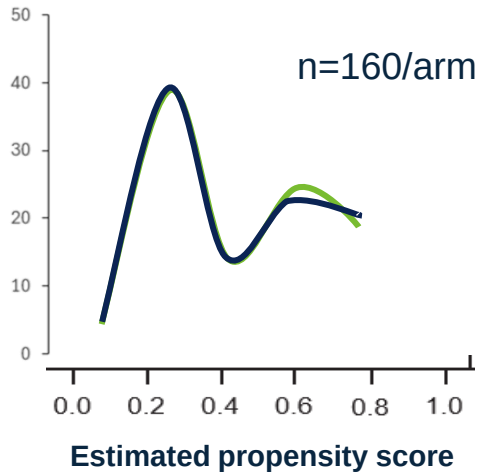
Propensity score matching†

AFTER matching‡



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1. McKay RR, et al. *Future Oncol* 2025;21:1365–1375.

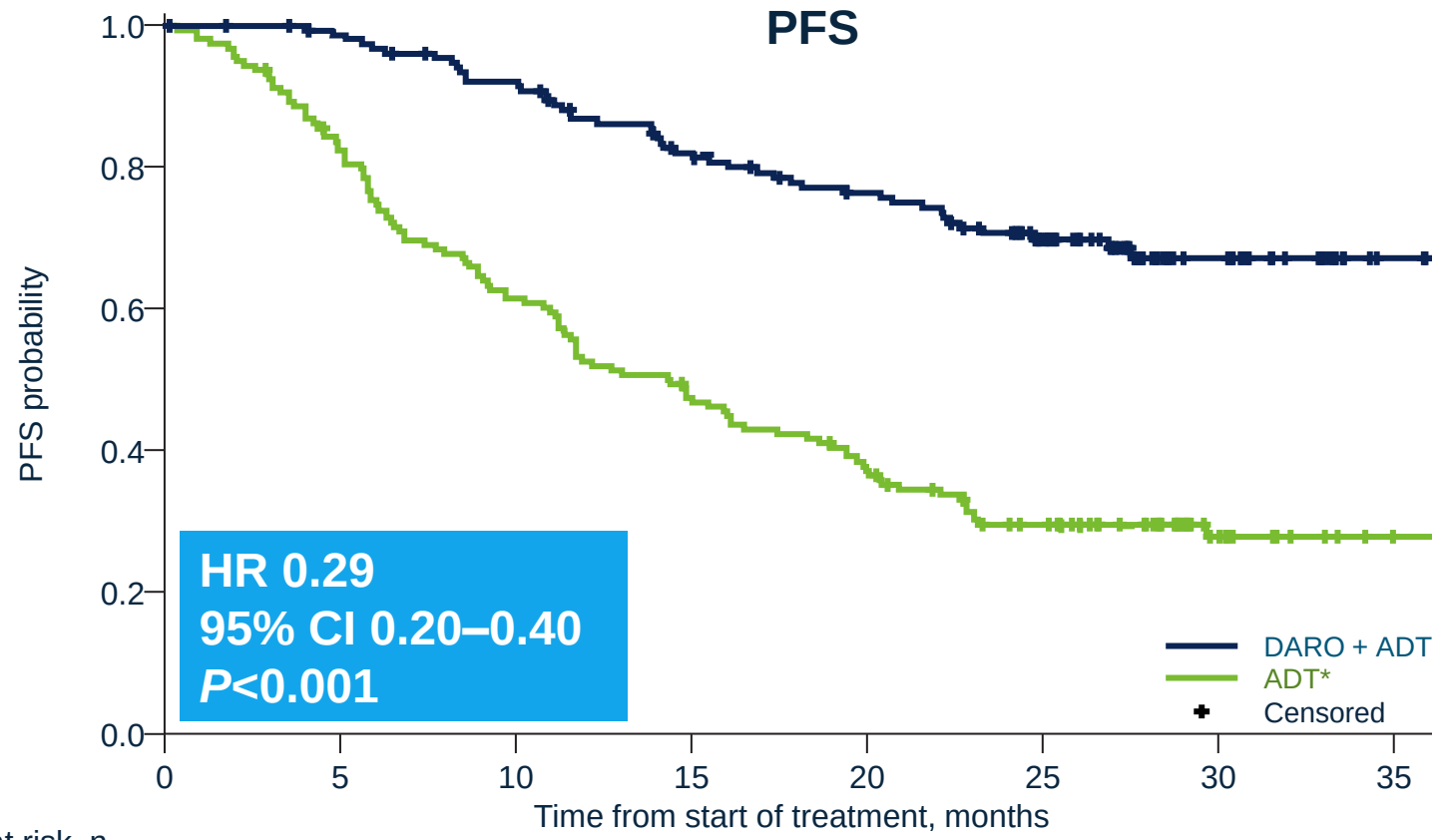
Matching resulted in well-balanced treatment arms[1]

Baseline characteristics		Darolutamide + ADT (n=160)	ADT alone (CHAARTED) (n=160)
Age, years	Median (range)	71 (45–91)	69 (39–90)
Age category, %	<68 years ≥68 years	40.0 60.0	39.4 60.6
ECOG performance status, %	0 1 2	81.9 15.6 2.5	80.6 19.4 0
Gleason score at initial diagnosis, %	<8 ≥8 Unknown	28.1 67.5 4.4	30.6 65.0 4.4
PSA, ng/mL	Median (range)	6.0 (0–7978)	9.8 (0–4071)
PSA category, %	≤10 ng/mL >10 ng/mL	62.5 37.5	50.0 50.0
Extent of disease, %	High volume with visceral metastases High volume without visceral metastases Low volume	23.1 37.5 39.4	20.6 36.3 43.1
Prior local therapy, %*	No (*de novo* mHSPC) Yes (recurrent mHSPC)	73.8 26.3	70.0 30.0

*Prior therapy is being used as a proxy for *de novo* (synchronous) versus recurrent (metachronous) mHSPC.

1. McKay RR, et al. *Future Oncol* 2025;21:1365–1375.

ARASEC met its primary endpoint, demonstrating significantly improved PFS with darolutamide + ADT vs ADT



	Events, n (%)	Median, months
DARO + ADT (n=160)	46 (28.8)	NE
ADT* (n=160)	111 (69.4)	14.3

Median follow-up

- DARO + ADT: 26.2 months
- ADT: 28.3 months†

PFS is defined as:

- PSA progression

or

- Clinical progression:
  - Increasing symptomatic bone metastases *or*
  - Radiographic progression (RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases) *or*
  - Clinical deterioration due to cancer per investigator opinion

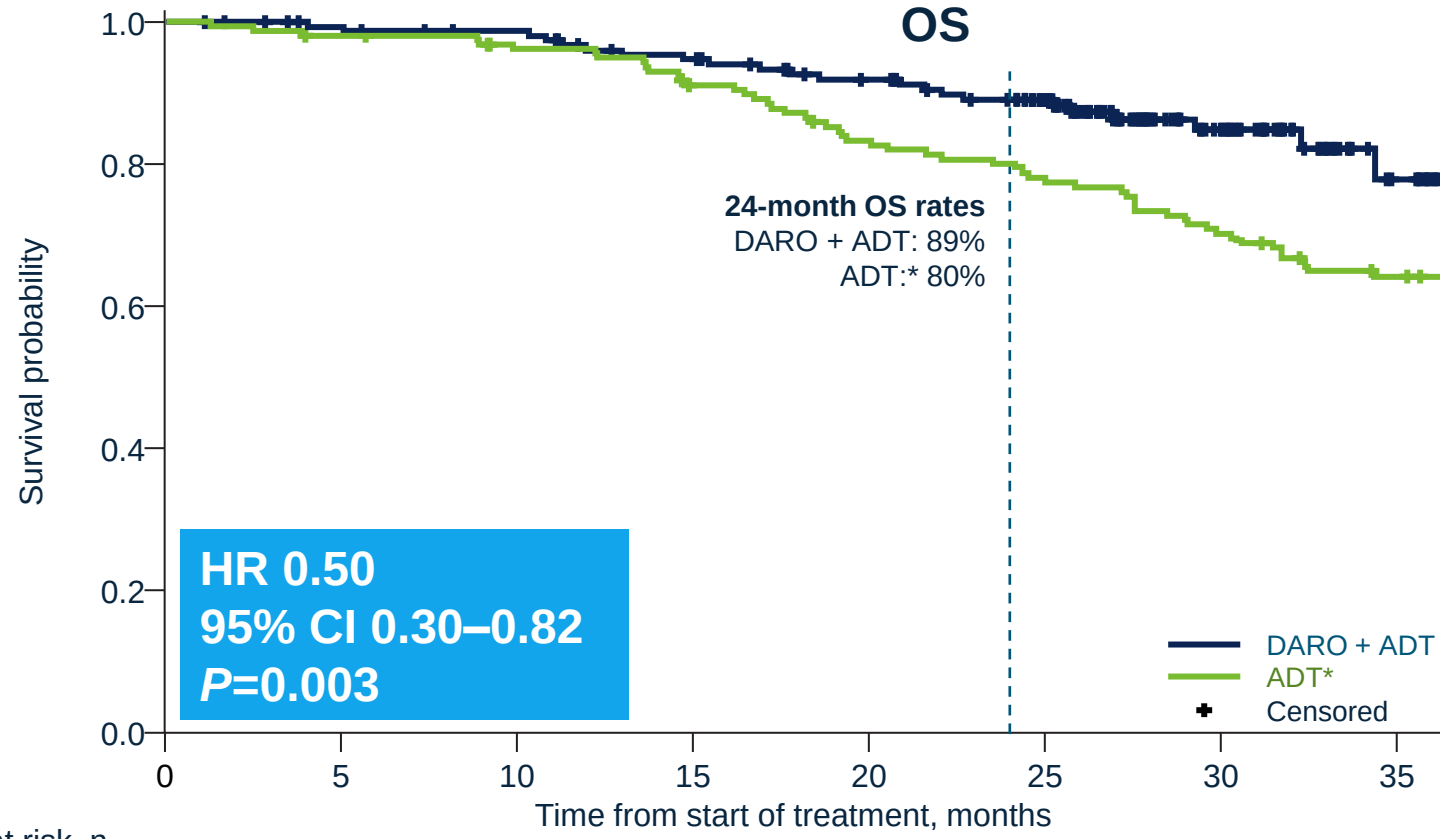
or

- Death

*CHAARTED.

†The CHAARTED ADT arm had a longer observation time than the ARASEC darolutamide arm. Hence, an algorithm was used to provide data from CHAARTED with similar maturity to those in the darolutamide arm at data cut-off. The median follow-up was then computed as the median time to censoring using a method described by Betensky RA. *Clin Trials* 2015;12:403–408.

Darolutamide + ADT significantly improved OS vs ADT



Patients at risk, n

DARO + ADT	160	154	150	140	129	116	52	16
ADT*	160	156	150	140	127	119	107	95

	Events, n (%)	Median, months
DARO + ADT (n=160)	22 (13.8)	NE
ADT* (n=160)	62 (38.8)	NE

*CHAARTED.

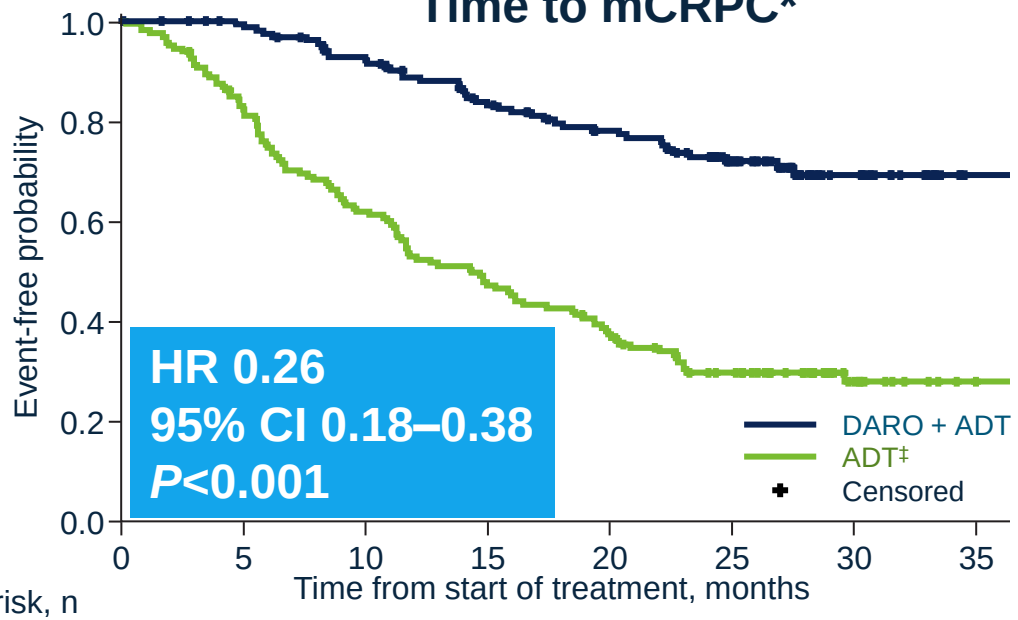
The OS benefit was achieved despite proportionally more patients in the ADT arm (65%) vs the darolutamide arm (26%) receiving subsequent life-prolonging therapy

	Darolutamide + ADT Matched population	ADT Matched population
Patients with mCRPC events, n	42	110
≥1 life-prolonging therapy, n (%)*	**11/42 (26.2)**	**71/110 (64.5)**
Abiraterone and/or enzalutamide	5 (11.9)	42 (38.2)
Docetaxel	7 (16.7)	49 (44.5)
Cabazitaxel	0	14 (12.7)
Sipuleucel-T	4 (9.5)	10 (9.1)

*Life-prolonging subsequent therapies for prostate cancer are defined as: abiraterone, apalutamide, enzalutamide, docetaxel, cabazitaxel, radium 223, sipuleucel-T, PSMA-617-Lu-177, rucaparib, and olaparib; some patients (n=30) in CHAARTED received radiotherapy as subsequent life-prolonging therapy. Some patients received more than one subsequent therapy.

Darolutamide + ADT significantly delayed time to mCRPC and radiographic PFS vs ADT

Time to mCRPC*

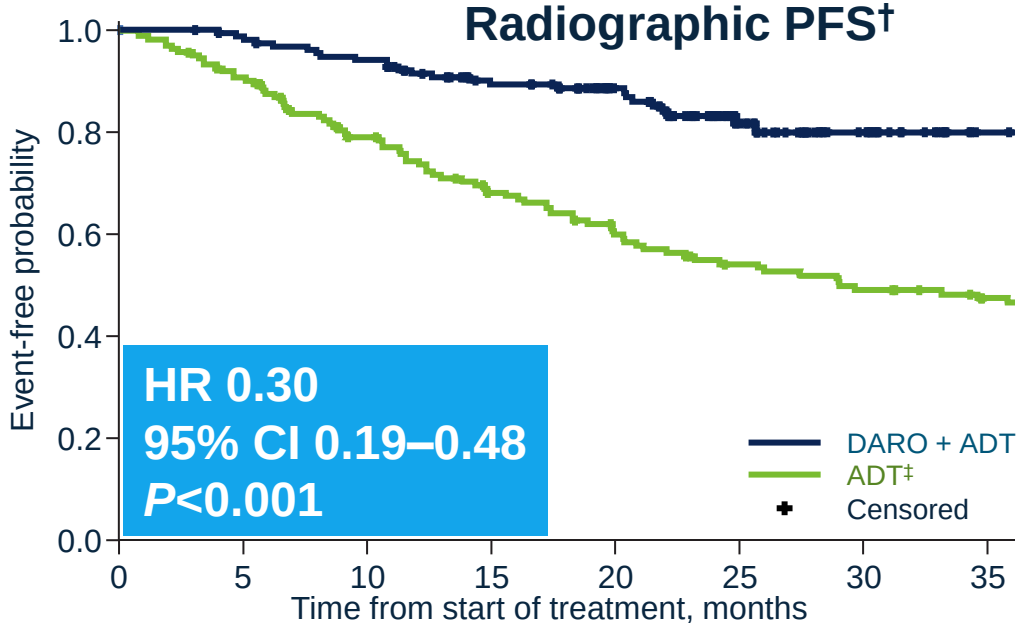


Patients at risk, n

DARO + ADT	160	152	137	119	105	71	33	9
ADT	160	129	97	73	57	39	14	4

	Events, n (%)	Median, months
DARO + ADT (n=160)	42 (26.3)	NE
ADT* (n=160)	110 (68.8)	14.3

Radiographic PFS†



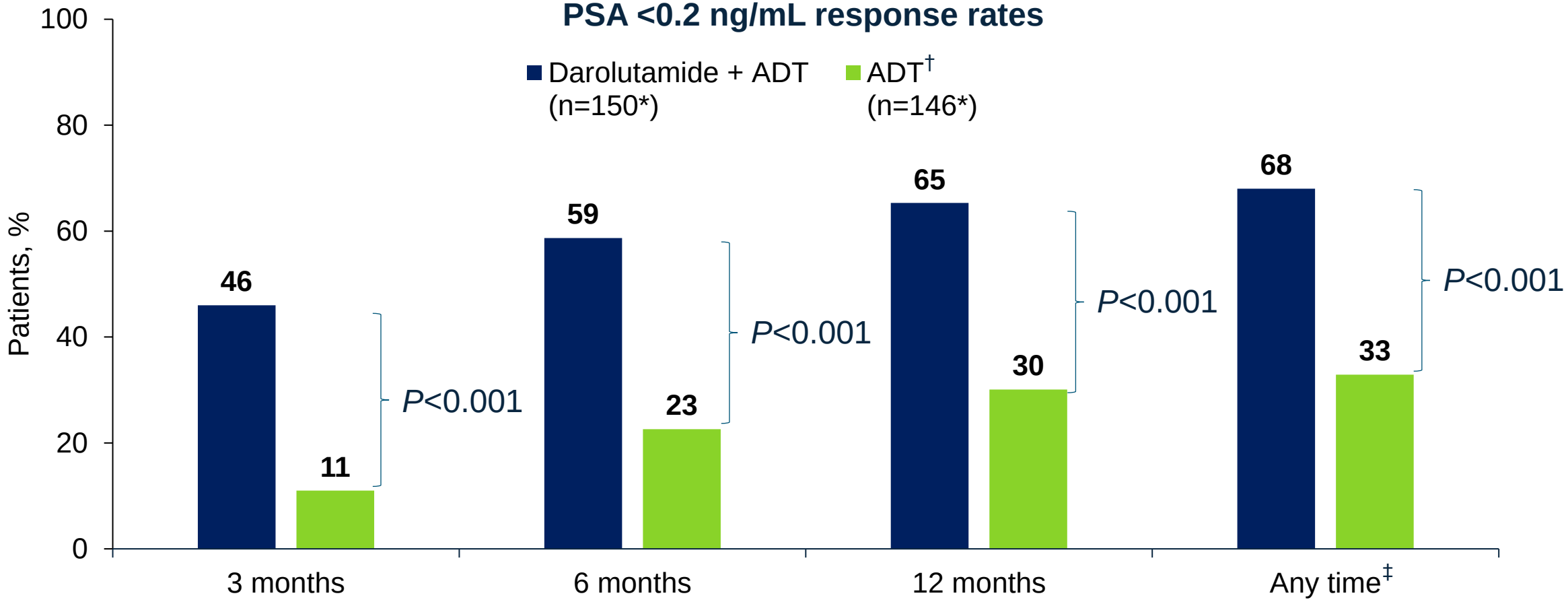
	160	151	143	122	101	51	23	2
	160	143	118	98	84	73	66	58

Events, n (%)	Median, months
25 (15.6)	NE
79 (49.4)	29.0

As in CHAARTED, regular imaging was not mandatory in ARASEC, with assessments in both arms according to local standard of care

*Time to mCRPC is defined as PSA progression OR clinical progression (increasing symptomatic bone metastases *or* radiographic progression [RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases] *or* clinical deterioration due to cancer per investigator's opinion), whichever occurred first.
†Radiographic PFS is defined as time to radiographic progression [RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases] *or* death, whichever occurred first.
‡CHAARTED.

PSA <0.2 ng/mL response rates were more than doubled in the darolutamide arm vs the ADT arm at all time points assessed



*PSA response was assessed in patients with baseline PSA ≥0.2 ng/mL.
†CHAARTED.
‡"Any time" is defined as PSA <0.2 ng/mL reported at any time during the study after enrollment until 30 days after last dose or start of new anticancer therapy; median follow-up 26.2 months in the darolutamide arm and 28.3 months in the ADT arm (follow-up duration in the ADT arm was adjusted to match the follow-up duration in the darolutamide arm).

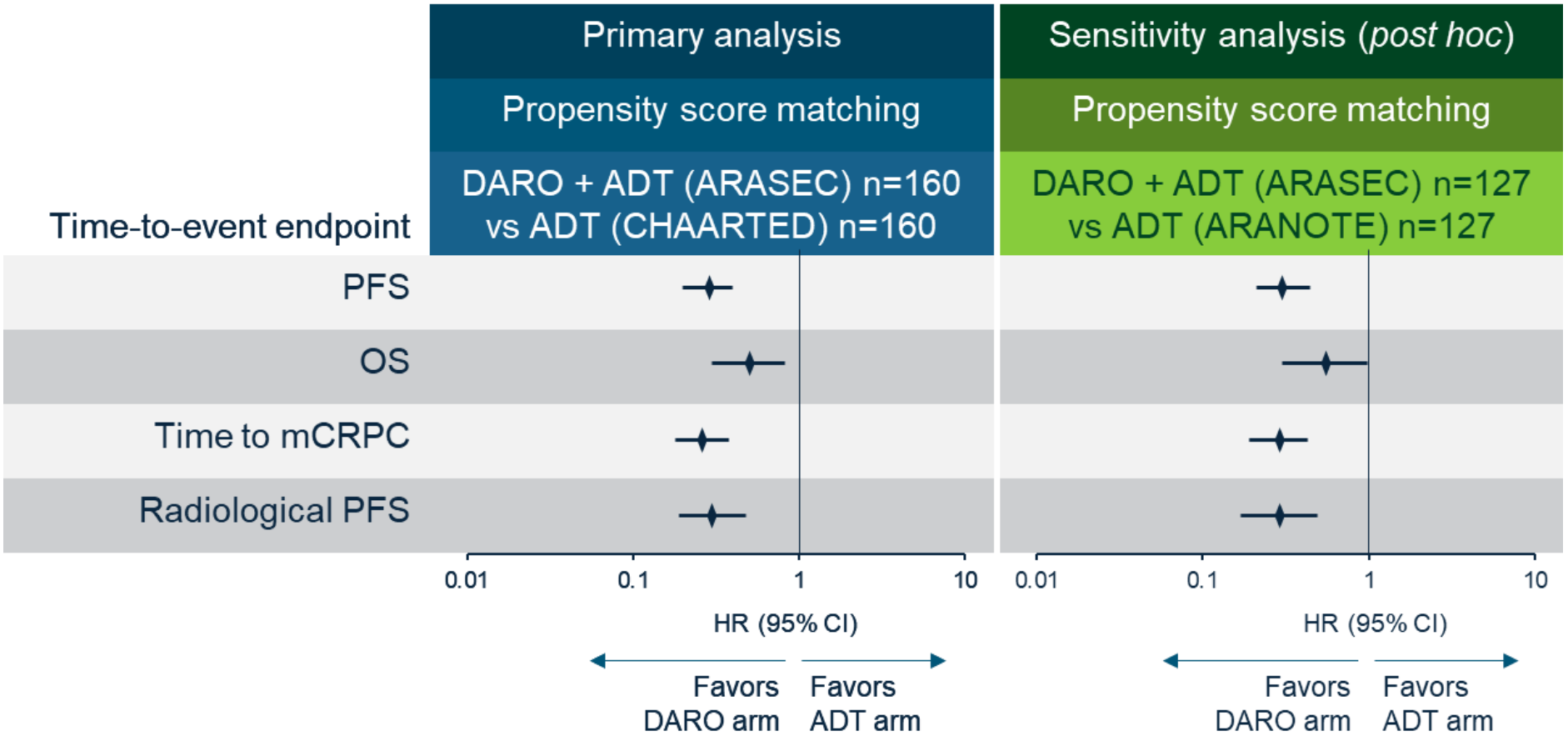
Sensitivity analysis addressing time bias

Q How does darolutamide + ADT perform vs a **contemporary ADT arm**?

Sensitivity analysis

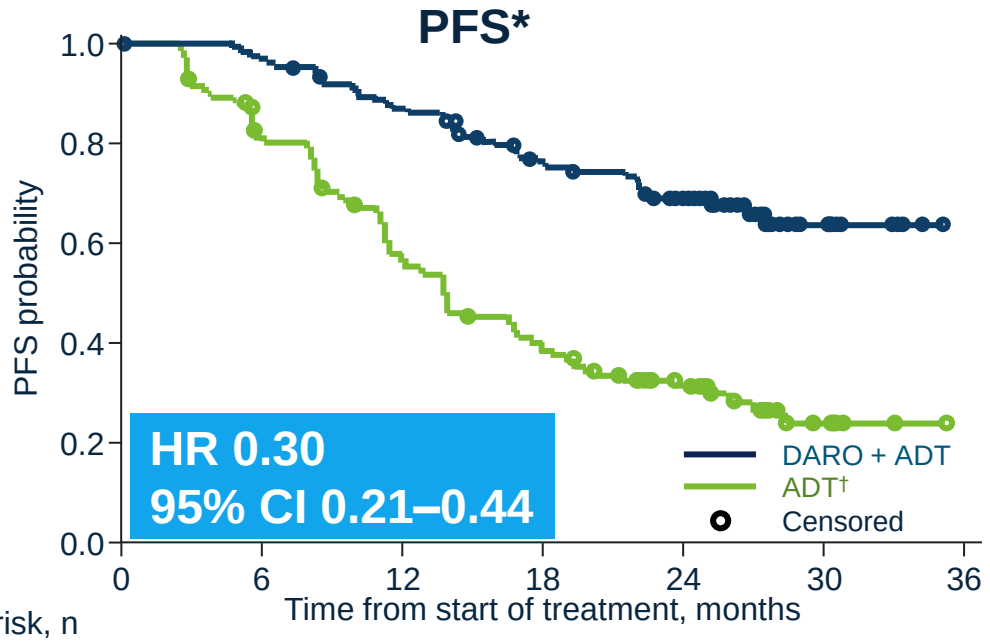
ARASEC darolutamide arm was compared *post hoc* with the **ARANOTE ADT** arm using the same **propensity score matching** as the primary analysis (n=127/arm)

The sensitivity analysis vs a contemporary phase 3 cohort strongly supports the ARASEC primary findings, with all confidence intervals, including for OS, below 1



*Using the same covariates and matching criteria as the primary analysis vs CHAARTED.

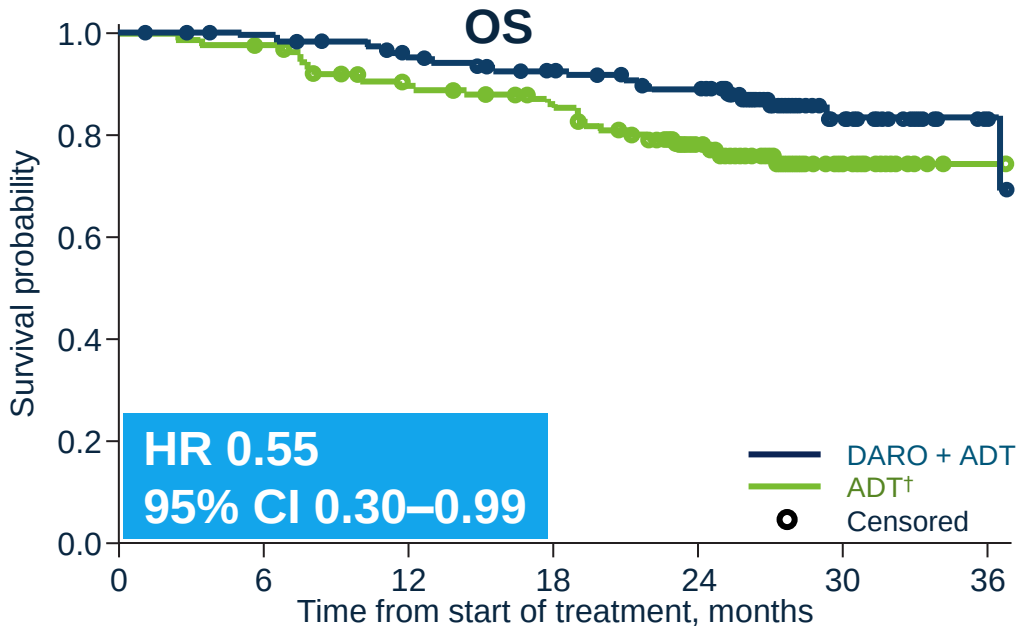
In the sensitivity analysis vs ARANOTE, darolutamide + ADT prolonged PFS and OS vs ADT alone



Patients at risk, n

DARO + ADT	127	120	106	87	74	17	0
ADT	127	99	66	45	28	7	0

	Events, n (%)	Median, months
DARO + ADT (n=127)	40 (31.5)	NE
ADT (n=127)	87 (68.5)	13.8



	127	123	114	106	98	33	6
	127	123	108	99	72	23	1

	Events, n (%)	Median, months
DARO + ADT	18 (14.2)	NE
ADT	29 (22.8)	NE

*In ARASEC, PFS was defined as PSA progression OR clinical progression (increasing symptomatic bone metastases *or* radiographic progression [RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases] *or* clinical deterioration due to cancer per investigator's opinion), *or* death, whichever occurred first. In ARANOTE PSA progression was based on the current PCWG3 criteria and was evaluated with the investigator-assessed clinical deterioration component for ARASEC. Harmonizing these differences resulted in little difference in results reported here.
†ARANOTE.

Sensitivity analysis addressing selection bias

Sensitivity analysis

Q How does darolutamide + ADT perform vs a **contemporary ADT arm**?

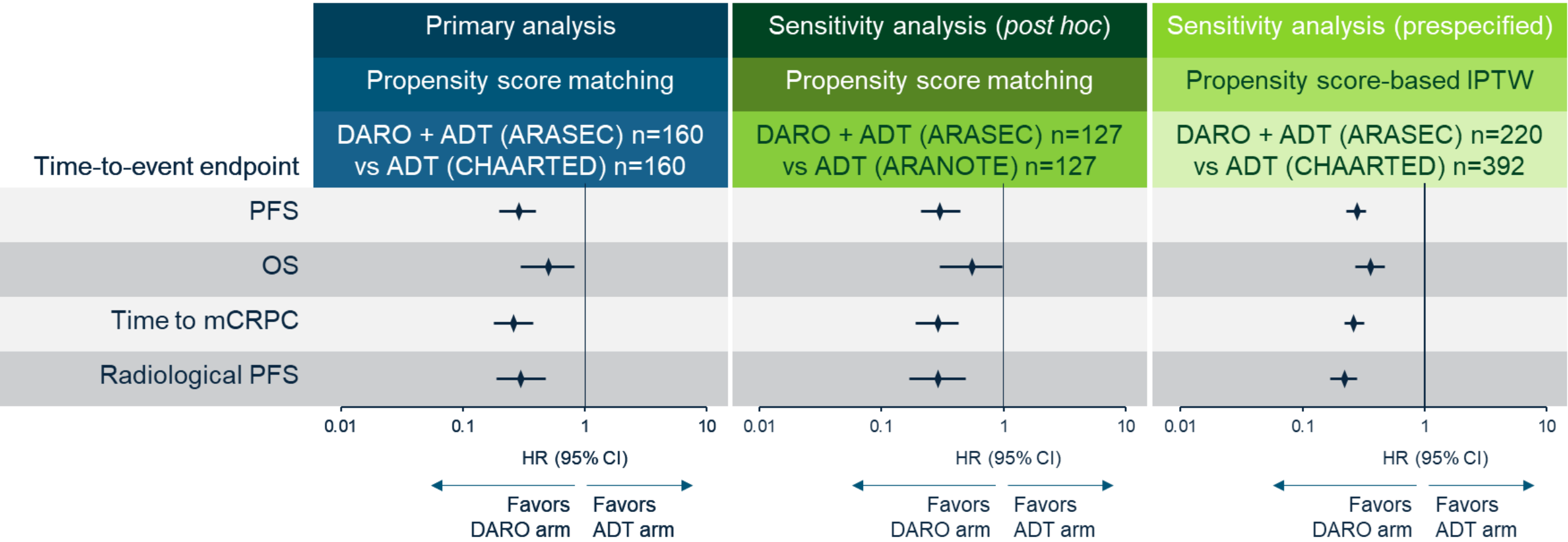
→ ARASEC darolutamide arm was compared *post hoc* with the **ARANOTE ADT** arm using the same **propensity score matching** as the primary analysis (n=127/arm)

Q Do the outcomes change if we include the **unmatched patients**?

→ Prespecified analysis in **all enrolled patients** in the ARASEC darolutamide and CHAARTED ADT arms, using propensity score-based **IPTW** to adjust for differences in baseline characteristics between arms

IPTW, inverse probability of treatment weighting.

The sensitivity analysis in the broader match-eligible population also strongly supports the ARASEC primary findings



IPTW, inverse probability of treatment weighting.

The safety and tolerability profile of darolutamide is in line with the well-established safety profile of darolutamide

TEAEs, n (%)	Darolutamide + ADT ARASEC match-eligible population (n=223) Open-label	TEAEs, n (%)	ADT ARANOTE safety analysis set (n=221) Blinded
Any grade	214 (96.0)	Any grade	199 (90.0)
Worst severity		Worst severity	
Grade 1	37 (16.6)	Grade 1	42 (19.0)
Grade 2	92 (41.3)	Grade 2	78 (35.3)
Grade 3	77 (34.5)	Grade 3	63 (28.5)
Grade 4	3 (1.3)	Grade 4	4 (1.8)
Grade 5*	5 (2.2)	Grade 5*	12 (5.4)
Serious	52 (23.3)	Serious	52 (23.5)
Leading to treatment discontinuation	18 (8.1)	Leading to treatment discontinuation	20 (9.0)†

Safety data were not recorded in detail in the CHAARTED ADT arm[1]

*No grade 5 events were deemed to be related to study drug.
†Discontinuation of placebo.
1. Sweeney CJ, et al. *N Engl J Med* 2015;373:737–746.

Conclusions

- ARASEC provides further evidence for the efficacy and safety of darolutamide + ADT in mHSPC, reinforcing findings from ARANOTE, in a US population
  - Darolutamide + ADT resulted in significant PFS (HR 0.29), OS (HR 0.50), and PSA response (*P*<0.001) vs ADT alone
  - Sensitivity analysis vs contemporary trial (ARANOTE) control arm strongly supports robustness of results
- First study in prostate cancer to use propensity score matching with external phase 3 trial control arms

Potentially practice-changing study design

Avoids placebo arm, alleviating patient concerns

Reduces costs; facilitates rapid accrual and endpoint analysis

We thank the patients, their families, and all of the investigators who participated in ARASEC, CHAARTED, and ARANOTE

We thank the National Cancer Institute NCTN/NCORP for providing the CHAARTED patient-level data included in the analyses

Thank you for your attention

View the slides and accompanying video