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Matching-adjusted indirect comparison (MAIC) between enzalutamide (ENZA) and darolutamide (DARO) doublet therapy for metastatic hormone-sensitive prostate cancer (mHSPC)

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Objectives

- **To assess the comparative efficacy of ENZA + ADT versus DARO + ADT in the treatment of patients with mHSPC using the MAIC methodology**

Conclusions

- **Patients with mHSPC treated with ENZA + ADT had a significantly lower risk of radiographic progression or death and of progression to castration resistance compared to patients treated with DARO + ADT**
- **Similar results were observed in the DOC-naïve population**
- **Findings from this study can help inform treatment decisions for patients with mHSPC**

Plain Language Summary

Please scan this QR code with your smartphone app to view a plain language summary of the accepted scientific abstract.

References

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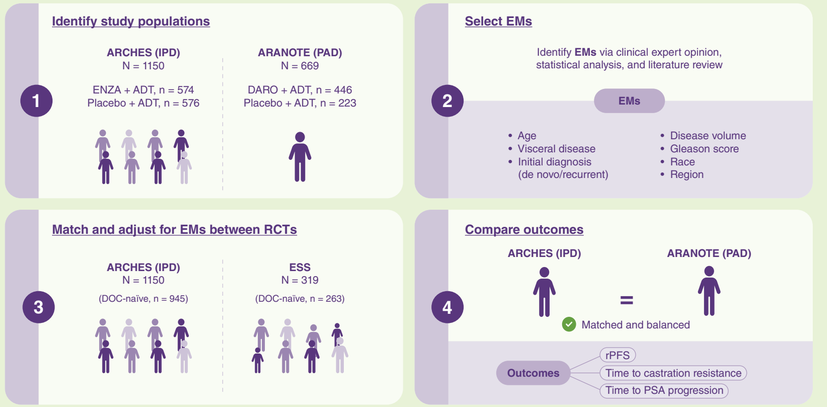
Background

- ENZA and DARO are androgen receptor pathway inhibitors (ARPIs) used as treatment options (as doublet therapy in combination with androgen-deprivation therapy [ADT]) for patients with mHSPC[1,2]
- In the phase 3 ARCHES (NCT02677896) double-blind randomized controlled trial (RCT) in patients with mHSPC (N = 1150), ENZA + ADT (n = 574) significantly reduced the risk of metastatic progression or death compared to placebo + ADT (n = 576)[1]
- In the phase 3 ARANOTE (NCT04736199) double-blind RCT in patients with mHSPC without prior use of chemotherapy (including docetaxel [DOC]) or immunotherapy (N = 669), DARO + ADT (n = 446) significantly delayed radiographic progression or death compared to placebo + ADT (n = 223)[2]
- Adverse events (AEs; any grade) occurring in >10% of patients receiving ENZA + ADT (ARCHES) included hot flash (n = 155; 27.1%), fatigue (n = 112; 19.6%), and arthralgia (n = 70; 12.2%); AEs (any grade) occurring in >10% of patients receiving DARO + ADT (ARANOTE) included anemia (n = 91; 20.4%), arthralgia (n = 55; 12.4%), and urinary tract infection (n = 52; 11.7%)[1,2]
  - There was a similar rate of discontinuation due to AEs in patients receiving ENZA + ADT (n = 41; 7.2%) compared with patients receiving DARO + ADT (n = 27; 6.1%)
- In the absence of direct head-to-head RCTs, MAIC analysis enables indirect efficacy comparisons by adjusting for differences in effect modifiers (EMs) between trials, thus minimizing biases due to population differences[3–5]

Methods

- The MAIC analysis compared the ARCHES and ARANOTE RCTs, with placebo + ADT as the common comparator (**Figure 1**)
- Individual patient data (IPD) from ARCHES were adjusted to match baseline characteristics of published aggregate data (PAD) from ARANOTE[1,2,6]
  - Adjustment weights were estimated using the quasi-Newton optimization method to account for discrepancies in populations regarding EMs, as identified by clinical experts, statistical assessment, and a review of the relevant literature[3,6]
- Radiographic progression-free survival (rPFS), time to castration resistance, and time to prostate-specific antigen (PSA) progression were compared using Cox proportional hazards model, incorporating the estimated weights for ARCHES patients
  - Sensitivity analyses were performed with Eastern Cooperative Oncology Group Performance Status (ECOG PS) as an additional EM
  - In all comparisons, DARO + ADT served as the reference treatment
- Outcomes were analyzed in the total study population and in the subgroup of DOC-naïve patients; for the ARCHES subgroup of DOC-naïve patients (n = 945), 471 patients received ENZA + ADT and 474 patients received placebo + ADT[1]
  - The MAIC analysis did not include a DOC-exposed population, as patients with prior DOC use were excluded from ARANOTE[2]

Figure 1. The MAIC method used to compare the efficacies of ENZA + ADT and DARO + ADT



Results

- Assessment of heterogeneity between the ARCHES and ARANOTE study designs and populations revealed differences in sample size, geography, and length of follow-up (**Table 1**), as well as baseline disease characteristics and demographics (**Table 2**)
- The adjustment for the multiple EMs yielded an estimated effective sample size (ESS) of 319 for the total population and 263 for the DOC-naïve population; in both cases, the ESS was sufficient to ensure reliable estimates

Table 1. Differences between the ARCHES and ARANOTE RCTs

	ARCHES	ARANOTE
Efficacy population	ITT	FAS
Sample size in efficacy population	ENZA + ADT: 574 Placebo + ADT: 576	DARO + ADT: 446 Placebo + ADT: 223
Geography	Argentina, Australia, Belgium, Canada, Chile, Denmark, Finland, France, Germany, Israel, Italy, Japan, Korea, New Zealand, Poland, Romania, Russia, Slovakia, Spain, Sweden, Taiwan, United Kingdom, United States of America	Australia, Brazil, Canada, Chile, China, India, Latvia, Lithuania, New Zealand, Peru, Russia, South Africa, Spain, Taiwan, Ukraine
Treatment discontinuation	Until disease progression, unacceptable toxicity, or any other discontinuation criteria were met	Until disease progression, unacceptable toxicity, initiation of new anticancer therapy, patient/physician decision, or study drug interruption ≥28 consecutive days
Median follow-up	13.6 months (1st data cut-off date based on rPFS)	25.3 months (1st data cut-off date based on rPFS)
Study unblinding and treatment crossover	Study unblinding took place after the primary analysis (1st data cut-off date) and 180 (31.3%) progression-free patients assigned to placebo + ADT crossed over to open-label ENZA + ADT	After primary analysis, and conditional on positive results, an open-label phase may start, which would imply a cross over of patients on placebo + ADT to DARO + ADT
Schedule of visits	**Treatment period**: Visit 1 (Day 1); Visit 2 (Week 5); Visit 3 (Week 13) and subsequent visits every 12 weeks	**Treatment period**: Visit 1 (Day 1); Visit 2 (Week 12) and subsequent visits every 12 weeks
	Safety FUP: 30 days after last dose or prior to initiation of new antineoplastic therapy, whichever occurred first	**Active FUP period**: • EoT Visit: 30 days after last dose or before starting a new anticancer therapy • Active FUP visits: every 12 weeks from discontinuation of treatment for approximately 1 year
	Long-Term FUP period: approximately every 12 weeks after Safety FUP period	**Long-Term FUP period**: approximately every 12 weeks after Active FUP period
Schedule of assessments	**Assessed every 12 weeks:** • **CT/MRI and bone scan**: until radiographic disease progression • **PSA**: until Safety FUP visit • **Survival status, new antineoplastic therapies for prostate cancer, symptomatic skeletal events**: until end of Long-Term FUP • **QoL (including BPI-SF)**: until start of new antineoplastic therapy	**Assessed every 12 weeks:** • **CT/MRI and bone scan, PSA**: until radiological disease progression or change of anticancer therapy • **Survival status, subsequent anticancer therapies**: until end of Long-Term FUP • **Symptomatic skeletal events**: until end of Active FUP • **Pain progression (BPI-SF)**: until end of Active FUP
Endpoints (primary and secondary)	• rPFS • Time to castration resistance • Time to PSA progression • OS • Time to initiation of new antineoplastic therapy • PSA undetectable rate (PSA <0.2 ng/mL) • Time to pain progression	• rPFS • Time to castration resistance • Time to PSA progression • OS • Time to initiation of subsequent anticancer therapy • Rates of PSA <0.2 ng/mL • Time to pain progression

BPI-SF, Brief Pain Inventory – Short Form; **CT**, computed tomography; **EoT**, end of treatment; **FAS**, full analysis set; **FUP**, follow-up; **ITT**, intention-to-treat; **MRI**, magnetic resonance imaging; **OS**, overall survival; **QOL**, quality of life.

- In the MAIC analysis of the total population, patients treated with ENZA + ADT showed a significantly lower risk of radiographic progression or death by 46% (hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0.32–0.93; *P* = 0.03) and of progression to castration resistance by 43% (HR: 0.57; 95% CI: 0.34–0.94; *P* = 0.03) than those receiving DARO + ADT (**Table 3**)
- Similar results were observed in the DOC-naïve population (**Table 3**): compared to DARO + ADT, patients treated with ENZA + ADT had a significantly lower risk of radiographic progression or death by 53% (HR: 0.47; 95% CI: 0.26–0.84; *P* = 0.01) and of progression to castration resistance by 54% (HR: 0.46; 95% CI: 0.27–0.79; *P* = 0.01)
- Time to PSA progression for ENZA + ADT was similar to DARO + ADT in both the total population (HR: 0.61; 95% CI: 0.29–1.30; *P* = 0.20) and the DOC-naïve population (HR: 0.48; 95% CI: 0.21–1.10; *P* = 0.08) (**Table 3**)
- In sensitivity analyses, the comparative effectiveness of ENZA + ADT and DARO + ADT remained similar in direction and significance for all outcomes; however, adjusting for ECOG PS yielded a reduction in ESS (n = 196)

Table 2. Imbalances in baseline disease and demographic characteristics between the ARCHES and ARANOTE RCTs

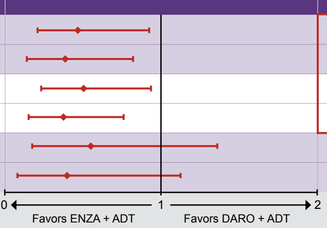
Study	Population	Median Age, (Range)	Race White, n (%)	Race Asian, n (%)	Race Black or African American, n (%)	Region North America, n (%)	Region Europe and RoW, n (%)[a]	Region Latin America, n (%)	Region Asia, n (%)	Region Other, n (%)
ARCHES	ENZA + ADT, n = 574	70 (46–92)	466 (81.2)	75 (13.1)	8 (1.4)	86 (15.0)	341 (59.4)	32 (5.6)	104 (18.1)	11 (1.9)
	Placebo + ADT, n = 576	70 (42–92)	460 (79.9)	80 (13.9)	8 (1.4)	77 (13.4)	344 (59.7)	30 (5.2)	113 (19.6)	12 (2.1)
ARANOTE	DARO + ADT, n = 446	70 (43–93)	251 (56.3)	144 (32.3)	41 (9.2)	0 (0.0)	186 (41.7)	119 (26.7)	141 (31.6)	0 (0.0)
	Placebo + ADT, n = 223	70 (45–91)	125 (56.1)	65 (29.1)	24 (10.8)	0 (0.0)	88 (39.5)	72 (32.3)	63 (28.3)	0 (0.0)

Study	Population	ECOG PS 0, n (%)	ECOG PS 1, n (%)	Any prior use of DOC, n (%)	Visceral disease present, n (%)	Any prior use of ADT, n (%)	Median PSA (Range), ng/mL	Gleason score ≥8, n (%)
ARCHES	ENZA + ADT, n = 574	448 (78.0)	125 (21.8)	103 (17.9)	64 (11.1)	534 (93.2)	5.4 (0.0–4,823.5)	386 (67.2)
	Placebo + ADT, n = 576	443 (76.9)	133 (23.1)	102 (17.7)	64 (11.1)	514 (89.2)	5.1 (0.0–19,000.0)	373 (64.8)
ARANOTE	DARO + ADT, n = 446	235 (52.7)	199 (44.6)	0 (0.0)	53 (11.9)	446 (100)	21.4 (0.02–15,915.0)	311 (69.7)
	Placebo + ADT, n = 223	98 (43.9)	117 (52.5)	0 (0.0)	27 (12.1)	223 (100)	21.2 (0.02–8,533.0)	146 (65.5)

RoW, rest of world.
[a]Includes 2 patients from Canada in ARANOTE.

Table 3: Indirect treatment comparison of ENZA + ADT versus DARO + ADT

Outcome	Population	ESS	Matching-adjusted estimates, forest plot[a]	Matching-adjusted estimate, HR[a] (95% CI); *P*-value	Unadjusted Bucher estimate[b], HR[a] (95% CI); *P*-value
rPFS	Total population	319		**0.54 (0.32–0.93); 0.03**	0.72 (0.50–1.05); 0.09
	DOC-naïve population	263		**0.47 (0.26–0.84); 0.01**	0.69 (0.46–1.01); 0.06
Time to castration resistance	Total population	319		**0.57 (0.34–0.94); 0.03**	0.70 (0.50–0.98); 0.04
	DOC-naïve population	263		**0.46 (0.27–0.79); 0.01**	0.63 (0.44–0.90); 0.01
Time to PSA progression	Total population	319		0.61 (0.29–1.30); 0.20	0.61 (0.39–0.96); 0.03
	DOC-naïve population	263		0.48 (0.21–1.10); 0.08	0.58 (0.37–0.91); 0.02



[a]DARO + ADT served as the reference treatment for all comparisons.
[b]Estimates from the Bucher method should be interpreted with caution due to the assumption that patient populations should be balanced in EMs between trials. The direction of relative effects was aligned between the two methods.

LIMITATIONS

- Some sources of bias could not be fully addressed in the MAIC analysis (e.g., length of follow-up and clinical heterogeneity), and any imbalances in covariates not adjusted for in the analysis were assumed to not impose considerable biases in the estimated relative treatment effects
- Adjustment of some EMs that lacked overlap between ARCHES and ARANOTE, such as region and race, substantially reduced the ESS; however, these adjustments were crucial for obtaining reliable MAIC estimates
- Data immaturity for both trials, and the lack of information on the method underlying the median follow-up estimate in ARANOTE, do not allow a definite conclusion regarding the potential impact of these considerations in the MAIC estimates
- This analysis does not consider how safety may affect provider prescription decisions