Objective computerized cognitive assessment in men with metastatic castrate-resistant prostate cancer (mCRPC) randomly receiving darolutamide or enzalutamide in the ODENZA trial

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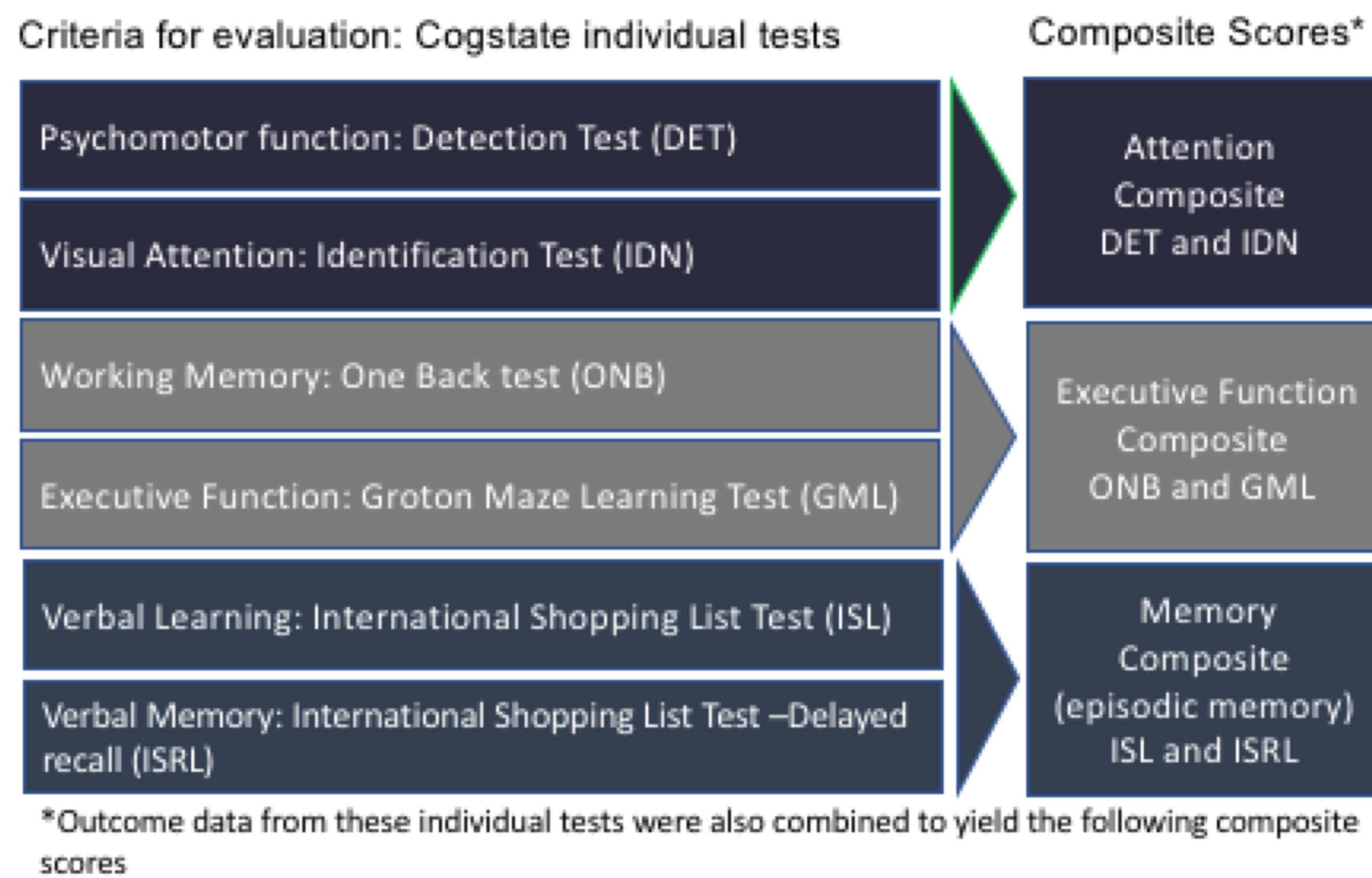
BACKGROUND

Darolutamide (Daro) and enzalutamide (Enza) are both next generation androgen receptor inhibitors. Unlike Enza, Daro has a low Blood-brain barrier penetration, which may reduce fatigue and cognitive impairment. ODENZA is a prospective, randomized, open-label, multicenter, cross-over, preference, phase 2 trial of Daro and Enza in patients (pts) with mCRPC. Pts (n=249) were randomized 1/1 to receive Daro 1200 mg/d for 12 weeks followed by Enza 160 mg/d for 12 weeks or the reverse sequence. Numerically more patients with early mCRPC preferred Daro over Enza, mostly driven by fatigue, although the difference did not reach significance (Colomba et al, ASCO 2021). **Cognitive assessment using computerized cognitive tests (COGSTATE) was a key secondary endpoint of ODENZA.**

METHODS

Cognitive test were prospectively realized by patients with laptop and questionnaire. Changes from baseline were assessed during each 12 weeks period. Treatment effects were analyzed using a mixed model for repeated measures. Effect sizes were classified as clinically meaningful when greater than or equal to 0.5.

Figure 1.

Criteria for evaluation: Cogstate individual tests → Composite Scores*

Psychomotor function: Detection Test (DET)
Visual Attention: Identification Test (IDN)
→ Attention Composite DET and IDN

Working Memory: One Back test (ONB)
Executive Function: Groton Maze Learning Test (GML)
→ Executive Function Composite ONB and GML

Verbal Learning: International Shopping List Test (ISL)
Verbal Memory: International Shopping List Test –Delayed recall (ISRL)
→ Memory Composite (episodic memory) ISL and ISRL

*Outcome data from these individual tests were also combined to yield the following composite scores

RESULTS

Table 1. Summary of Results for Each Individual Cognitive Test and Composite Score Across Overall Assessment Period (every 12 weeks period)

Composite (individual tests)	LS Means Difference (Daro vs. Enza)	P-value	Effect Size
Attention Composite	0.12	0.2122	0.15
Psychomotor function: Detection Test (DET	0.02	0.0954	0.19
Visual Attention: Identification Test (IDN)	0.01	0.6076	0.06
Executive Function Composite	0.09	0.2426	0.15
Working Memory: One Back test (ONB)	0	0.6471	-0.06
Executive Function: Groton Maze Learning Test (GML)	6.7	0.1109	0.2
Memory Composite	0.35	**0.0000*****	0.54
Verbal Learning: International Shopping List Test (ISL)	2.23	**0.0000*****	0.54
Verbal Memory: International Shopping List Test –Delayed recall (ISRL)	0.73	**0.0075****	0.29

*p value [0.01 to .05], ** p value [0.001 to <.01], *** p value <0.001

LS - Least Squares

Figure 2. Cogstate Memory Composite Score by Assessment Period and Visit (Modified Intent-to-Treat)

Enza Daro
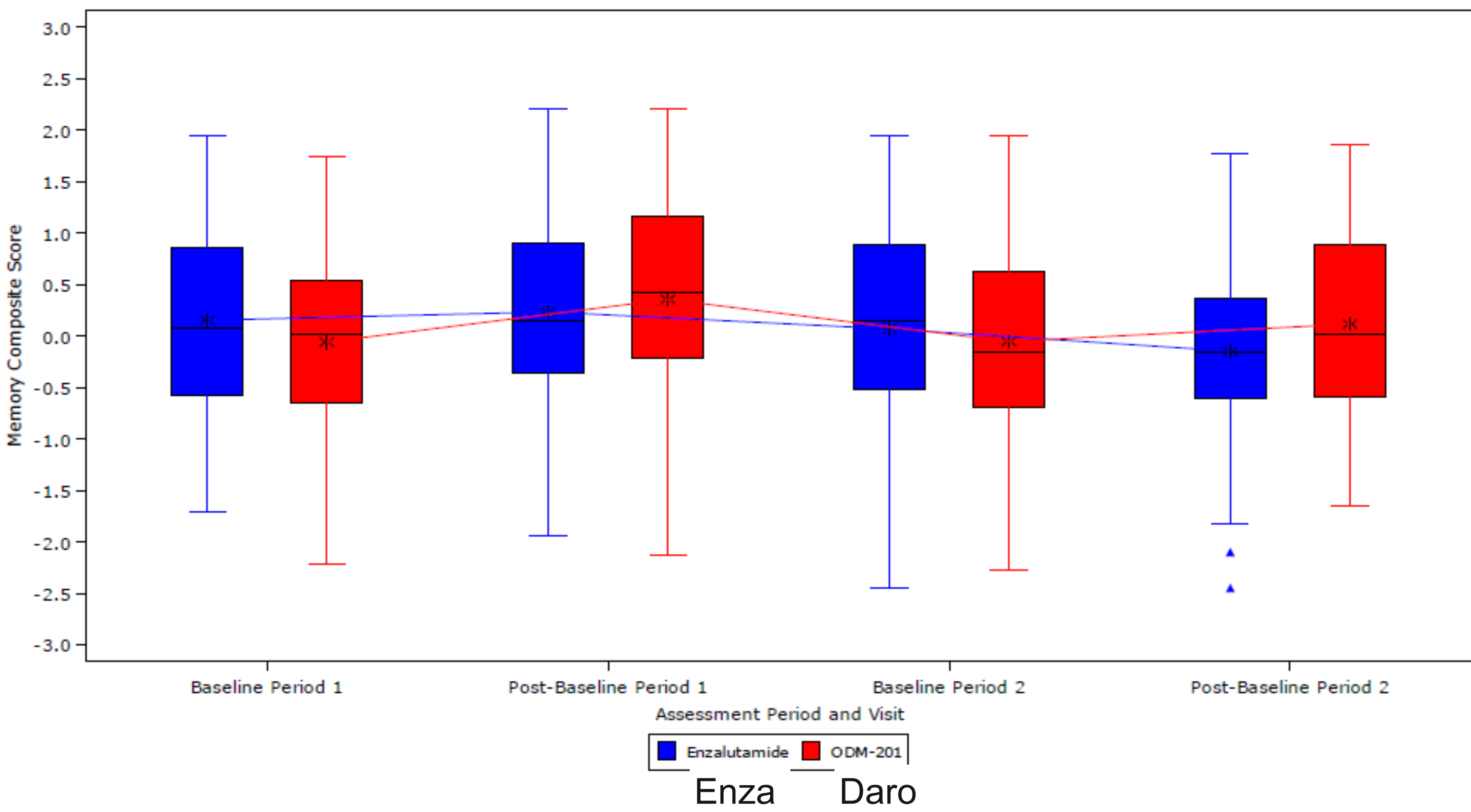
Box: interquartile range (first and third) and median, Symbol: mean, Whiskers: min/max, Outlier: > 1.5(IQR). Higher score means better performance.
Note: Score from Assessment Period 1 Post-Baseline is equivalent to score from Assessment Period 2 Baseline for individual tests (i.e., DET, IDN, ONB, GML, ISL, ISRL tests).

- Cognitive data were available in 193 patients among 250 patients enrolled in ODENZA trial.
- **Performance on verbal learning (ISL) was significantly better with Daro versus Enza** at each of the post-baseline assessments, within both periods and when averaged over periods. Effects were clinically meaningful at the second period **(0.62, p=0.0001) and overall (0.54, p<0.0001).**
- **Performance on verbal memory (ISRL) was also significantly better with Daro** at the second period and when averaged over periods, although the effect sizes were less meaningful **(second period: 0.4, p=0.01 and overall: 0.29, p=0.0075).**
- The composite scores were in line with individual scores, with a **moderate benefit in episodic memory** after treatment with Daro compared to Enza.

CONCLUSION

- In men with mCRPC, 12 weeks treatment with Darolutamide was associated with a statistically significant and clinically meaningful benefit (e.g., effect size > 0.5 in magnitude) in episodic memory compared to Enza.
- The favorable effect of Daro on episodic memory over Enza was observed for both the acquisition of new information as well as for the recall of that information after a brief delay.
- Non-significant trends for executive function were also observed with Daro.

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