A phase 2 trial of darolutamide to enhance prostate-specific membrane antigen expression in patients with localized prostate cancer (Daro-PET).

Jéssica Vasconcellos , Camila Mosci, Marcelo Queiroz, Camila Togni, Daniel Moser, Oseas Castro Neves Neto, Felipe M. Cruz, Thiago S. Hemerly, Alexandre K. Taneno, Isabella C. Henriques, Mariana P. de Macedo[6] Rodrigo N. Ramos, Mariana A. Morini, Isabela W. Cunha, Jose Mauricio Mota.

Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil & Instituto do Câncer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil

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BACKGROUND

- Androgen suppression may transiently increase PSMA expression, with potential implications for PSMA PET detection and PSMA-targeted therapies;
- Available evidence predominantly derive from studies in the metastatic castration-resistant setting, with limited or absent data in localized, castration-sensitive disease.

METHODS

- Daro-PET **(NCT05900973)** is a phase 2 single-arm trial evaluating if short-course darolutamide increases PSMA expression in high-risk localized prostate cancer;
- **Baseline PSMA PET/CT → 7 days of darolutamide 600 mg twice daily → repeat PSMA PET/CT;**
- Two-stage Simon design (80% power, one-sided α=0.05): 12 patients in stage 1, expansion to 16 after 1 event, with ≥3 events defining a positive trial;
- **Primary endpoint:** the proportion of patients with a ≥20% increase in SUVmax from PSMA-PET 1 to PSMA-PET 2; **Secondary endpoints:** tumor volume, SUVmean, total lesion PSMA, new metastases, safety, and per-protocol analyses;
- Efficacy analyses were performed in the intention-to-treat (ITT) and per-protocol populations (radiotracer dose of 4.0 ± 1.0 mCi with ≤30% variation between PSMA PETs).

RESULTS

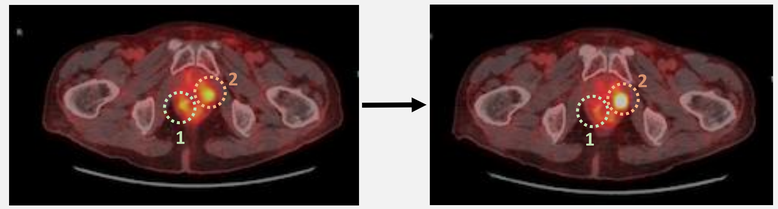
Between July 2023 and March 2025, 16 patients were enrolled.

Table 1. Baseline characteristics.

Characteristic	Cohort, N=16
Age, median (IQR) – years	61 (55.5 – 70.5)
ISUP grade – N (%)	
≥4	9 (56)
Clinical T stage – N (%)	
cT2	6 (37.5)
cT3	10 (62.5)
Total PSA, median (IQR) – ng/ml	10.01 (6.41–11.24)
Total testosterone, median (IQR) – ng/dL	314 (258.3–392.9)
Lymph node involvement at baseline PET, n (%)	
Positive	4 (25)
Negative	12 (75)
Multifocal prostate uptake at baseline PET, n (%)	4 (27)

- All patients completed the protocol with full treatment adherence with no adverse events. Two patients did not undergo prostatectomy by shared decision-making;
- **In the ITT population, 5 patients (31%) had any SUVmax increase after darolutamide, with 3 patients (18.8%; 90% CI, 5.3–41.7) achieving a ≥20% increase (range: 36.5% to 62%) (Figure 1);**
- Results were similar in the per-protocol population (N=14), with 5 patients (36%) with any SUVmax increase and 3 patients (21%) with an SUVmax ≥20% increase;
- **Seven patients (50%; 90% CI 26.4–73.6) showed increased tumor volume (range: 6.2% to 98.6%). SUVmean and total lesion PSMA increased in 3 patients (21.4%);**
- No new pelvic or extrapelvic metastases were detected after darolutamide treatment.

Figure 1. PSMA PET scans pre- and post-darolutamide from a representative patient with multifocal disease.



Lesion 1: SUVmax: 9.6; SUVmean: 5.3
Lesion 2: SUVmax: 5.2 ; SUVmean:2.8
Volume: 1.2 mL

SUVmax: 4.6 (Δ -52%); SUVmean:2.4 (Δ -52%)
SUVmax: 7.1 (Δ +36.5%); SUVmean:2.8 (Δ +25%)
Volume: 2.1 mL (Δ +75%)

Three patients had 2 prostatic uptake foci, with heterogeneous changes in PSMA uptake after darolutamide (Table 2).

Patient ID	Focus 1: Δ SUVmax (%) / Gleason score	Δ SUVmax (focus 2) (%) / Gleason score
#3	-31.5 (Gleason 3+3)	-8.0 (Gleason 4+3)
#8	-52.0 (Gleason 4+3)	+36.5 (Gleason 4+4)
#12	+62.0 (Gleason 4+4)	+8.3 (Gleason 3+3)

CONCLUSIONS

A 7-day treatment with darolutamide increased PSMA expression in a subset of localized prostate cancer, with notable heterogeneity in response; translational studies are planned to investigate the mechanisms involved.

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Author contact: jose.mota@hc.fm.usp.br
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