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S100A9 Identifies Distinct Circulating Myeloid Cell Subsets in Metastatic Prostate Cancer

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Background: S100A9 is a calcium-binding protein involved in inflammation and immune regulation, predominantly expressed in granulocytes and immunosuppressive monocytes. Its role in the systemic immune landscape of metastatic prostate cancer (mPCa) remains unclear.

Objective: This prospective observational study aimed to characterize S100A9 expression in circulating myeloid cells from patients with mPCa using liquid biopsy and to explore treatment-associated changes.

Methods: Peripheral blood samples were collected from patients with mPCa (castration-sensitive and castration-resistant) and healthy donors (controls) enrolled between January 2024 and June 2026 at Instituto de Oncología Ángel H. Roffo (Argentina). Serum, plasma, and

leukocyte fractions were processed and stored in the institutional biobank. Flow cytometry was used to quantify S100A9-expressing monocytes ($S100A9^+CD14^+$) and granulocytes ($S100A9^+CD15^+$). Patient samples were obtained at baseline and at the first response evaluation (~12 weeks).

Results: A total of 25 patients with mPCa and 15 controls were included. The median age of patients was 71 years (IQR 65.2–74.7). At baseline, patients exhibited a higher proportion of $S100A9^+$-monocytes than controls (median-[CI]: 3.3%-[2.2-4.3] vs 2.6%-[1.6-3.1] respectively, p=0.045), which further increased at treatment response evaluation (median-[CI]: 4.3%-[3.3-5], (p=0.022). In contrast, the overall percentage of $S100A9^+$ granulocytes did not differ significantly between patients and controls or between baseline and follow-up. However, granulocytes were classified into two distinct subpopulations according to S100A9 expression ("Middle-High" and "Very High"). The Very High subset identified two groups of patients: one comparable to controls (~10%) and another with a median of 33% of these cells.

Conclusions: Circulating $S100A9^+$ monocytes were significantly increased in patients with mPCa and further expanded after treatment, suggesting treatment-associated modulation of the myeloid compartment. In addition, we identified previously unrecognized granulocyte subpopulations with distinct S100A9 expression profiles, supporting functional heterogeneity within circulating myeloid cells. These findings highlight a potential immunomodulatory role for S100A9 in the systemic response to therapy. Longitudinal studies in a larger cohort are ongoing to determine the prognostic and predictive value of these immune subsets in mPCa.

The final analyses of this first cohort are ongoing and will be presented in the poster.