

Title: Plasma-derived extracellular vesicles and PSMA PET/CT imaging for predicting response to ¹⁷⁷Lu-PSMA-617 in patients with metastatic prostate cancer

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Background:

¹⁷⁷Lu-PSMA-617 (LuPSMA) has transformed the treatment landscape for metastatic prostate cancer (mPC), but biomarkers are urgently needed to improve patient selection. Baseline PSMA PET/CT imaging and circulating tumor DNA have shown promise in predicting which patients with APMR disease are more likely to have treatment response to LuPSMA. Plasma-derived extracellular vesicles (EVs) are emerging blood-based markers of tumor burden, and its utility remains incompletely defined. We analyzed baseline EVs and PSMA PET/CT imaging pre-LuPSMA treatment for a contemporary prospective Mayo Clinic cohort of patients with mPC.

Methods:

Blood samples, clinical data, and baseline PSMA PET/CT imaging features were prospectively collected from 51 pts who initiated LuPSMA between 12/2024 and 12/2025 at Mayo Clinic. Small and large EVs were incubated with fluorescently conjugated antibodies (PSMA, STEAP1, CEACAM5, and TROP2) and enumerated using nanoscale flow cytometry. PSA50 ($\geq 50\%$ decline from baseline PSA, if detectable at baseline) and RECIP 1.0 criteria of complete response (CR) or partial response (PR) were used as response endpoints to LuPSMA. Ten healthy donors and 36 patients with localized prostate cancer post-radical prostatectomy were used as controls.

Results:

Baseline clinical characteristics, the levels of total, large, and small, and large/small ratios of PSMA, STEAP1, CEACAM5, and TROP2 EVs, and PSMA PET/CT data are shown in the Table. For patients with mPC, 100% had prior androgen receptor pathway inhibitor (ARPI), 83% had prior docetaxel, median number of prior lines of systemic therapy was 1 (range 1-3), and 47% received LuPSMA in combination with ARPI. PSA50 response was 54% for 39 evaluable patients. RECIP response was 42% in 43 evaluable patients.

Total EVs were significantly higher for all subtypes tested for mPC compared to controls (Table). For PSA50 response, the strongest baseline EV predictors were the high CEACAM5 large/small EV ratio (AUC 0.735, $p=0.013$) and high TROP2 large/small EV ratio (AUC 0.772, $p=0.019$). PSMA SUVmean and SUVmax did not significantly predict outcomes for RECIP response or PSA50 response (AUC 0.602 and 0.542; and AUC 0.569 and 0.521, respectively). Higher large CEACAM5 and large TROP2 EV levels (AUC 0.707, $p=0.023$; and AUC 0.716, $p=0.017$, respectively) were associated with RECIP response, as well as

TROP2 large/small EV ratio (AUC 0.684, p=0.042) and a trend for CEACAM5 large/small EV ratio (AUC 0.647, p=0.107).

Conclusions:

Baseline CEACAM5 and TROP2 EVs, particularly the number of large-sized EVs and a higher large/small EV ratio, demonstrated a predictive value for PSA50 and RECIP response to LuPSMA. Plasma-derived EV biomarkers may provide predictive information beyond baseline PSMA PET/CT imaging, supporting the development of integrated liquid biopsy and imaging-based approaches for treatment stratification. EV proteomics, circulating tumor DNA analyses, longitudinal EV and PSMA PET imaging analyses, and validation with a larger cohort are ongoing.

Table: Median values for mPC pre-LuPSMA, post-RP for localized prostate cancer, and healthy donors

	mPC (n=51)	post-RP (n=36)	p-value between mPC and post-RP	Healthy donors (n=10)	p-value between mPC and healthy donors
Age (years, range)	73 (57-87)	66 (56-77)		55 (50-57)	
Prior lines (range)	1 (1-3)	-		-	
Gleason score (range)	9 (7-10)	7 (6-9)		-	
PSA (ng/mL, range)	1.0 (0-182)	-		-	
PSMA PET/CT features					
PSMA PET/CT SUVmean (range)	6 (1.9-49)	-		-	
PSMA PET/CT SUVmax (range)	16.2 (3.3-157.4)	-		-	
Number of PSMA-avid lesions (range)	6 (2-144)				
Total tumor volume (mL, range)	22 (0-822)	-		-	
EV features					
PSMA EV/mL	3.7×10^6	2.1×10^6	<0.001	1.4×10^6	0.040
Large PSMA EV/mL	1.3×10^6	0.53×10^6	<0.001	0.36×10^6	0.018
Small PSMA EV/mL	2.2×10^6	1.5×10^6	0.020	1.1×10^6	0.161
Ratio Large/Small PSMA EV	0.68	0.39	0.004	0.28	0.156
STEAP1 EV/mL	30×10^6	9.6×10^6	<0.001	7.8×10^6	<0.001
Large STEAP1 EV/mL	5.0×10^6	2.3×10^6	<0.001	1.2×10^6	0.011
Small STEAP1 EV/mL	26×10^6	7.4×10^6	<0.001	6.6×10^6	<0.001
Ratio Large/Small STEAP1 EV	0.25	0.27	0.194	0.20	0.149
CEACAM5 EV/mL	17×10^6	3.9×10^6	<0.001	4.2×10^6	0.014
Large CEACAM5 EV/mL	7.2×10^6	2.1×10^6	<0.001	1.6×10^6	0.012

Small CEACAM5 EV/mL	3.0 x 10 ⁶	1.8 x 10 ⁶	0.004	1.3 x 10 ⁶	0.216
Ratio Large/Small CEACAM5 EV	1.5	0.95	0.007	1.4	0.144
TROP2 EV/mL	13 x 10 ⁶	3.7 x 10 ⁶	<0.001	3.6 x 10 ⁶	0.009
Large TROP2 EV/mL	4.0 x 10 ⁶	0.71 x 10 ⁶	<0.001	0.67 x 10 ⁶	0.010
Small TROP2 EV/mL	5.4 x 10 ⁶	2.9 x 10 ⁶	0.007	3.0 x 10 ⁶	0.162
Ratio Large/Small TROP2 EV	0.64	0.24	0.003	0.27	0.091

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Conflicts of Interest:

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Travel, Accommodations, Expenses - Binacea; MECC Global Meetings

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Speakers' Bureau - Sanofi

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Other Relationship - Caris Centers of Excellence

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PROSTATE CANCER

Travel, Accommodations, Expenses - Genentech/Roche

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No Relationships to Disclose

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Patents, Royalties, Other Intellectual Property - I have patent filings related to cancer biomarkers, and have received royalties related to licensed technology.

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