

Monitoring Circulating Cancer Associated Macrophage-Like Cell PD-L1 Predicts Clinical Outcomes in Metastatic Breast Cancer Treated with Immune Checkpoint Inhibitors

¹Sonia Muthuraj, ²Daniel L. Adams, ³Massimo Cristofanilli, ³Carolina Reduzzi, ⁴William V. Williams, ⁴Giuseppe Del Priore, ⁴Blaise Bayer, ⁵Chaitali Nangia, ⁶Cha-Mei Tang, ⁷Richard G. Pestell, ⁸Jacob P Lalezari, ⁸Joseph Meidling, ⁹Saranya Chumsri

¹Rutgers University, New Brunswick, NJ, USA, ²CreatvBio., Monmouth Junction NJ, USA, ³Weill Cornell Medicine, New York, NY, USA, ⁴BriaCell Therapeutics Corp., Philadelphia, PA 19104, USA, ⁵Hoag Hospital, Newport Beach, CA, USA, ⁶Creatv MicroTech, Inc., Rockville, MD, USA, ⁷Pennsylvania Cancer and Regenerative Medicine Research Center, Baruch S Blumberg Institute, Wynnewood, PA, USA, ⁸CytoDyn, Vancouver, WA, USA, ⁹Mayo Clinic Cancer Center, Jacksonville, FL, USA

ABSTRACT

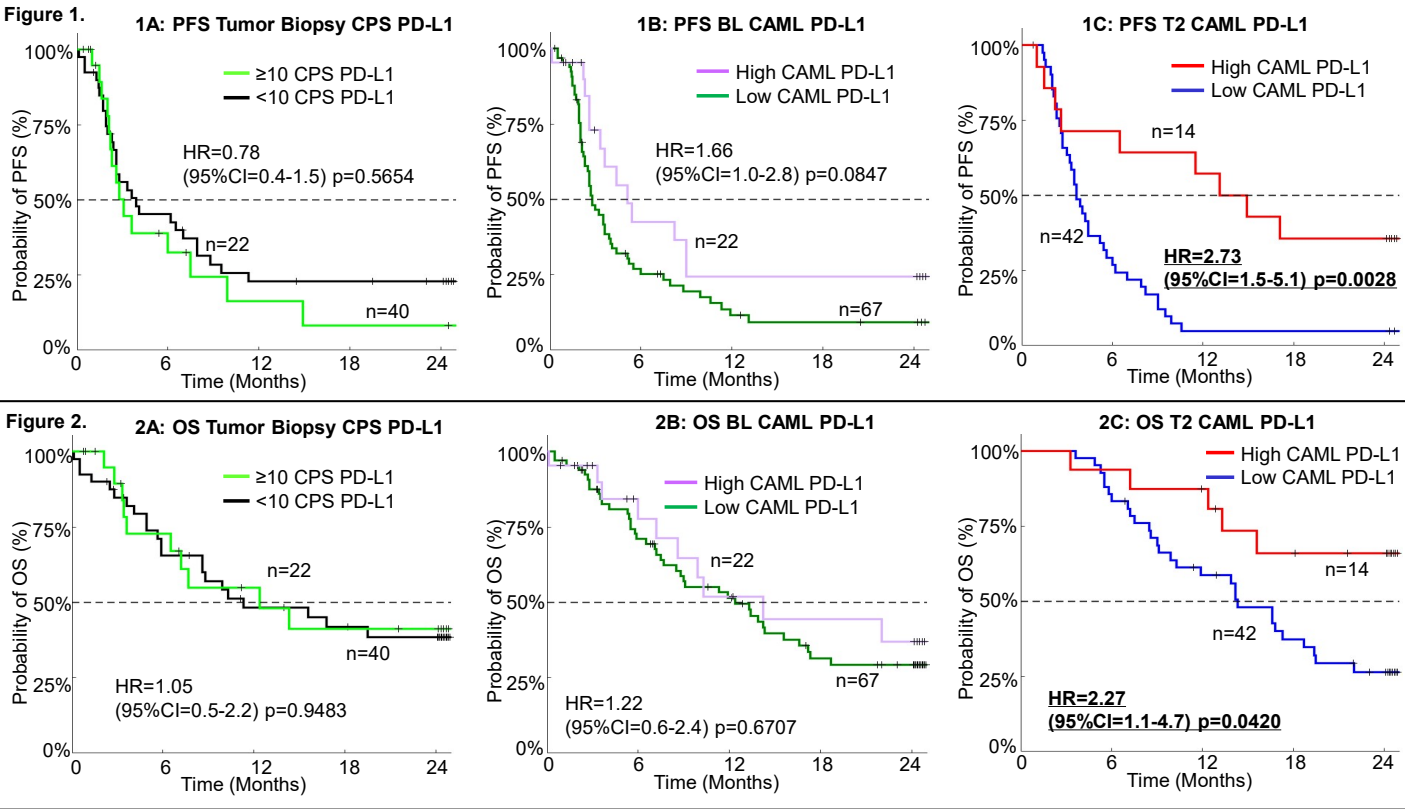
PD-L1/PD-1 immune checkpoint inhibitors (ICI) show benefit in metastatic breast cancer (mBC), specifically Triple Negative Breast Cancer (TNBC) if the IHC biopsy tumor combined positive scores (CPS) is $\geq 10\%$. However, some patients (pts) with $<10\%$ CPS benefit from ICIs and many pts $\geq 10\%$ will recur. Poor ICI response is often attributed to the dynamic nature of PD-L1 which may upregulate or downregulate during therapeutic intervention. Recent studies have shown PD-L1 upregulation in Cancer Associated Macrophage-Like cells (CAMLs), which are giant phagocytic macrophages that engulf tumor before entering circulation, predicts ICI response. We prospectively conducted an analysis on n=111 mBC pts prior to starting ICIs to monitor CAML PD-L1 pre & post ICI initiation to evaluate progression free survival (PFS) & overall survival (OS) at 2 years.

MATERIALS & METHODS

A multi-institutional prospective pilot study in mBC pts receiving ICIs after failing ≥ 1 prior lines of therapy (n=58 Pembrolizumab, n=40 Retifanlimab, n=10 Atezolizumab, & n=3 Nivolumab), NCT03838367, NCT04313075 NCT04504942, NCT03066947 & NCT03106415. Anonymized peripheral blood (7.5ml) was taken at Baseline (BL) pre ICI, post ICI induction (T1) (~37 days) and ~3 months post ICI induction (T2) (~114 days). CAMLs were isolated on Celsie microfilters & PD-L1 was categorized as low or high. Tumor CPS was defined as low ($<10\%$) or high ($>10\%$). CAML's PD-L1 & tissue CPS were compared to PFS & OS by univariate & multivariate analysis at two years.

Table 1. Clinical Parameters

Hormone Status	ER+	43 (39%)
	PR+	34 (31%)
	HER+	5 (5%)
	TNBC	66 (60%)
Treatment Type	Pembrolizumab	58 (52%)
	Retifanlimab	40 (36%)
	Atezolizumab	10 (9%)
	Nivolumab	3 (3%)
CAML PD-L1 at T0	Low	67 (60%)
	High	22 (20%)
CAML PD-L1 at T1	Low	58 (52%)
	High	22 (20%)
CAML PD-L1 at T2	Low	42 (38%)
	High	15 (14%)
Tissue PD-L1	$<1\%$	15 (14%)
	$\geq 1\%$	47 (42%)
	$<10\%$	40 (36%)
	$\geq 10\%$	22 (20%)
	Unknown	49 (44%)
Race	White	52 (47%)
	Black	7 (6%)
	Other	4 (4%)
	Unknown	48 (43%)
ECOG	0	48 (43%)
	≥ 1	29 (26%)
	Unknown	34 (31%)
Median Prior Met Lines (Range)		2 (1-13)
Median Age (Range)		59 (32-77)



RESULTS

- N=111 pts, median age=59 years (32-77); 39% (n=43/111) ER+, 31% (n=34/111) PR+, 5% (n=5/111) HER2+, & 60% (n=66/111) TNBC.
- PD-L1 IHC CPS was not significantly different than CAML PD-L1 (ANOVA p<0.0001)
- Patients with tissue CPS score ≥ 10 did not correlate with better PFS nor OS (Figs 1A & 2A)
- 87% (n=96/111) had a BL blood sample, with high CAML PD-L1 not correlated to PFS (HR=1.66, p=0.0847) nor OS (HR=1.22, p=0.6707) (Figs 1B & 2B)
- 72% (n=80/111) had a T1, with high CAML PD-L1 being significant for better PFS (HR=1.86, p=0.0276) but not OS (HR=1.28, p=0.5663). (Data not shown)
- 51% (n=57/111) had a T2, with high CAML PD-L1 being significant for better PFS (HR=2.73, p=0.0028) and OS (HR=2.27, p=0.0420) (Figs 1C & 2C)

Declaration of Interest

These studies were sponsored by BriaCell Therapeutics Corp, Creatv MicroTech Inc, CytoDyn, Inc, Merck & Co. and Pfizer. S. Muthuraj previously had a paid undergraduate research internship at Creatv MicroTech Inc. Travel and registration expenses were reimbursed by Creatv MicroTech Inc.

CONCLUSIONS

- Monitoring dynamic PD-L1 changes in circulating tumor immune cells (i.e. CAMLs) appears to predict benefit to PD-L1/PD-1 ICIs in mBC patients
- Further expanded studies are needed to validate these findings.

REFERENCES

- Adams et al. Phenotyping and Clinical Utility of phagocytic polyploid giant cancer macrophages in blood. Can Lett. 2025, 631 (218007)
- Jiao X, et al. Leronlimab, a humanized monoclonal antibody to CCR5, blocks breast cancer cellular metastasis and enhances cell death induced by DNA damaging chemotherapy. Breast Can Res. 2021, 23 (1):11
- Wiseman et al. Results of a phase I/IIa trial of SV-BR-1-GM inoculation with low-dose cyclophosphamide and interferon alpha (Bria-IMT) in metastatic breast cancer. Hum Vacc & Immuno. 2024, 20:1 (2379864)
- Chumsri, et al. Pembrolizumab in combination with binimetinib in patients with unresectable locally advanced or metastatic triple negative breast cancer. Clin Can Res. 2025, 31(10) 1885