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Contact: dan@creatvmicrotech.com
301-983-1650

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Monitoring Upregulation of PD-L1 in Cancer Associated Macrophage-Like Cells in Blood Predicts Clinical Outcomes in Metastatic Cancer Patients Treated with PD-L1 Immunotherapies

Daniel L. Adams[1], Massimo Cristofanilli[2], Carolina Reduzzi[2], William V. Williams[3], Giuseppe Del Priore[3], Saranya Chumsri[4], Toshiaki Iwase[5], Naoto T. Ueno[5], Alexis B. Duffy[1], Cha-Mei Tang[6]

[1]Creatv MicroTech, Monmouth Junction, NJ 08852, [2]Weill Cornell Medicine, New York, NY 10021, , [3]BriaCell Therapeutics Corp., Philadelphia, PA 19104, [4]Mayo Clinic Cancer Center, Jacksonville, FL 32224, [5] University of Hawai'i Cancer Center, Honolulu, HI 96813, [6]Creatv MicroTech, Rockville, MD 20850

ABSTRACT

Numerous studies have shown the efficacy of PD-L1/PD-1 based immunotherapies (IMT) for treating patients with metastatic Breast Cancer (mBC) when there is high expression of PD-L1 in their tumor cells and/or tumor immune cells. However, many patients with high PD-L1 tumors do not respond to IMT, and some patients with negative/low PD-L1 tumors may respond. The poor correlations between Immunohistochemistry (IHC) scores and IMT responses are often attributed to the dynamic nature of PD-L1 which may upregulate after chemotherapy, radiation, or other systemic therapies, which is not quantified by IHC tumor staining. Recently, a number of clinical trials have described PD-L1 upregulation in giant phagocytic stromal macrophages found in circulation, i.e. Cancer Associated Macrophage-Like cells (CAMLs), that correlates with IMT responses in solid tumors. We conducted a prospective pilot study to monitor the peripheral blood of n=67 mBC patients undergoing systemic treatment with IMT in combination with other therapies, to evaluate CAML PD-L1 score prior to & post IMT induction with clinical outcome analysis at 2 years.

MATERIALS & METHODS

In a prospective pilot study of previously treated mBC patients n=67, new lines of systemic therapy were started in combination with IMT for active progressive metastatic disease. Demographics can be found in Table 1. We isolated CAMLs from 7.5 ml baseline (T0) blood using the LifeTracDx® PD-L1 test and scored PD-L1 as high or low. If possible, a follow-up sample (T1) was taken (~39 days) after IMT induction. Patient's progressive free survival (PFS) and overall survival (OS) hazard ratios (HRs) were analyzed by censored univariate analysis based on RECIST v1.1 over 2 years.

Table 1: Demographic Table

Histology	IDC	52 (78%)
	ILC	2 (3%)
	IBC	2 (3%)
	Other	11 (16%)
ICI Treatment	Pembrolizumab	57 (85%)
	Nivolumab	2 (3%)
	Atezolizumab	8 (12%)
CAML PD-L1 at T0	Low/Negative	35 (52%)
	Medium/High	28 (42%)
CAML PD-L1 at T1	Low/Negative	27 (40%)
	Medium/High	25 (37%)
Tissue PD-L1	<1%	1 (2%)
	≥1%	45 (67%)
	Unknown	21 (31%)
Hormone	ER positive	25 (37%)
	PR positive	26 (39%)
	HER-2 positive	9 (13%)
	TNBC	35 (52%)
Race	White	43 (64%)
	Black	7 (10%)
	Hispanic	4 (6%)
	Asian	3 (5%)
	Other	11 (16%)
ECOG	0	34 (51%)
	≥1	33 (49%)
Visceral	Positive	43 (64%)
	Negative	24 (36%)
Age		Median=58.2 (range 32-73)
Prior Therapies for mBC		Median=2 (range 0-14)

Figure 1. T0 CAML PD-L1 PFS

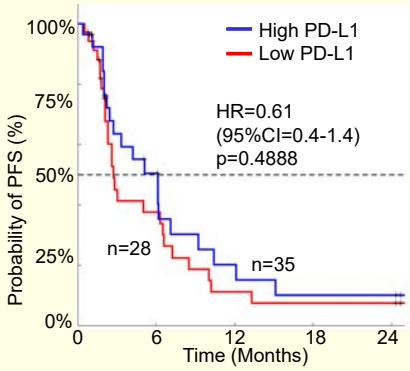


Figure 1. T0 CAML PD-L1 OS

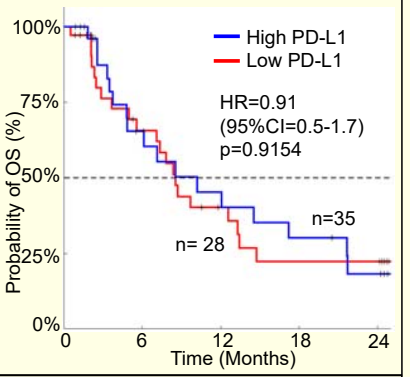


Figure 2. T1 CAML PD-L1 PFS

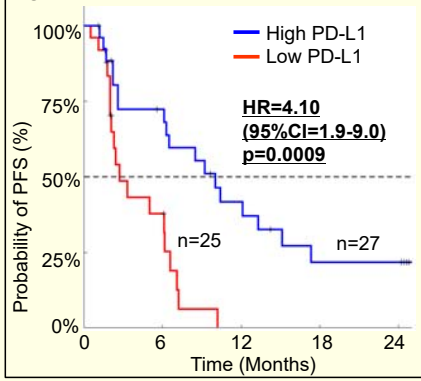
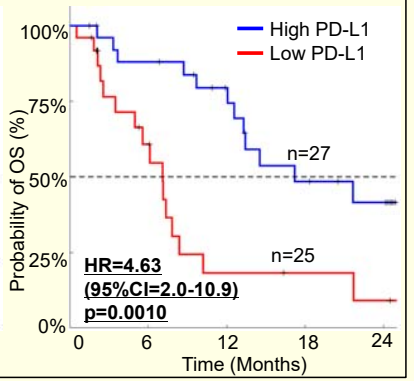


Figure 2. T1 CAML PD-L1 OS



RESULTS

- Baseline T0 PD-L1 CAML data was available for 94% (n=63/67) of patients
- 44% (n=28/63) of patients had high CAML PD-L1 which was not correlated with PFS or OS (Fig 1)
- Post IMT, T1 PD-L1 CAML data, was available for 78% (n=52/67) of patients
- 58% (n=30/52) of patients had high CAML PD-L1 which significantly correlated with improved PFS and improved OS (Fig 2)
- Patients with consistently low CAML PD-L1 at T0 & T1 had the poorest responses (Fig 3)
- Patients with increased CAML PD-L1 after IMT induction had better responses (Figs 2 & 3)
- Patients with consistently high PD-L1 at T0 & T1 had the best response rates (Fig 3 & 4)

Figure 3. CAML PD-L1 Changes Between T0 and T1

	mPFS	mOS
Low to Low N=16	2.4 (2.0-6.0)	6.9 (5.0-8.4)
High to Low N=10	6.0 (2.0-7.1)	6.4 (3.5-12.1)
Low to High N=12	6.3 (2.6-10.0)	**13.1 (13.1->24.0)**
High to High N=14	**13.8 (6.1->24.0)**	**21.0 (17.2->24.0)**

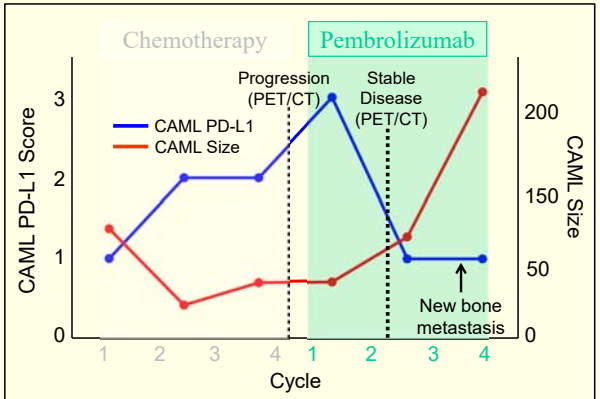


Figure 4. Monitoring PD-L1 and CAML size. CAML size initially dropped after start of chemotherapy, followed by a gradual increase, corresponding to progression by PET/CT. In parallel PD-L1 in CAMLs increased. Patient started pembrolizumab and had initial stable (partial response) disease by PET/CT. However, CAML size then increased and CAML PD-L1 decreased, which corresponded with new progressive disease.

CONCLUSIONS

- We describe a blood-based biopsy which can monitor dynamic PD-L1 changes in circulating tumor immune cells and may predict enhanced clinical benefit to PD-L1 IMTs in mBC.
- While an initial pilot study on a small population of patients, PD-L1 expression on CAMLs appears to identify patients with improved IMT responses and suggests larger validation studies are needed.

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