

Monitoring PD-L1 Expression in Cancer-Associated Macrophage-Like Cells as Predictor of Clinical Outcomes in Metastatic Cancer Patients Treated with PD-L1 Immunotherapies

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ABSTRACT

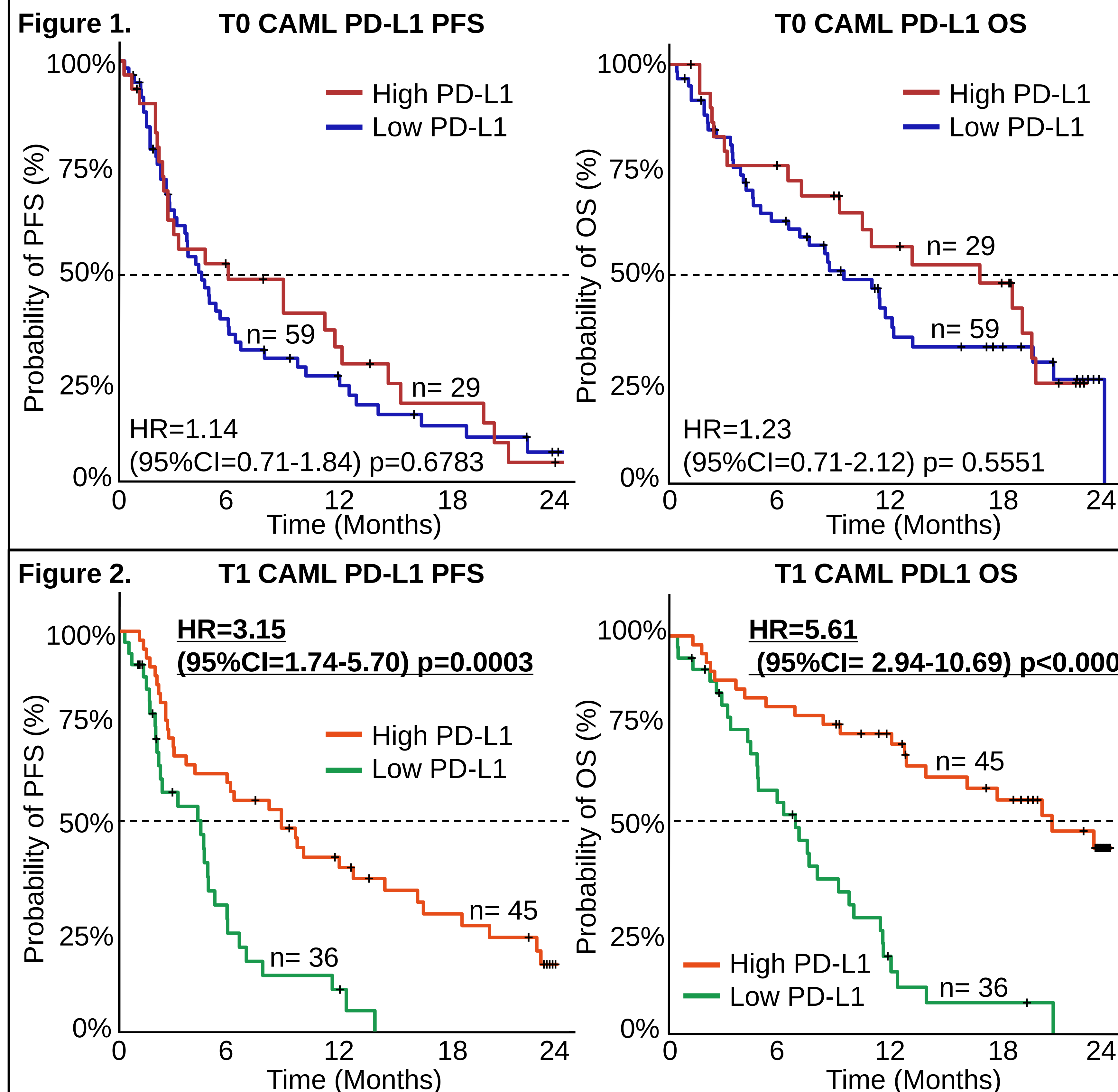
Studies have described the efficacy of immunotherapies (IMT) utilizing programmed death 1 receptor and its ligand (PD-L1) for treating solid tumors. However, many patients (pts) fail to respond to IMT, necessitating better predictive biomarkers for improved stratification. Poor IMT responses are often attributed to the dynamic nature of PD-L1 likely changing after chemotherapy or radiation, but typically quantified by static immunostaining. Recent studies have described PD-L1 upregulation in giant phagocytic stromal cells, i.e. Cancer associated macrophage-like cells (CAML), circulating macrophages that engulf tumor before entering circulation and may predict IMT responses. We conducted a pilot study to monitor the peripheral blood of metastatic cancer pts undergoing systemic treatment with IMT in combination with other therapies, to evaluate CAML PD-L1 prior to & post IMT induction with clinical correlation at 2 years.

MATERIALS & METHODS

In a prospective pilot study of n=111 metastatic cancer pts, [breast (n=42), lung (n=46), renal cell (n=10), prostate (n=5), esophageal (n=5) & colon (n=3)] (Table 1), all starting new lines of systemic chemotherapy in combination with IMT. IMT included pembrolizumab [n=69], nivolumab [n=23], atezolizumab [n=13], or durvalumab [n=6] for new recurrent metastasis (n=45) or with previously treated progressive metastasis (n=66). 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 (~56 days) after IMT induction. Pts' 2 year progressive free survival (PFS) and overall survival (OS) hazard ratios (HRs) were enumerated by censored univariate analysis based on RECIST 1.1.

Table 1. Clinical Parameters

Cancer Type	Breast Cancer	42 (38%)
	Lung Cancer	46 (41%)
	Renal Cell Carcinoma	10 (9%)
	Other	13 (12%)
Treatment Type	Pembrolizumab	69 (62%)
	Nivolumab	23 (21%)
	Atezolizumab	13 (12%)
	Durvalumab	6 (5%)
CAML PD-L1 at T0	Low/Negative	59 (67%)
	Medium/High	29 (33%)
CAML PD-L1 at T1	Low/Negative	36 (44%)
	Medium/High	45 (56%)
Tissue PD-L1	<1%	16 (14%)
	≥1%	53 (48%)
	Unknown	42 (38%)
Male:Female		48:63
Race	White	83 (75%)
	Black	8 (7%)
	Hispanic	4 (4%)
	Other	16 (14%)
ECOG	0	50 (45%)
	≥1	61 (55%)
Visceral	Positive	60 (54%)
	Negative	51(46%)
Age	<65	64 (58%)
	≥65	47 (42%)



RESULTS

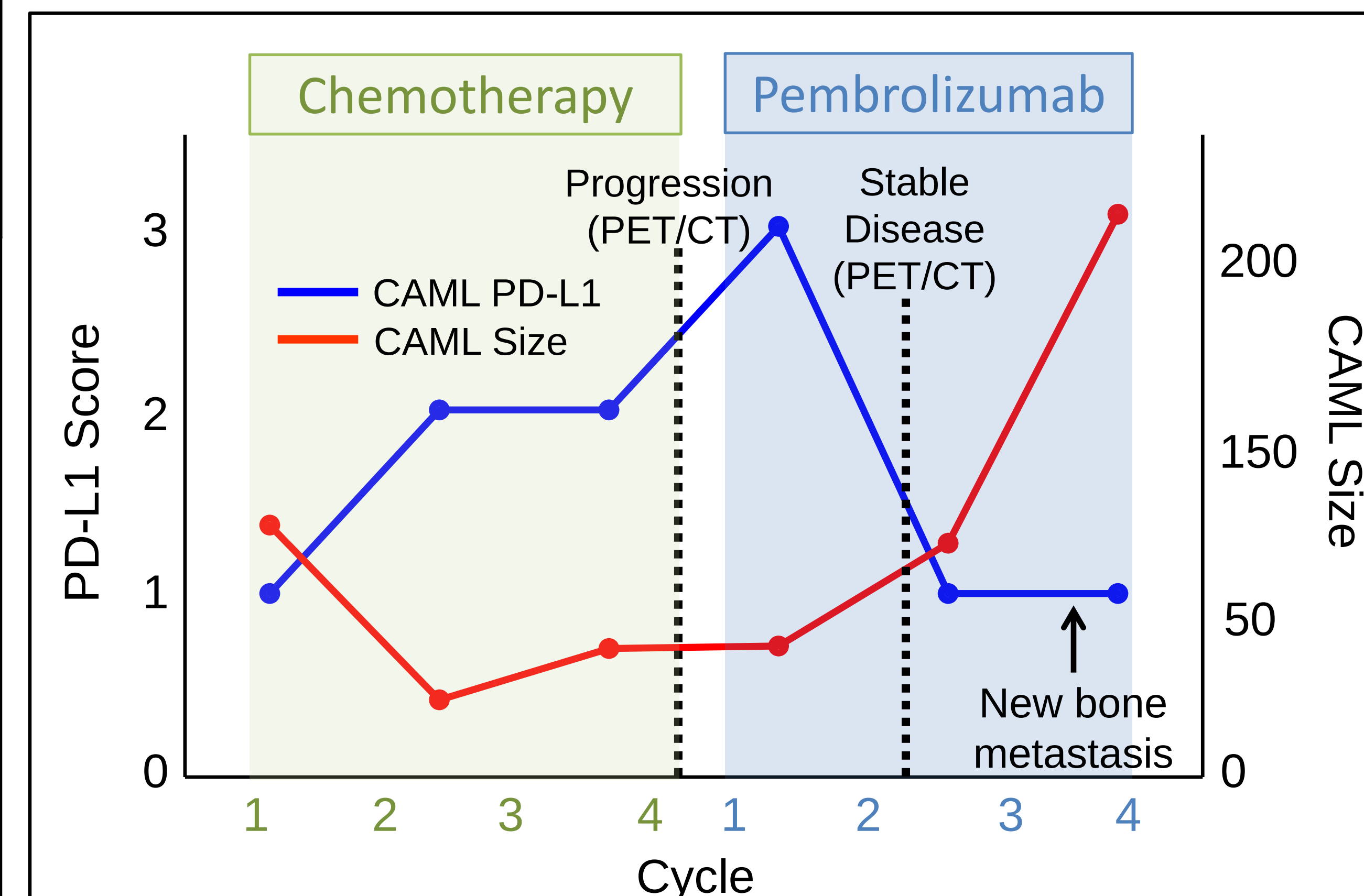
- T0 samples were available for 79% (n=88/111) of patients (two patients had 0 CAMLs and 22 patient samples failed assay).
- T1 samples were available for 73% (n=81/111) of patients.
- At T0, high CAML PD-L1 was not correlated with improved PFS (HR=1.14, p=0.6783) or OS (HR=1.23, p=0.5551). (**Fig 1**)
- At T1, high CAML PD-L1 was significantly correlated with improved PFS (**HR=3.15, p=0.0003**) and OS (**HR=5.61, p<0.0001**). (**Fig 2**)
- Pts with consistently low PD-L1 at T0 & T1 had the poorest responses (mPFS=3.5 mons, mOS=7.5 mons). (**Fig 3**)
- Pts with consistently high PD-L1 had the best responses (**mPFS=6.9 mons and mOS=13.4 mons**). (**Fig 3**)

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

	mPFS	mOS
Low to Low N=20	3.5 (0.27-14.5)	7.5 (0.46-21.7)
High to Low N=7	3.3 (0.67-21.1)	7.9 (2.67-21.07)
Low to High N=18	4.0 (1.3-24.0)	18.5 (1.83->24.0)
High to High N=13	6.9 (1.1-24.0)	13.4 (1.13->24.0)



CONCLUSIONS

- We describe a cancer agnostic blood-based biopsy to monitor dynamic PD-L1 changes in circulating tumor immune cells (i.e. CAMLs)
- Monitoring the PD-L1 in CAMLs appears to offer a dynamic perspective on immune response modulation over time
- In mBC, mNSCLC, mRCC, and other aggressive cancers, high PD-L1 expression in CAMLs after starting IMT appeared prognostic for increased IMT benefit.

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