Sequential monitoring of tumor macrophage fusion cells in the circulation of metastatic breast cancer and their prognostic value

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ABSTRACT

Tumor Macrophage Fusion Cells (TMFCs) are hybrids fusions of tumor cells and macrophage/immune cells (**Figure 1**) recently documented in advanced solid tumors, such as metastatic Breast Cancer (mBC). Further, TMFCs are found in the blood of patients (pts) as a CD45+/CD14+ binucleated subtype of standard circulating tumor cells (CTCs), which are Cytokeratin+ (CK+) & CD45 negative, but distinct from highly hyperploidy cells known as cancer associated macrophage-like cells. However, no study has explored the clinical meaning of TMFCs in blood. To better elucidate the clinical meaning of TMFCs, we prospectively pooled 137 mBC pt samples prior to induction of new therapy, ie baseline (BL) and after therapy induction (FU). Both TMFCs or standard CTCs were identified and enumerated to analyze their prognostic value for progression-free survival (PFS) and overall survival (OS).

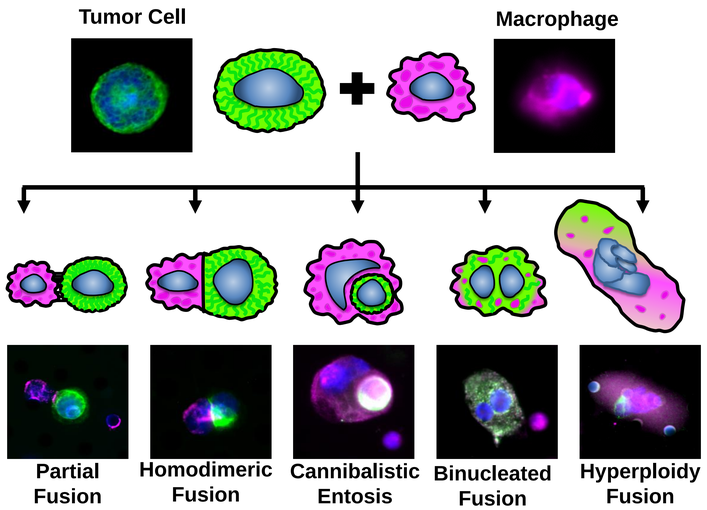

Figure 1: Various subtypes of tumor/macrophage fusion cells. All except Hyperploidy Fusion cells are included in the TMFC analysis.

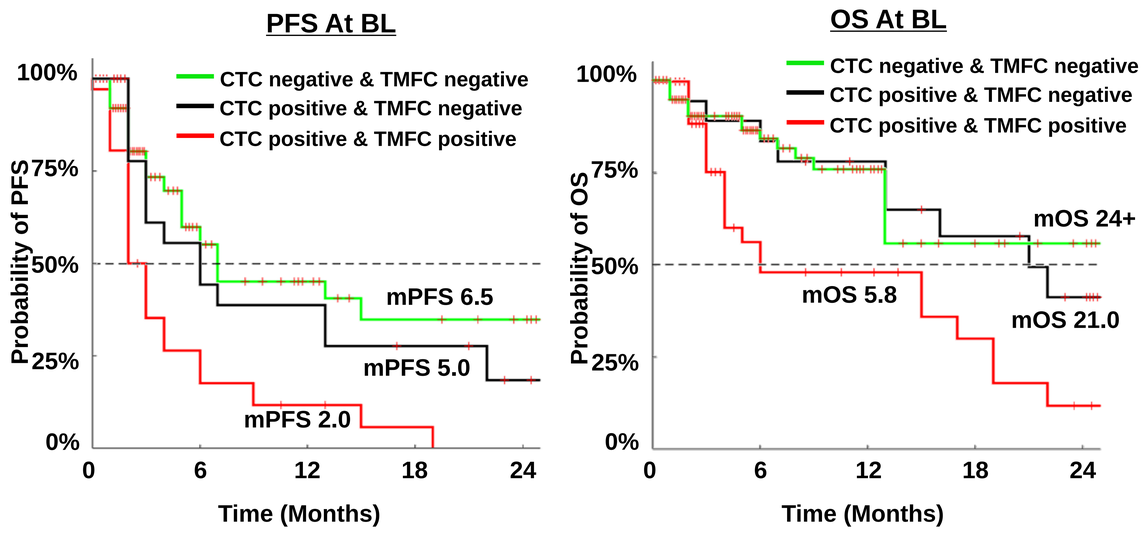

Figure 2A&B: Cox Proportional Survival Analysis of PFS and OS for No CTCs (Green Line), with CTCs (Black Line) or with TMFCs (not including hyperploidy fusion cells) (Red Line) at BL.

RESULTS

- TMFCs were detected in 26% at BL and 27% at FU
- TMFCs were significantly prognostic for worse PFS and OS at both BL and FU
- Any type of CTCs were detected in 39% at BL and 38% at FU
- Any type of CTCs were significantly prognostic for worse PFS but not OS at BL. At FU, CTCs were significantly prognostic for worse PFS and OS.
- At BL, pts without CTCs or TMFCs had the best survival outcomes (**Figs 2**), followed by patients with just CTC, and patients with TMFCs having the worst outcomes.
- TMFCs at BL and FU were the only significant independent parameters for PFS and OS (**Table 2**).

CONCLUSIONS

- TMFCs appears to represent a subgroup of CTCs with additional prognostic value not previously analyzed.
- Presence of TMFCs correlates with significantly worse PFS and OS versus patients without CTCs, or versus patients with normal CTCs.
- Patients with drops in TMFC populations after induction of new treatments had better outcomes, indicating responses to specific treatment types.

Table 1. Demographic Table

Median Age (Range)		58 (25-92)
Race	Caucasian	79 (58%)
	Black	13 (9%)
	Asian	11 (8%)
	Hispanic	4 (3%)
	Not Reported	30 (22%)
Histology	IDC (IBC)	76 (56%)
	ILC	7 (5%)
	Other/unknown	2/52 (39%)
Hormone		
	Positive (ER+/PR+/HER2+)	72 (53%) (51/34/21)
	Negative (TNBC)	60 (44%)
unknown		5 (4%)
# Prior Lines Therapies	0	16 (12%)
	1	22 (16%)
	2	33 (34%)
	≥3	66 (48%)
Therapy Type	Chemo Alone	49 (36%)
	Hormone	8 (6%)
	Immunotherapy	49 (36%)
	Other Targeted	31 (23%)
Number of Metastatic Sites	1	71 (52%)
	≥2	66 (48%)
CTC at BL	0	83 (61%)
	≥1	54 (39%)
CTC at FU	0	45 (62%)
	≥1	28 (38%)
TMFCs at BL	0	101 (74%)
	≥1	36 (26%)
TMFCs at FU	0	53 (73%)
	≥1	20 (27%)

Table 2. Univariate & Multivariate Table

Variable			PFS HR (95%CI)	Uni PFS (p value)	Multi PFS (p value)	OS HR (95%CI)	Uni OS (p value)	Multi OS (p value)
Age <65 vs ≥65	106	31	1.3 (0.8-2.2)	0.349		1.5 (0.7-2.8)	0.360	
Race Cauc vs Other	85	22	1.4 (0.8-2.6)	0.333		2.1 (1.0-4.3)	0.072	
Histology (IDC v other)	84	13	1.1 (0.6-2.4)	0.861		0.6 (0.3-1.6)	0.462	
Hormone Pos v TNBC	72	60	1.5 (0.9-2.4)	0.169		1.6 (0.8-2.8)	0.212	
# Prior Ther. <2 v ≥2	38	89	2.3 (1.4-3.7)	**0.002**	0.886	1.5 (0.8-2.8)	0.328	
Hormone Ther. vs Other	8	129	1.5 (0.6-3.7)	0.516		1.3 (0.4-3.8)	0.850	
# Met Sites 1 vs ≥2	71	66	1.6 (0.9-2.7)	0.154		1.0 (0.5-2.1)	0.926	
CTCs+ (BL)	54	83	2.3 (1.4-3.8)	**<0.001**	0.092	1.7 (1.0-3.2)	0.096	0.589
CTCs+ (FU)	28	45	4.1 (1.9-8.8)	**<0.001**	0.344	3.2 (1.3-8.2)	**0.027**	0.149
TMFCs+ (BL)	36	101	3.7 (2.1-6.6)	**<0.001**	0.950	3.1 (1.6-6.1)	**<0.001**	**0.014**
TMFCs+ (FU)	20	53	5.7 (2.4-13.8)	**<0.001**	**0.042**	8.5 (2.9-24.6)	**<0.001**	0.993
Increase in CTCs	21	52	4.0 (1.7-9.5)	**0.003**	0.371	4.7 (1.4-12.7)	**0.021**	0.798
Increase in TMFCs	18	55	4.5 (1.8-11.1)	**0.002**	0.123	7.6 (2.6-22.4)	**<0.001**	0.821

MATERIALS & METHODS

In this prospective study, we collected 7.5 mL blood samples from n=137 mBC pts enrolled in prospective trials from multiple institutions before starting new treatment lines for newly progressive mBC. If possible, an optional FU sample was collected (n=73) after BL (median=4.9 weeks). TMFCs in this analysis did not include Hyperploidy Fusion cells (i.e. CAMLs). TMFCs & CTCs were isolated using a CellSieve™ microfilter and differentiated by staining for CK, CD45, CD14, and DAPI. Cox proportional regression hazard ratios (HRs) with 95% Confidence Intervals (95%CI) for PFS & OS by univariate & multivariate analyses were based on RECIST v1.1, determined by local institutional pathologist over 24 months (M).

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