PET-CT and Liquid Biopsy for Monitoring Breast Cancer Bone Metastasis (P-CLIMB)

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Background

- Bone metastases (mets) develop in 50-70% of patients with metastatic breast cancer (MBC).[1]
- Skeletal Related Events occur in up to 64% of cases of bone mets due to breast cancer without bisphosphonate treatment and are associated with significant morbidity and decline in quality of life.[1]
- 180,000 patients living with MBC in the United States with 30-45% having bone mets as their only site of disease ('bone-only'/BO-MBC).[1,2]
- Patients with BO-MBC are frequently excluded from clinical trials because bone mets are not 'measurable'.[3]
- We *hypothesize* that ctDNA tumor fraction (TF) in combination with PET-CT will provide superior monitoring of bone mets.
- In prior work, ctDNA TF was detectable in similar proportion of patients with bone only (versus non-bone only) advanced breast cancer and remained prognostic in bone-only setting (**Figure 1).**[4]

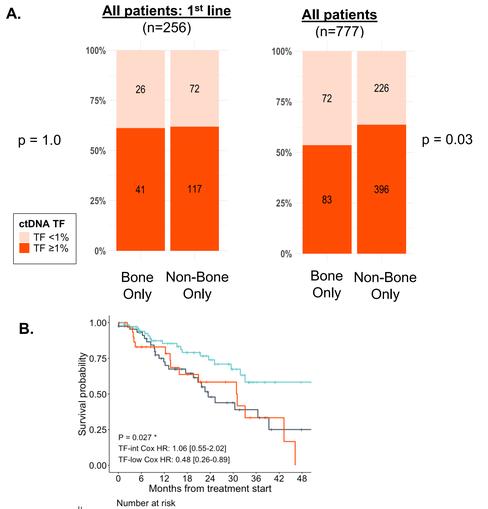


Figure 1. Real-World Analysis of Tumor Fraction in Bone Only Versus Non-Bone Only Advanced Breast Cancer
A. Tumor fraction values from FoundationOne®Liquid CDx* circulating tumor DNA (ctDNA) assay of <1% and >1% were proportionally similar in a Real World Outcomes analysis of the Flatiron Health-Foundation Medicine genomic database (FH-FMI CGDB). **B**. Tumor fraction remains prognostic among patients with bone-only advanced breast cancer (log-rank p=0.027). TF high = >10%, TF int = 1% -10%, TF low = <1%.

Methods

- **Eligibility Criteria:** Patients included with any hormone receptor, on any line of systemic therapy and undergoing standard-of-care PET-CT.
- **Blood collection:** Blood collection occurred within 30 +/- 7 days of each PET-CT. 20mL blood was collected in Streck tubes, processed to component parts, and banked.
- **ctDNA Assay:** Analysis by the laboratory developed test FoundationOne®Monitor ctDNA assay for research assessment of ctDNA TF (accounting for aneuploidy, variant allele frequency, fragment length, clonal hematopoiesis [CH], and genomic alterations for 324 genes at each timepoint).
- **Image Analysis:** Deidentified PET-CT scans reviewed by a study radiologist on VISAGE PACS to determine SUVmax (PET Maximum Standardized Uptake Value) plus number of skeletal vs. nonskeletal lesions.
- **Study Cohorts:** Participants were categorized into two cohorts: Cohort 1: Bone only or bone-lymph node (BO/L-MBC; Cohort 2: Bone + visceral metastases (BV-MBC).

Figure 2. Consort Diagram

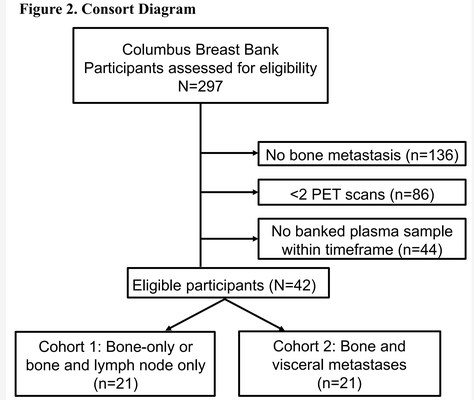
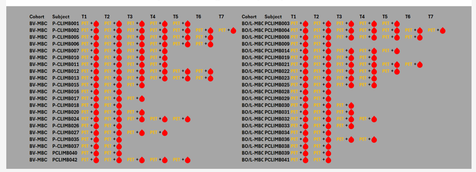


Figure 3. Serial samples and scans available per included Banking Participant
A total of 42 patients (21 BO/L-MBC, 21 BV-MBC) completed a total 160 PET-CT & ctDNA pairs, range 2-7 per patient.



Results

Table 1. Participant Characteristics

	BO/L-MBC (N=21)	BV-MBC (N=21)	Total (N=42)	P-value
Age at Initial Diagnosis				
Mean (SD)	59.2 (12.5)	51.5 (13.0)	55.4 (13.2)	0.058*
Median	62.0	55.0	59.0	
Range	33.0, 77.0	30.0, 73.0	30.0, 77.0	
Age at Metastatic Diagnosis				
Mean (SD)	64.3 (11.9)	55.1 (13.4)	59.7 (13.4)	**0.023***
Median	65.0	57.0	63.5	
Range	33.0, 79.0	31.0, 73.0	31.0, 79.0	
Primary Receptor Status, n (%)				0.74§
ERpos, HER2neg	17 (81.0%)	16 (76.2%)	33 (78.6%)	
HER2pos	3 (14.3%)	2 (9.5%)	5 (11.9%)	
TNBC	1 (4.8%)	3 (14.3%)	4 (9.5%)	
Metastatic Receptor Status, n (%)				0.89§
ERpos, HER2neg	16 (76.2%)	14 (66.7%)	30 (71.4%)	
HER2pos	2 (9.5%)	4 (19.0%)	6 (14.3%)	
TNBC	3 (14.3%)	3 (14.3%)	6 (14.3%)	
T1 Tumor Fraction, %				0.28†
Mean (SD)	2.2 (4.0)	4.9 (9.7)	3.5 (7.5)	
Range	0.0, 13.0	0.0, 29.0	0.0, 29.0	

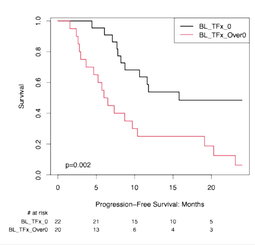
* Two sample t-test; § Fisher Exact test; † Wilcoxon rank sum

ctDNA Tumor Fraction showed only moderate correlation to imaging features.

Table 2. Correlations Between SUV max and Number of Lesions with Cohort at T1, T2

Cohort		SUVmax at T1		# total lesions T1	
		Spearman correlation	P-value	Spearman correlation	P-value
BO/L-MBC	TF at T1	0.43	0.054	0.21	0.35
BV-MBC	TF at T1	0.47	0.034	0.24	0.30
		SUVmax at T2		# total lesions T2	
BO/L-MBC	TF at T2	0.55	0.01	0.39	0.08
BV-MBC	TF at T2	0.60	0.004	0.39	0.08

Figure 4. Baseline ctDNA TF (0 versus >0) was associated with progression-free survival



Results

T1:T2 TF change was not different between cohorts.

Table 3. T1:T2 TF Change (Wilcoxon Rank Sum Test)

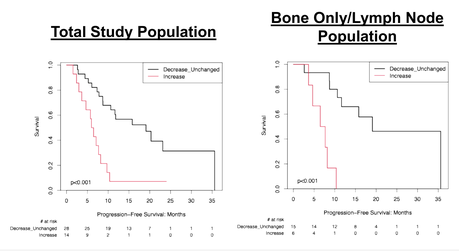
	Cohort			
	Bone Only/LN (N=21)	Bone-Visceral (N=21)	Total (N=42)	P-value
TF change				0.8964*
N	21	21	42	
Mean (SD)	1.1 (7.3)	1.7 (17.7)	1.4 (13.4)	
Median	0.0	0.0	0.0	
Range	-11.0, 26.0	-28.6, 63.8	-28.6, 63.8	

For total study population, T1:T2 TF change and SUVmax change were each significantly associated with clinician-interpreted imaging response.

Table 4. Correlations Between SUV max and Treatment Response with cohort at T1, T2

	Best Objective Response				
	Partial Response (N=14)	Mixed (N=4)	Progression (N=7)	Stable (N=17)	P-value
TF change					0.0059*
N	14	4	7	17	
Mean (SD)	-5.3 (10.06)	5.5 (14.27)	11.4 (23.56)	1.7 (6.35)	
Median	0.0	3.0	1.5	0.0	
Range	-28.6, 0.5	-8.9, 25.0	-1.1, 63.8	-3.1, 26.0	
SUVmax change					0.0022§
N	14	4	7	17	
Mean (SD)	-4.9 (5.10)	-0.7 (6.73)	3.2 (2.78)	0.3 (4.06)	
Median	-4.1	-0.9	3.2	0.2	
Range	-14.5, 4.0	-8.7, 7.8	0.6, 8.3	-7.1, 10.8	

Figure 5. T1:T2 ctDNA TF change (increase vs. decrease or stable) is significantly associated with progression-free survival (PFS)



Results

Figure 6. Association of T1:T2 ctDNA TF change with progression-free survival in patients with 'stable' disease (SD) by PET-CT

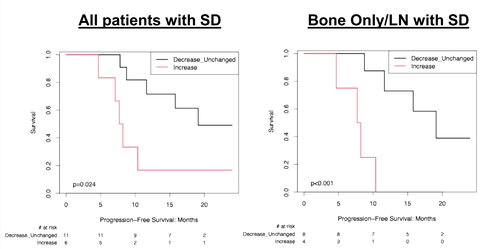
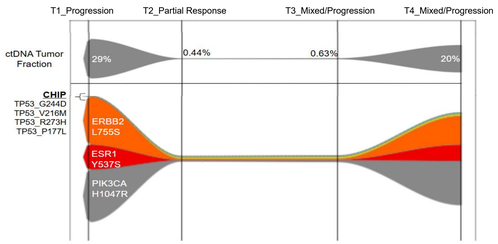


Figure 7. Genomic Alterations Across Serial Samples



Detailed evaluation of specific genomic alterations revealed expansion of known resistance mutations (including *ESR1*, *ERBB2*, and *PTEN*) in advance of imaging and clinical progression.

Conclusion

- In patients with BO/L-MBC, ctDNA TF was significantly associated with PFS, even in the setting of PET-CT imaging interpreted as 'stable.'
- Response assessment by ctDNA offers a clinically useful adjunct to clinical imaging for MBC metastasized to bone.
- ctDNA-based assessment could expand the definition of measurability to include those with BO/L-MBC.

References and Funding

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*Ct DNA TF is neither FDA reviewed nor approved.