Implementation of Liquid Biopsy in a Real-World Clinical Setting: Guiding Treatment Decisions in Metastatic Breast Cancer through Genomic Profiling

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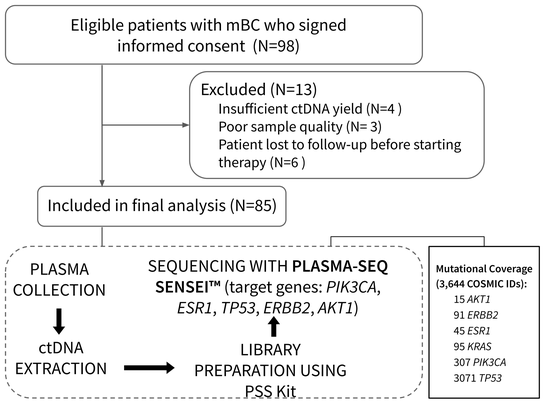
INTRODUCTION

Metastatic breast cancer (mBC) exhibits tumor evolution and genomic heterogeneity with somatic alterations linked to progression and therapeutic resistance. We conducted a prospective Real-World Data study to evaluate ctDNA-detected mutations (MUT) via LB and their association with clinical outcomes.

METHODS

Prospective, single-center study including 98 mBC patients undergoing pre-treatment ctDNA analysis (mainly at the start of first- or second-line metastatic therapy) following written informet consent. Plasma was collected in Streck® tubes and analyzed with the Plasma-SeqSensei™ BC panel (Sysmex®), targeting *PIK3CA, ESR1, ERBB2, AKT1* and *TP53*. Progression-free survival on first-line therapy (PFS1) was defined as the interval from initiation of first-line metastatic therapy to radiologic progression or death and was evaluated in all patients treated in this setting, irrespective of ctDNA sampling time. An exploratory analysis was conducted in the subgroup with baseline ctDNA. PFS2 and PFS3 were assigned when ctDNA was obtained at the start of second- or third-line therapy. Survival was estimated using Kaplan–Meier curves and compared by log-rank according to ctDNA mutational status. Significance set at 0.05.

Figure 1. Study population and liquid biopsy processing



RESULTS

Table 1. Baseline characteristics by mutation status (PIK3CA and ESR1)

Characteristic	All patients (N=85)	*PIK3CA* Mutant (N=26)	*PIK3CA* Wild-type (N=59)	P Value	*ESR1* Mutant (N=15)	*ESR1* Wild-Type (N=70)	P Value
Age, median (range)	61 (51–69)	57 (50–66)	62 (50–73)	0.078	64 (56–72)	59 (48–70)	0.101
<65	54 (64%)	21 (80%)	33 (56%)	0.03	9 (60%)	45 (64%)	0.774
>65	31 (36%)	5 (19%)	26 (44%)		6 (40%)	25 (36%)	
Sex (female)	84 (99%)	–	–	-	–	–	–
Histology							
Ductal	69 (81%)	22 (85%)	46 (80%)	0.678	14 (93%)	55 (77%)	0.359
Lobular	16 (19%)	4 (15%)	12 (20%)		1 (7%)	15 (23%)	
Grade							
I–II	66 (77%)	22 (84%)	44 (83%)	0.857	12 (80%)	54 (84%)	0.704
III	13 (15%)	4 (15%)	9 (17%)		3 (20%)	10 (16%)	
Missings	6 (8%)						
Endocrine therapy-naïve				0.227			0.339
Yes	31 (42%)	11 (43%)	20 (34%)		5 (33%)	26(37%)	
No	54 (58%)	15 (57%)	39 (66%)		10 (67%)	44 (63%)	
Subtype							
Luminal A	38 (46%)	15 (58%)	23 (41%)	0.519	6 (43%)	32 (47%)	0.125
Luminal B	39 (47%)	10 (38%)	29 (52%)		39 (50%)	32 (47%)	
HER2	4 (4%)	1 (4%)	3 (5%)		0 (0%)	4 (6%)	
Triple negative	1 (1%)	0 (0%)	1 (2%)		1 (7%)	0 (0%)	
Missings	3 (2%)						
Site							
Non-visceral	51 (60%)	12 (46%)	39 (66%)	0.067	10 (67%)	41 (59%)	0.772
Visceral	34 (40%)	14 (54%)	20 (34%)		5 (33%)	29 (41%)	

Distinct clinical associations by mutation:

- ***TP53*** mutations were more frequent in grade III tumors (61.5% vs 38.5%; p = 0.04)
- ***ERBB2*** mutations were enriched in lobular histology (66.7% vs 15.2%; p = 0.01)
- ***ESR1*** mutations were significantly more frequent in pre-treated patients (10/36; 27.8%) compared with treatment-naïve patients (5/49; 10.2%, p=0.046)
- ***PIK3CA*** mutations were significantly more frequent in younger patients (<65 years: 21/54 vs ≥65 years: 5/31; p = 0.03)

Figure 2. Timing and clinical context of liquid biopsy in mBC patients

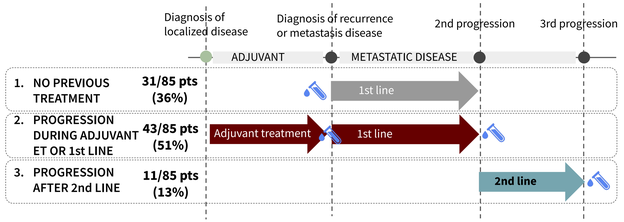
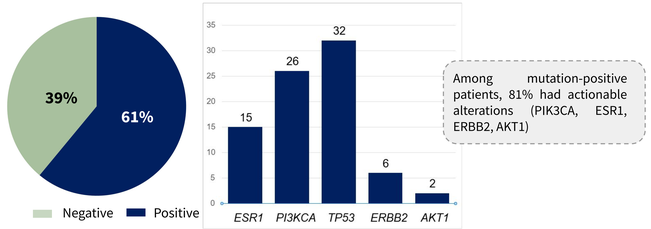


Figure 3. ctDNA positivity rate in mBC patients



Among mutation-positive patients, 81% had actionable alterations (PIK3CA, ESR1, ERBB2, AKT1)

Figure 4. ctDNA mutation prevalence in treatment-naïve vs pretreated Patients

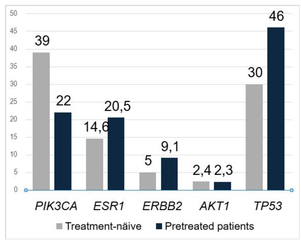
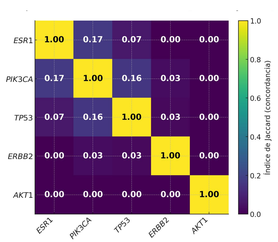


Figure 5. Genomic concordance among ctDNA mutations (Jaccard Index)



Figures 6 and 7. Prevalent PIK3CA and ESR1 variants detected by ctDNA

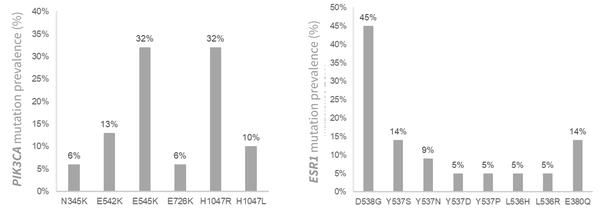
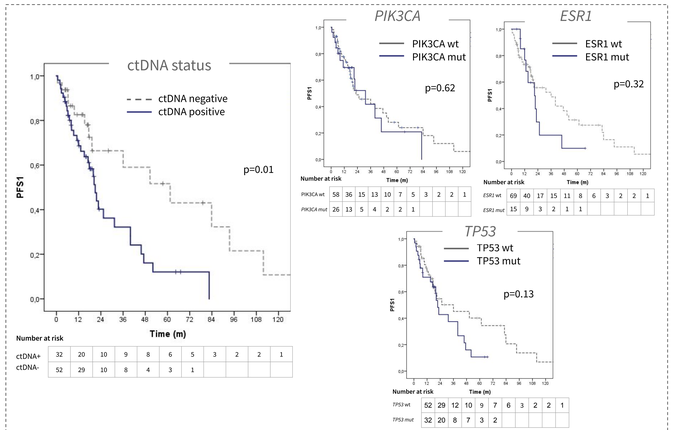


Figure 8. Kaplan–Meier estimates of PFS1 by ctDNA status and mutations



ctDNA-positive patients (≥1 mutation) had significantly shorter PFS1 than ctDNA-negative patients (20.0 vs 61.0 months, p=0.01). No significant associations were observed for PIK3CA, ESR1, or ERBB2 (all p>0.5). TP53 mutations showed a non-significant trend toward shorter PFS1 (p=0.13). In the baseline CDK4/6 inhibitor–naïve subgroup (n=49), high censoring (78%) limited statistical power and PFS1 differences were not significant, although curve patterns mirrored the overall cohort. PFS2 and PFS3 analyses were heterogeneous across treatment lines and did not show mutation-related differences.

CONCLUSIONS

- Ultrasensitive ctDNA testing was feasible and clinically informative in mBC.
- ctDNA positivity (≥1 mutation) was associated with significantly shorter PFS1.
- No individual mutation (PIK3CA, ESR1, ERBB2, TP53) showed prognostic value; TP53 showed only a non-significant trend toward shorter PFS1.
- The heterogeneous timing of ctDNA sampling highlights the need for standardized implementation in routine practice.

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Disclosures:

The author declare no disclosures

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