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Tracking structural variants in ctDNA using a high-sensitivity assay predicts relapse in the post-neoadjuvant setting: the multicenter ALIENOR trial

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Background

- Up to 30% of patients whose tumour did not achieve a complete pathological response (pCR) after neoadjuvant chemotherapy relapse within 5 years[1].
- Could we identify these patients several months before a clinical relapse with detection of circulating tumour DNA (ctDNA) using serial sampling every 6 months?
- ctDNA assessment methods used in patients with advanced breast cancer are not sensitive enough in early breast cancer. In previous pivotal cohorts, landmark detection rates have been low[2,3].
- In this study, we assessed the clinical validity of an ultra-sensitive ctDNA assay based on structural variants[4], with serial sampling in patients whose tumour did not achieve a pCR after neoadjuvant chemotherapy.
- We report the first of two pre-planned analyses from the ALIENOR study (NCT03357120) (3-years from last patient enrolled).

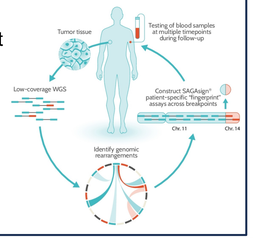
Objectives

Primary:
- Prognostic value of positive ctDNA at any time point during follow-up after surgery

Secondary:
- Median lead-time from ctDNA detection to clinical relapse
- Prognostic value of detected ctDNA at a landmark pre-adjuvant time point (10 to 63 days post-surgery)
- Prognostic value of detected ctDNA at any time point and median lead-time by BC group (ER+/HER2-, HER2-positive, triple-negative).

Methods and Materials: ctDNA analysis

- WGS of tumour tissue at low coverage and structural variant (SV) identification
- RUO version of SAGA's ctDNA technology using up to 8 SVs (SAGA Diagnostics)
- Multi-target bespoke dPCR assay to monitor MRD using serially collected plasma time points



Main Inclusion Criteria and Study Design

Main inclusion criteria
- invasive breast cancer
- any subtype
- stage II (N+ only) or III
- neoadj. chemo. 6-8 cycles

Neoadjuvant chemotherapy

Surgery

Adjuvant treatment

Follow-up for 5 y.

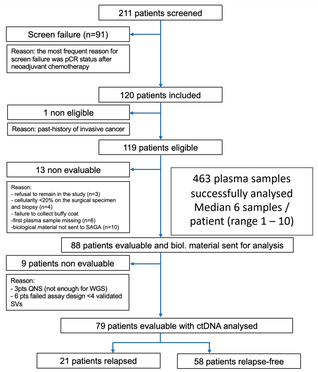
Plasma sample every 6 m. for 5 y.

Landmark pre-adjuvant time point (10-63 d. post-surgery)

Informed consent signed before surgery (and participation confirmed after surgery in non pCR cases only)

1st planned analysis (3 years from last patient enrolled)

Patient Cohort and Tumor Characteristics



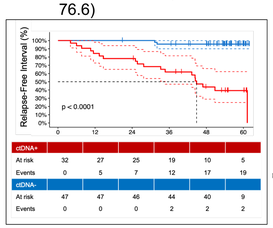
			79 (100%)
N (eval. pop.)			
Median age			52 (26-79)
Clinical stage		II	36 (45.6%)
		III	43 (54.4%)
Histological type		IDC	73 (92.4%)
		ILC	1 (1.3%)
		Both	1 (1.3%)
		Other	4 (5.1%)
Subtype		ER+HER 2-	39 (49.4%)
		Triple neg.	18 (22.8%)
		HER2+	20 (25.3%)
		Other	2 (2.5%)
RCB class		1	4 (5.2%)
		2	32 (41.6%)
		3	36 (46.8%)
		Not known	5 (6.5%)

Table 1: Cohort Characteristics

Median follow-up (from surgery): 54.5 m.

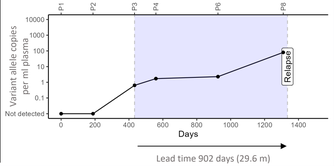
Results: Relapse-Free Interval in ctDNA+ and ctDNA- groups

- Pts with ctDNA+ (at any time point) had shorter RFI: HR 20.6 (P<0.0001; 95%CI: 4.8-88.8)
- 3 yr RFI
  - ctDNA+: 62.3% (95%CI: 71.7-89.0)
  - ctDNA-: 95.7% (95%CI: 43.3-76.6)



- **100% sensitivity (19/19) for non-intracranial, non-local relapse**
- 90% sensitivity (19/21) including local (1 pt) and brain-only met (1 pt)
- Median lead time from first ctDNA+ to relapse: 12m (range 3.2-60.6m)

Example: patient with cT4dcN1 HER2+ tumour → lead time 29.6 m



Results: Cox regression analysis (unadjusted univariate)

The univariate analysis showed ctDNA status provided statistically significant associations with RFI (HR: 20.59) which was not observed using standard clinicopathological factors alone

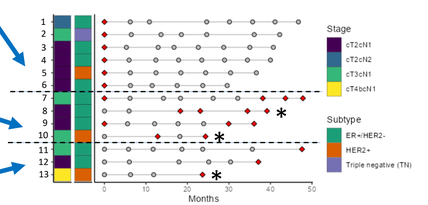
		N	Hazard ratio	95% CI	p-value
Clinical stage		79			
	Stage II	-	1	-	-
	Stage III	-	1.11	0.47 - 2.64	0.81
Subtype		77			
	Triple neg.	-	1	-	-
	ER+ HER2-	-	0.72	0.24 - 2.15	-
	HER2+	-	1.31	0.42 - 4.14	0.49
RCB class		74			
	I	-	1	-	-
	II	-	0.67	0.14 - 3.08	-
	III	-	0.34	0.07 - 1.67	0.29
Age at diagnosis		79			
	18-40	-	1	-	-
	>40	-	1.56	0.36 - 6.74	0.55
ctDNA detection at any time point in follow-up		79			
	No	-	1		-
	Yes	-	20.59	4.78 - 88.76	<0.0001
ctDNA detection at landmark time point		79			
	No	-	1		-
	Yes	-	2.49	1.01 - 6.17	<0.05

Results: Out of 32 pts with positive ctDNA, thirteen were relapse-free at the time of database lock (May 2024)

6 patients ctDNA+ at the first landmark time-point only (pre-adjuvant treatment) but subsequently cleared on adjuvant therapy

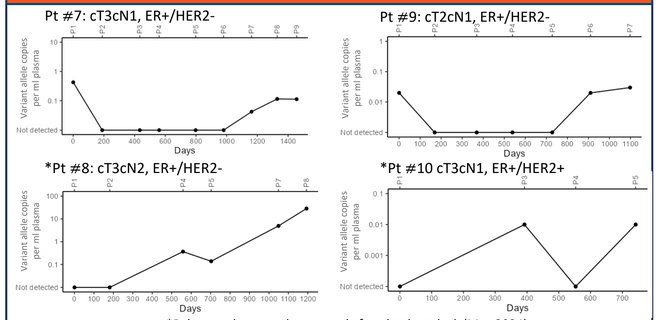
4 patients ctDNA+ at multiple time-points.

3 patients ctDNA+ at the last visit only



*Relapse subsequently occurred after database lock (May 2024)

Results: Focus on the 4 patients ctDNA+ at multiple time-points



*Relapse subsequently occurred after database lock (May 2024)

Longer follow up is required in this cohort of high-risk patients.

Discussion

- Serial ctDNA assessment using a novel SV-based dPCR assay is highly prognostic with lead-times up to 61 months over clinical relapse.
- Landmark-only ctDNA detection followed by clearance on therapy might represent micrometastatic disease controlled or eradicated by adjuvant treatment.
- This was the first of 2 pre-planned analyses and follow up is ongoing. This is particularly important in cases with ctDNA detection without relapse to fully characterize clinical accuracy and lead-times associated with SV-based ctDNA surveillance.

Conclusions

Our results demonstrate the clinical validity of this ultra-sensitive assay and should motivate the conduct of prospective randomized trials to assess the clinical utility in patients with high risk breast cancer.

Contact

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References

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