Clinical Utility of Circulating Tumor Cell Enumeration-Based Liquid Biopsy in Patients with Metastatic Breast Cancer: A Review of the Peer-Reviewed Clinical Literature

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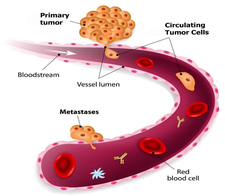
INTRODUCTION

Circulating Tumor Cell (CTC) enumeration is a liquid biopsy testing approach for which the peer-reviewed evidence base has grown rapidly in recent years, especially in metastatic breast cancer (MBC) the U.S. FDA-cleared CellSearch® CTC test. In this research, we aimed to assess the published peer-reviewed evidence of clinical utility for the CellSearch® CTC test in MBC.



METHODS

A comprehensive PubMed search and literature review was conducted investigating the clinical utility of the CellSearch® CTC assay in MBC. Clinical utility was defined as clinical usefulness in: (**A**) Cancer staging/ stratifying tumor aggressiveness, and prognosis, (**B**) Monitoring cancer progression/ treatment response, and (**C**) Cancer treatment selection/ response prediction. More than 130 relevant peer-reviewed publications from 2004–2022, including meta-analyses that included CellSearch CTC, were identified and reviewed. When the search identified preliminary study results in peer-reviewed publications, we also included any follow-on study results published in conference proceedings. All sources of presented data are cited.

CONCLUSIONS

The peer-reviewed clinical literature confirms the clinical utility of CTC enumeration in MBC for disease stratification, prognosis and monitoring, and treatment selection and response prediction (confirmed in a randomized phase 3 trial, in which CTCs were used to determine treatment), with implications for CTCs to be applied in routine clinical practice as a tool for treatment decisions and more efficient allocation of healthcare resources.

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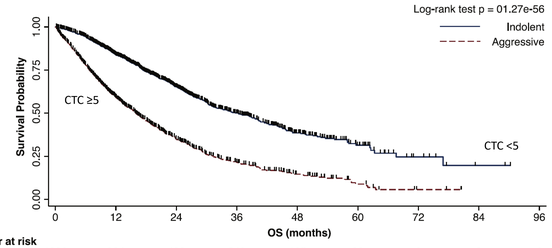
RESULTS OF CLINICAL UTILITY ASSESSMENT FOR CELLSEARCH® CIRCULATING TUMOR CELL (CTC) TESTING IN METASTATIC BREAST CANCER (MBC)

(A) CTC enumeration can be used as a standardized universal biomarker to identify patients with the most aggressive Stage IV disease

A pooled analysis[1] of 2,436 MBC patients showed CTC enumeration into <5 and ≥5 CTC can stratify Stage IV disease into two important subgroups: Stage $IV_{indolent}$ and $IV_{aggressive}$ irrespective of standard clinical and molecular factors with statistically longer overall survival (OS) for Stage $IV_{indolent}$ patients.

This was true for all groups of patients analyzed:

- Patients with *de novo* advanced disease at diagnosis
- Hormone receptor (HR)-positive patients
- HER2-positive patients
- Triple-negative patients
- Treatment-naïve patients
- Patients with prior treatment
- Patients with visceral metastasis
- Patients with bone-only metastasis



(B) Serial CTC enumeration is clinical useful in conjunction with standard radiologic assessments for monitoring disease progression

Multiple studies demonstrated utility in monitoring disease status and at least six included comparisons of CTCs to radiographic imaging:

Ref	n	Conclusions
2	138	Assessment of CTCs is an earlier, more reproducible indication of disease status than current imaging methods.
3	102	Detection of CTCs during Tx monitoring accurately predicts prognosis beyond metabolic response (FDG-PET/CT).
4	108	Presence of extensive bone mets by FDG-PET/CT is associated with increased CTC numbers. CTCs strongly prognostic.
5	68	Detectable changes in CTCs preceded imaging detection by ≥2 months.
6	107	Change in CTCs was highly correlated with imaging before and after Tx. CTCs can predict the effect of treatment earlier than imaging modalities.
7	294	CTCs provide substantial prognostic information and are an independent factor associated with PFS and OS, and strongly correlated with imaging.

Serial CTC monitoring has several advantages over radiographic imaging:

- Significantly lower interreader variability
- Less costly and time consuming, more easily performed at shorter intervals
- Shows results at earlier time-points

Which makes CTC monitoring clinical useful in conjunction with standard assessments for improved patient management.

(B) CTC-response between baseline and post-treatment follow-up indicates impact of therapy on Overall Survival (OS) in MBC

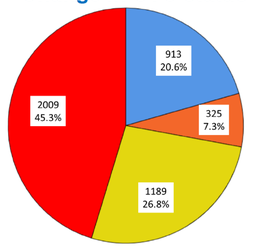
Evidence for the significance of CTCs in MBC staging and prognosis was confirmed a comprehensive pooled analysis of globally collected data from >25 published studies and includes 4,436 patients (PREDICT – Global Pooled Analysis).[8-10]

Clinical Trial / Study / Institution	n	%
CALGB 40502 (Alliance)	455	10.3
CALGB 40503 (Alliance)	219	4.9
COMET	222	5.0
DETECT study program (DETECT III, DETECT IV, DETECT V, ongoing)	306	6.9
IMMC-01 multicenter study	189	4.3
N1031	30	0.7
NSABP B-06	105	2.4
SWOG 0500	279	6.3
TBCRC 001	79	1.8
European pooled analysis (EPAC; including updated data sets)	1,043	23.5
MDACC institutional study	376	8.5
Multi center Chinese study (CBCSG004)	209	4.7
Multi center Japanese study	106	2.4
Single institutional data (Athens, Aviano, Brussels, Georgetown, Heidelberg, Hamburg, Heraklion, Montpellier, Rome, Rotterdam, Santiago de Compostela)	818	18.4
TOTAL	**4,436**	**100.0**

Conclusions global pooled analysis:

- Follow-up CTC assessments at 28 days after Tx initiation strongly predict OS.
- Patients with CTC-response had significantly increased OS (32.3 vs 17.3 months, HR 0.48).
- Early treatment monitoring is predictive for OS in all tumor subtypes and in both patients treated with endocrine (ET) and chemotherapy (CT).
- These results provide strong evidence for clinical validation of CTC monitoring as early treatment response marker in advanced breast cancer and suggest the potential for clinical utility.

Change in CTC status from baseline to first follow up

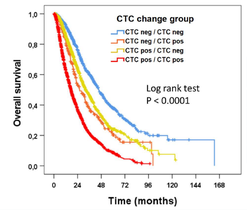


CTC change group
(cutoff for CTC positivity: ≥ 1 CTC)

- CTC neg / CTC neg
- CTC neg / CTC pos
- CTC pos / CTC neg
- CTC pos / CTC pos

Time from baseline CTC assessment to first follow up CTC assessment:
Median: 28 days
Interquartile range: 22 – 52 days

Overall survival according to change in CTC status from baseline to first follow up



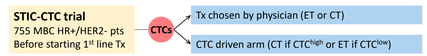
All CTC change groups

	Median OS (months)	Hazard ratio	95 % CI	p-value
neg/neg (n = 913)	45.6	reference		
neg/pos (n = 325)	26.1	1.79	1.51 – 2.13	< 0.0001
pos/neg (n = 1189)	32.3	1.49	1.31 – 1.68	< 0.0001
pos/pos (n = 2009)	17.3	3.14	2.81 – 3.51	< 0.0001

Note: Cutoff for CTC positivity ≥ 1 CTC)

(C) CTC enumeration in HR+/HER2- MBC is clinically useful for treatment selection/ predicting response to specific therapies

The STIC-CTC trial randomized patients to be treated according to physician's choice or according to CTC result.[11,12] CTC scores: ≥5 CTC/7.5ml is CTC^{high}; <5 CTC/7.5ml = CTC^{low}



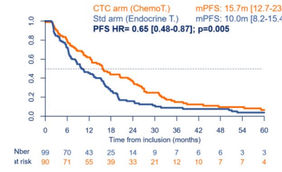
For 40% of patients Tx changed due to CTC assessment. PFS and OS improved in 25% of patients with clinical low risk and CTC^{high} scores.

The STIC CTC trial supports the clinical utility of CTC in metastatic HR+/HER2- patients with a high Level of Evidence.
Therapy management implications for the discordant patient groups:

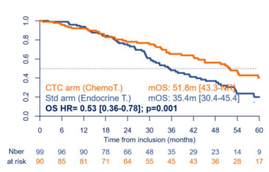
$Clin_{low}$/CTC^{high} patients (25.0%)
Major OS benefit with chemotherapy
ΔmOS = 16 months

$Clin^{high}$/CTC_{low} patients (13.6%)
Chemotherapy not beneficial
Endocrine Therapy remains standard of care

Progression-Free Survival



Overall Survival



Statistically significant and clinically meaningful survival benefit (PFS & OS) in patients with high CTC count treated with chemotherapy