Circulating Tumor Cells (CTCs): Clinical relevance

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- **Analytical performance**
  how accurately and reliably the test detects the analyte(s) of interest;

- **Clinical validity**
  how well the test relates to the clinical outcome of interest (such as survival or response to therapy);

- **Clinical utility**
  Whether the results of the test provide information that contributes to and improves current optimal management of the patient’s disease
### Table 1. Tumor Marker Utility Grading System Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Prospective, marker primary objective. Well-powered or meta-analysis.</td>
</tr>
<tr>
<td>II</td>
<td>Prospective, marker the secondary objective.</td>
</tr>
<tr>
<td>III</td>
<td>Retrospective, outcomes, multivariate analysis (most currently published marker studies are level of evidence III).</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective, outcomes, univariate analysis.</td>
</tr>
<tr>
<td>V</td>
<td>Retrospective, correlation with other marker, no outcomes.</td>
</tr>
</tbody>
</table>

CTCs with Cellsearch Before Therapy: Predicting OS at metastatic stage

Breast
n=177

Logrank p < 0.0001

< 5CTCs
n = 89 (50%)

≥ 5CTCs
n= 88 (50%)

10.9 Months

21.9 Months

Colorectal
n=451

Logrank p < 0.0001

< 3CTCs
n = 334 (74%)

≥ 3CTCs
n = 117 (26%)

8.5 Months

19.1 Months

Prostate
n=219

Logrank p < 0.0001

< 5CTCs
n = 94 (43%)

≥ 5CTCs
n= 125 (57%)

11.5 Months

21.7 Months

Cristofanilli et al
NEJM August 2004
JCO March 2005

Cohen et al
JCO July 2008

De Bono et al
CCR October 2008
Evaluation and Prognostic Significance of Circulating Tumor Cells in Patients With Non–Small-Cell Lung Cancer

MG Krebs, J Clin Oncol 29. © 2011

### Main studies In Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>N</th>
<th>Baseline &amp; PFS</th>
<th>Baseline &amp; OS</th>
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Prospective, multicentric, statistically powered with CTC validity as 1st objective
All pts received 1st line chemotherapy for MBC
Establishment and validation of circulating tumor cell-based prognostic nomograms in first-line metastatic breast cancer patients

1st line nomogram

- > 500 1st line metastatic patients – in collaboration with MDACC

 Estimates of PFS and OS in an individual patient

Mostly validated for OS / Less significant for PFS

A Giordano¹, B Egleston², D Hajage³, J Bland², G Hortobagyi⁴, J Reuben¹, JY Pierga⁵, MCristofanilli⁶, FC Bidard Clin Cancer Res 2013

http://cancernomograms.com/CTCOnline.html
Tumor markers

CA15-3, CEA, or CA-27.29, if elevated at time of treatment initiation, can be helpful for therapy monitoring.

However, they should not be used solely for decision making with respect to change of therapy.

In particular, an early rise in the tumor marker level within the first 4-6 weeks of starting new therapy may occur as a result of a tumor flare, and should not prompt a change in therapy unless there is other supportive evidence of progressive disease.

Circulating tumor cells (CTCs)

Detection and dynamics of CTCs after start of treatment for MBC have shown prognostic relevance and are associated with progression-free survival.

However, its proper role in the clinical management of patients with MBC has yet to be fully defined.
M1 patients – Validity: Ongoing European meta-analysis

1944 individual data from 20 studies, from 17 centers, from 7 European countries

PFS & OS
Baseline
Changes
New thresholds
Comparison with markers
Nomograms
Value in patient with no evaluable disease

➔ next 2013’ congresses (ESMO & SABCS)       FC Bidard et al
Results – CTC at baseline

Prognostic value – univariate analysis

Progression-Free Survival
N= 1,899 patients
HR = 1.92
p<0.0001

Overall Survival
N= 1,944 patients
HR = 2.77
p<0.0001
Acknowledgments

Paris
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K Pantel

Homburg
E Solomayer

Ulm
W Janni

Antwerp
D Peeters
SJ van Laere
A Rutten
L Dirix

Brussels
M Ignatiadis

Cambridge
C Caldas
SJ Dawson

London
J Stebbing
J Krell

Milan
F Nole
MT Sandri
E Munzone
L Zorzino

Brescia
S Grisanti
C Almici
F Consoli

Cremona
D Generali
A Bottini

Roma
P Gazzaniga
C Raimondi

Padova
R Zamarchi

Heraklion
D Mavroudis
E Politaki
S Agelaki

Valencia
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R Vidal-Martinez
V Caranana

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JA Garcia-Saenz
E Diaz-Rubio

Madrid (H12O)
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Barcelona
L de Mattos-Arruda

Pamplona
A Fernandez de Lascoiti

Nuovo-Soldati Fundation for cancer research

IDDI
H Johannes

Unconditional funding to IDDI
K Baeten
Clinically Maturing CTC Technology

Clinical Utility: Characterization
- DETECT 3

Clinical Validation: Characterization
- Endocrine Therapy Index

Clinical Utility: Enumeration
- SWOG S0500
- BioMarker Qualification
- CirCe01
- STIC

Clinical Validation: Enumeration
- FDA Clearance Breast, prostate, colorectal

R. Mc Cormack ACTC Athens 2012
**STIC CTC METABREAST**

**Inclusion**
- N=994
- M+ HR+ HER2- patients before any treatment
- Patients who can be treated either by chemoT or hormone T.
- PS 0-2

**Randomization**
- Stratified on center, PS and metastasis-free interval

**Standard arm**
- N=497

**CTC-arm**
- N=497

**BASELINE CTC COUNT BLINDED**

**BASELINE CTC COUNT DISCLOSED**

- clinician choice
- CTC-driven decision

- Hormone therapy
- Chemotherapy
- Hormone therapy
- Chemotherapy

- Tumor evaluation until progression
- Tumor evaluation until progression

- ≥ 5CTC/7.5ml
- < 5CTC/7.5ml

- Primary medical endpoint: PFS (non-inferiority)
- Co-primary economical endpoint: cost/benefit ratio
- 2nd endpoints: OS, toxicities, QoL, subgroup analyses
- The study will also address what is the optimal strategy (centralized vs local CTC lab.) from the economical viewpoint

The study will also address what is the optimal strategy (centralized vs local CTC lab.) from the economical viewpoint.

Institut Curie Paris (coordination)
Institut Curie St Cloud
Hôp. Europ. Georges Pompidou
Hôp. Tenon
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Centre G.F. Leclerc
Centre A. Vautrin
ICO Nantes
Centre C. Régaud
Centre L. Bérard
CHU de Lyon
Institut Paoli Calmette
CHU de Marseille
Centre Azureen de Cancérologie
CHU de Nice
Centre Antoine Laccassagne
### Secondary objective of STIC Metabreast

Change in treatment given by physician according to CTC level in the first 77 patients in the investigational arm CTC (Arm B):

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Treatment planned by physician in absence of information on CTC = Hormonotherapy</th>
<th>Level of CTC</th>
<th>Level of CTC</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 5 CTC</td>
<td>52</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>≥ 5 CTC</td>
<td>11</td>
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</table>

**Hormonotherapy confirmed**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Treatment planned by physician in absence of information on CTC = Chemotherapy</th>
<th>Level of CTC</th>
<th>Level of CTC</th>
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<td></td>
<td>&lt; 5 CTC</td>
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<td>15</td>
</tr>
<tr>
<td></td>
<td>≥ 5 CTC</td>
<td>10</td>
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</table>

**Chemotherapy confirmed**

In **33% of patients** randomized in investigational arm CTC (26/77 patients), CTC level determination lead to change in first line treatment choice for ER positive HER2 negative metastatic breast cancer.
Change in treatment given by physician according to CTC level (con’t)

<table>
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<tr>
<th>Level of CTC</th>
<th>Number of patients</th>
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<td>65</td>
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</tr>
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<td>TOTAL</td>
<td>52</td>
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Treatment planned by physician in absence of information on CTC = Hormonotherapy

<table>
<thead>
<tr>
<th>Level of CTC</th>
<th>Number of patients</th>
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<td>170</td>
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<tr>
<td>493</td>
<td>1</td>
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<tr>
<td>TOTAL</td>
<td>25</td>
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</tbody>
</table>

15 patients treated with Hormonotherapy

11 patients treated with Chemotherapy
MONITORING INFORMATIONS
LANDSCAPE: a Unicancer phase II study with lapatinib and capecitabine in patients with brain metastases from HER2-positive metastatic breast cancer before whole brain radiotherapy

CTC/7.5ml at baseline and changes under treatment
Correlation with CNS-OR, (n=40)

<table>
<thead>
<tr>
<th>Date of sampling</th>
<th>CTC Status</th>
<th>CNS-OR (%)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Baseline (n=41)</td>
<td>0 at baseline</td>
<td>(81)</td>
<td>NS</td>
</tr>
<tr>
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<td>≥ 1 at baseline</td>
<td>(57.9)</td>
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</tr>
<tr>
<td>Day 21 (n=38)</td>
<td>0 at day 21</td>
<td>(80.6)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>≥ 1 at day 21</td>
<td>(33.3)</td>
<td></td>
</tr>
</tbody>
</table>

Pierga 2013 Ann Oncol
Results – *Early CTC changes during treatment*

*Baseline & week 3-5*  

*European Meta-Analysis*

Similar OS curves were obtained with later CTC changes (6-8 weeks)  

Bidard FC et al

**Overall Survival**

N= 672 patients; p<0.0001

<table>
<thead>
<tr>
<th>Stable neg: &lt;5 - &lt;5</th>
<th>327</th>
<th>104</th>
<th>41 [37-53]</th>
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<tbody>
<tr>
<td>Decrease: ≥5 - &lt;5</td>
<td>149</td>
<td>70</td>
<td>27 [22-31]</td>
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<tr>
<td>Increase: &lt;5 - ≥5</td>
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<td>22 [12-NE]</td>
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<tr>
<td>Stable pos: ≥5 - ≥5</td>
<td>179</td>
<td>116</td>
<td>13 [9-16]</td>
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Landmark Analysis at 5 Weeks: Kaplan-Meier Curve of OS by Early Change in CTC

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<th>Months</th>
<th>OS</th>
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<td>30</td>
<td>0.2</td>
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<td>36</td>
<td>0.1</td>
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Number at risk:

- Stable neg: <5 - <5: 327
- Decrease: ≥5 - <5: 149
- Increase: <5 - ≥5: 17
- Stable pos: ≥5 - ≥5: 179
M1 patients – Validity: Comparison vs serum

QUESTION
Are elevated markers of prognostic impact for PFS in univariate analysis?

Bidard FC, Hajage D, Bachelot T, Delaloge S, Brain E, Campone M, Cottu P, Beuzeboc P, Rolland E, Mathiot C, Pierga JY
Breast Cancer Res 2012
M1 Patients – Utility: SWOG 0500

Screening
• M+ patient starting a 1st line of chemotherapy (L1)
• PS 0-3

Inclusion
• ≥5 CTC / 7.5ML AT BASELINE BEFORE L1

CTC Response
<5 CTC/7.5 ML

C2
C3

Randomization
• Stratified on HER2 status & measurable/bone only disease

Standard arm
N=60

C1
C2
C3

CTC-arm
N=60

L1

No CTC response
≥5 CTC/7.5 ML

L2

C1
C2

C3

SWOG 0500

Tumor evaluation every 3 months until progression

• To avoid early treatment discontinuation in the standard arm, patients and clinicians are blinded to the second CTC test
• Randomization stratified on HER2 status & measurable/bone only disease
• Primary endpoint: OS (superiority; hypotheses HR=0.59, P=81%)
• 2nd endpoints: PFS, toxicities, ...
• After clinical progression, pts may continue to subsequent lines of therapy as clinically appropriate.

Inclusion

- ≥5 CTC / 7.5ML AT BASELINE BEFORE L3

Randomization

- Stratified on center, PS and time from L1

Screening

- M+ patient starting a 3rd line of chemotherapy (L3)
- PS 0-4

Standard arm

N=152

CTC-arm

N=152

L3

C1 C2 C3

L4

C1 C2 C3

L5

C1

Primary endpoint: OS (superiority)

2nd endpoints: PFS, medico-economic study, toxicities, QoL, anxiety...

Threshold for « insufficient » CTC decrease has been obtained in a non-randomized preliminary part of the trial

CirCe01 – CTC arm
Inclusion #1101063

L3 : Vinorelbine
C1: 38 CTC
C2: 10 CTC
28/03/12

L4 : Gemcitabine
C1: 8 CTC
C2: 40 CTC
24/07/12
CTC-driven change after 1 cycle

L5 : Paclitaxel
C1: 40 CTC
C2: 2 CTC
07/03/13
7 months

L6 : Eribuline
C1: 33 CTC
C2: 0 CTC
>7 months
Ongoing
Detection of therapeutic target molecules on CTC
Example: HER2 in breast cancer

Potential benefit from anti-HER2 therapy (e.g., trastuzumab) also in patients with "HER2-negative" tumors (Paik et al., NEJM 2008)

<table>
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<tr>
<th></th>
<th>B</th>
<th>Composite</th>
<th>CK</th>
<th>DAPI</th>
<th>CD45</th>
<th>HER2</th>
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</table>

CTC with HER2 gene amplification

- HER2-pos. CTC in pats w HER2-neg. primary tumors
- HER2-neg. & HER2-pos. CTC after trastuzumab

Riethdorf/Pantel et al., Clinical Cancer Res 2010; Fehm/Pantel et al., Breast Cancer Res Treat 2010
Ignatidis/Sotiriou et al, PlosONE, 2011
Quantitative image analysis for HER2 staining with Cellsearch

Heterogeneity of HER2 expression

In metastatic breast cancer patients
N=117
Discordant results
→ 29% of patients with Her-2 positive primary tumor & ≥5 CTC count
→ 9% of patients with Her-2 negative primary tumor & ≥5 CTC count

M1 patients – Utility: DETECT III

DETECT III

Screening N=1426
- M+ HER2- patients before 1st-3rd line
- Planned treatment that have been tested in association with lapatinib: aromatase inhibitors, taxanes, capecitabine, vinorelbine, non pegylated liposomal doxorubicin

Inclusion N=228
- ≥1 CTC WITH HER2+ IMMUNOCYTOFLUORESCENCE

Randomization
- Stratified on hormone receptor status, lines of chemotherapy, type of palliative treatment, number of metastases, presence of bone metastases

Standard arm N=114 → Planned treatment
CTC-arm N=114 → Planned treatment + lapatinib

Primary endpoint: PFS (superiority)
2nd endpoints: OS, overall response rate, clinical benefit rate, QoL, CTC dynamics, safety & tolerability of lapatinib compliance to the study protocol, assessment of pain intensity
Patients with bone metastasis will also receive denosumab in both arms

T-DM1 is a novel ADC

Target expression: HER2
Monoclonal antibody: Trastuzumab

Cytotoxic agent: DM1
Highly potent cytotoxic agent

Linker: MCC
Systemically stable

Average drug: antibody ratio $\cong 3.5:1$
M1 patients – Utility: CircCe T-DM1

Bidard FC, Pierga JY, Soria JC, Thiery JP. Nat Rev Clin Oncol 2013
Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

52 Women with metastatic breast cancer

- Tumor tissue
  - Identification of somatic genomic alterations
    - Targeted sequencing of PIK3CA or TP53 mutations in all 52 women
      - 25 Had mutations
    - Whole-genome sequencing to identify mutations, SVs, or both in 9 of 52 women
      - 9 Had mutations or SVs
      - 30 Had mutations or SVs
        - 22 Had mutations only
        - 3 Had both mutations and SVs
        - 5 Had SVs only

- Serial computed tomography

- Serial blood samples collected
  - Serial blood samples analyzed
    - 141 Samples from 30 women underwent quantification of circulating tumor DNA
    - 126 Samples from 30 women underwent enumeration of circulating tumor cells
    - 114 Samples from 27 women underwent quantification of CA 15-3
      - 126 Samples underwent comparison of circulating tumor DNA vs. circulating tumor cells
      - 114 Samples underwent comparison of circulating tumor DNA vs. CA 15-3

Breast cancer disease includes a large number of RARE genomic segments. Treatment should include specific agent for each segment.

Stephens PJ et al. Nature. 2012 May 16;486(7403):400-4
Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA

Murtaza Nature 2013
CTC or cfDNA could be a Liquid Biopsy

But is solid biopsy already a reference for treatment?
SAFIR01: Study Flow in Metastatic breast cancer

Tumor Biopsy

molecular profiling

N=404

Identification of the molecular alteration

Targeted therapy according to the molecular profile

F André ASCO 2013
Predictive parameters of failure to provide genomic analysis

<table>
<thead>
<tr>
<th>p value</th>
<th>success</th>
<th>failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>p = 0.7884</td>
<td></td>
</tr>
<tr>
<td>Accrual</td>
<td>p = 0.0590</td>
<td></td>
</tr>
<tr>
<td>Nb patient included in the center</td>
<td>p = 0.3053</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>131</td>
<td>43 (24%)</td>
</tr>
<tr>
<td>lymph node</td>
<td>57</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Skin</td>
<td>47</td>
<td>19 (29%)</td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>16 (61%)</td>
</tr>
<tr>
<td>breast</td>
<td>17</td>
<td>9 (34%)</td>
</tr>
<tr>
<td>bone</td>
<td>3</td>
<td>11 (78%)</td>
</tr>
<tr>
<td>other</td>
<td>22</td>
<td>10 (31%)</td>
</tr>
</tbody>
</table>

No evidence for learning curve or center-effect
Liver and lymph nodes biopsies associated with a higher rate of success to provide genomic test

F André ASCO 2013
Ongoing personalized medicine program in France based on biopsy of metastasis

**Sponsor**
- Unicancer
- Gustave Roussy
- L Berard Lyon Curie Institute

**Pilot study**
- preSAFIR
  - (Arnedos, EJC, 2012)

**1st generation trials**
- SAFIR01
  - No NGS
- MOSCATO
  - (Hollebecque, ASCO 2013)
- WINTHER
- MOST
- SHIVA

**Randomized trials**
- SAFIR02
  - breast
- SAFIR02
  - lung

**Unified Database:**
- Pick-up the winner targets

**2nd generation Algorithm for Personalized medicine**

Overall: >2 000 planned patients (all tumor types), >800 already included
Breast Cancer: > 1 000 planned, >70 already treated
Goal: To generate optimal algorithm for individualized therapy
Conclusions

Enumeration of CTC in metastatic breast cancer
Prognostic marker
Monitoring tumor response
Level of evidence I Clinical Utility better than serum marker

Not only enumeration is needed
Liquid biopsy +++
Adjust strategy during treatment

CTC development paved the way for ctDNA:
Clinical Validity and Clinical Utility evaluation should follow the same process
TUMOR-BIOMARKER DIAGNOSTICS

Breaking a Vicious Cycle

Daniel F. Hayes et al, ScienceTranslationalMedicine 2013, 5, 196
Circulating Biomarkers Lab

Medical Oncology
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Dr V Diéras
& others
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C Simondi
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S Pelissier
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