European Journal of Cancer 63 (2016) 97–104

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Liquid biopsy-based clinical research in early breast cancer: The EORTC 90091-10093 Treat CTC trial

Michail Ignatiadis [a,b,*], Brigitte Rack [c], Francoise Rothé [b], Sabine Riethdorf [d], Charles Decraene [e], Hervé Bonnefoi [f], Christian Dittrich [g], Carlo Messina [h], Melanie Beauvois [i], Elisabeth Trapp [c], Theodora Goulioti [j], Konstantinos Tryfonidis [i], Klaus Pantel [d], Madeline Repollet [k], Wolfgang Janni [l], Martine Piccart [a], Christos Sotiriou [a,b], Saskia Litiere [i], Jean-Yves Pierga [e,m]

[a] *Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*
[b] *Breast Cancer Translational Research Laboratory, J. C. Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*
[c] *Department of Gynecology and Obstetrics, Ludwig-Maximilians-Universität, Munich, Germany*
[d] *Department of Tumor Biology, University Medical Center Hamburg-Eppendorf, Center of Experimental Medicine, Hamburg, Germany*
[e] *Circulating Biomarker Lab, SIRIC, Institut Curie, Paris, France*
[f] *Department of Medical Oncology, Institut Bergonié, Bordeaux, France*
[g] *Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna) and ACR-ITR VIEnna, Kaiser Franz Josef-Spital, Kundratstrasse 3, 1100 Vienna, Austria*
[h] *Medical and Scientific Affairs, F. Hoffmann-La Roche AG, Diagnostics Division, Basel, Switzerland*
[i] *European Organization for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium*
[j] *Breast International Group Headquarters, Brussels, Belgium*
[k] *Janssen Diagnostics LLC, NJ, USA*
[l] *Department of Gynecology and Obstetrics, Universitätsklinikum Ulm, Ulm, Germany*
[m] *Medical Oncology Department, Institut Curie, Université Paris Descartes, France*

Received 27 December 2015; received in revised form 3 April 2016; accepted 27 April 2016

KEYWORDS
CTC;
Adjuvant treatment;
Breast cancer

Abstract There is increasing evidence that breast cancer evolves over time under the selection pressure of systemic treatment. Today, treatment decisions in early breast cancer are based on primary tumour characteristics without considering the disease evolution. Chemoresistant micrometastatic disease is poorly characterised and thus it is not used in current clinical practice as a tool to personalise treatment approaches. The detection of chemoresistant circulating

* *Corresponding author*: Department of Medical Oncology & Breast Cancer Translational Research Laboratory, J. C. Heuson, Institut Jules Bordet, Université Libre de Bruxelles, Rue Héger-Bordet 1, 1000 Brussels, Belgium. Tel.: +32 2 541 72 81.
E-mail address: michail.ignatiadis@bordet.be (M. Ignatiadis).

http://dx.doi.org/10.1016/j.ejca.2016.04.024

tumour cells (CTCs) has been shown to be associated with worse prognosis in early breast cancer. The ongoing Treat CTC trial is the first international, liquid biopsy-based trial evaluating the concept of targeting chemoresistant minimal residual disease: detection of CTCs following adjuvant chemotherapy (adjuvant cohort) or neoadjuvant chemotherapy in patients who did not achieve pathological complete response (neoadjuvant cohort). This article presents the rational and design of this trial and the results of the pilot phase after 350 patients have been screened and provides insights that might provide information for future trials using the liquid biopsy approach as a tool towards precision medicine (NCT01548677).

1. Introduction

In breast cancer, results from metastatic and neoadjuvant studies inform about further development of a drug in the adjuvant setting. However, there is emerging evidence that results observed in metastatic and neoadjuvant studies might not always be applicable in the adjuvant setting. Pathological complete response (pCR) after neoadjuvant chemotherapy has been associated with improved event-free survival (EFS) and overall survival (OS) but pCR has not been validated as a surrogate end-point for EFS and OS [1–3]. The presence of *PIK3CA* mutations was associated with decreased pCR in several neoadjuvant trials evaluating different anti-human epidermal growth factor 2 (HER2) agents [4,5] but was not associated with differences in disease-free survival (DFS) and OS when evaluated in the adjuvant setting [6]. Moreover, lapatinib increased the rates of pCR when added to trastuzumab for women with HER2-positive breast cancer treated in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALLTO) trial [7] but failed to significantly improve DFS when added to trastuzumab in the ALTTO phase 3 trial [8]. These differences could be at least partly due to the treatment that the patients receive post-surgery. One might also hypothesise that the clonal composition and molecular profile of chemoresistant, micrometastatic disease might be different from those of primary tumour. Our inability to capture tumour heterogeneity and tumour evolution [9,10] and adapt our treatment accordingly is considered a major reason of cancer systemic treatment failure today. Thus, new therapeutic approaches might be evaluated focussing on real-time tumour evolution using a liquid biopsy [11,12] rather than focussing on the primary tumour. To test this hypothesis, one needs to evaluate the effects of a drug directly on targeting circulating tumour cells (CTCs), which can be captured easily from a simple blood draw and are accessible to serial evaluation. However, this hypothesis has not yet been validated clinically. In this context, the ongoing European Organisation for Research and Treatment of Cancer (EORTC) Treat CTC trial (clinical trials gov NCT01548677) is evaluating whether six cycles of trastuzumab decrease CTCs compared to observation (CTC detection rate at week 18) in women with HER2-negative early breast cancer who have completed (neo) adjuvant chemotherapy and surgery.

2. Prognostic value of CTCs in early breast cancer

CTCs detected after curative surgery for breast cancer are thought to be surrogates of minimal residual disease (MRD). We have demonstrated that the detection of cytokeratin 19 (CK19) messenger RNA (mRNA) in peripheral blood of breast cancer patients either before or after adjuvant chemotherapy was independently associated with shorter DFS and OS [13,14]. Recently, a prospective study of 2026 patients confirmed the independent prognostic relevance of CTC detection using the CELLSEARCH® technology both before and after the administration of adjuvant chemotherapy [15]. The association between CTC detection and poor outcome in breast cancer has also been demonstrated by smaller studies [16–18] and there are data including more than 2800 patients confirming these observations [19]. Since the majority of these women have only few cells per volume analysed, we performed an international study to evaluate the inter-reader variability for CTCs [20]. We observed that the median inter-reader agreement for CTC definition was lower for non-metastatic (91%) compared to metastatic (98%) patients suggesting that continuous training and independent image review are important when considering using CTC detection for treatment decisions in clinical trials in early breast cancer [20].

3. Pre-clinical and clinical data on trastuzumab efficacy in HER2 non-amplified breast cancer

There are several lines of evidence that trastuzumab may be effective at least in some patients with HER2 non-amplified tumours. Firstly, a subset of patients with primary tumours who were found to be HER2 negative after central review, in two large adjuvant trials, derived similar benefit from adjuvant