European Journal of Cancer 89 (2018) 27–35

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer

Andreas Schneeweiss [a,*], Stephen Chia [b], Tamas Hickish [c], Vernon Harvey [d], Alexandru Eniu [e], Maeve Waldron-Lynch [f], Jennifer Eng-Wong [g], Sarah Kirk [h], Javier Cortés [i]

[a] *National Center for Tumor Diseases, University Hospital, Heidelberg, Germany*
[b] *British Columbia Cancer Agency – Vancouver Centre, University of British Columbia, Vancouver, Canada*
[c] *Royal Bournemouth Hospital, Bournemouth University, Bournemouth, UK*
[d] *Regional Cancer and Blood Services, Auckland City Hospital, Auckland, New Zealand*
[e] *Cancer Institute "Ion Chiricuta", Cluj-Napoca, Romania*
[f] *Clinical Science, Global Product Development, Roche Products Limited, Welwyn Garden City, UK*
[g] *Product Development – Oncology, Genentech, Inc., South San Francisco, CA, USA*
[h] *PDBB – Biostatistics, Roche Products Limited, Welwyn Garden City, UK*
[i] *Ramón y Cajal University Hospital, Madrid and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Received 1 June 2017; received in revised form 11 October 2017; accepted 22 October 2017

KEYWORDS
Neoadjuvant therapy;
Pertuzumab;
Trastuzumab;
Breast cancer;
Safety;
Cardiotoxicity;

Abstract ***Background:*** We report long-term efficacy and cardiac safety outcomes in patients with HER2-positive early breast cancer treated with neoadjuvant pertuzumab plus trastuzumab with anthracycline-containing or anthracycline-free chemotherapy.
Methods: Descriptive efficacy analyses were conducted in patients randomised to group A (cycles 1–6: trastuzumab [8 mg/kg loading dose and 6 mg/kg maintenance] plus pertuzumab [840 mg loading dose and 420 mg maintenance], plus 5-fluorouracil, epirubicin and cyclophosphamide [FEC] [cycles 1–3; 500 mg/m^2 5-fluorouracil/100 mg/m^2 epirubicin/600 mg/m^2 cyclophosphamide] then docetaxel [cycles 4–6; 75 mg/m^2, escalated to 100 mg/m^2 if well tolerated]),

* *Corresponding author*: National Center for Tumor Diseases, University Hospital, Im Neuenheimer Feld 460, D-69120 Heidelberg, Germany. Fax: +49 (0)6221 56 1393.
E-mail address: andreas.schneeweiss@med.uni-heidelberg.de (A. Schneeweiss).

https://doi.org/10.1016/j.ejca.2017.10.021

Clinical efficacy;
Disease-free survival

B (cycles 1–3: FEC, cycles 4–6: trastuzumab plus pertuzumab plus docetaxel as mentioned previously) or C (cycles 1–6: trastuzumab plus pertuzumab plus docetaxel [75 mg/m^2, without dose escalation], and carboplatin [AUC 6]), five years after randomisation of the last patient. This study is registered with ClinicalTrials.gov, number NCT00976989.

Results: Three-year Kaplan–Meier survival estimates for disease-free survival (DFS) were 87% (95% confidence interval: 79–95), 88% (80–96) and 90% (82–97) in groups A–C, respectively. Progression-free survival (PFS) rates were 89% (81–96), 89% (81–96) and 87% (80–95). DFS hazard ratio for total pathological complete response (tpCR) versus no tpCR was 0.27 (0.11–0.64). During post-treatment follow-up, 2/72 (2.8%), 3/75 (4.0%) and 4/76 (5.4%) patients in groups A–C had any-grade left ventricular systolic dysfunction; eight (11.1%), 12 (16.0%) and nine (11.8%) patients experienced left ventricular ejection fraction declines ≥10% from baseline to <50%.

Conclusions: Long-term DFS and PFS were similar between groups. Patients who achieved tpCR had improved DFS. No new safety signals were identified.

1. Introduction

In human epidermal growth factor receptor 2 (HER2)–over-expressing breast cancer, combining the human anti-HER2 monoclonal antibodies pertuzumab and trastuzumab provides a more comprehensive signalling blockade than can be obtained with either antibody alone [1,2]. In the phase III CLEOPATRA trial in patients with HER2-positive metastatic breast cancer, pertuzumab plus trastuzumab and docetaxel improved overall survival (OS) and progression-free survival (PFS) compared with trastuzumab and docetaxel alone [3–5]. Subsequently, in the NeoSphere study, pertuzumab plus trastuzumab and docetaxel was shown to significantly improve the rate of pathological complete response (pCR) in the breast (bpCR) and in the breast and axilla (total pCR [tpCR]) when used in the neoadjuvant setting, compared with trastuzumab and docetaxel [6]. In these studies, efficacy gains were achieved with clinically manageable toxicity and without significant increases in cardiac toxicity [4,6].

HER2-targeted treatment with trastuzumab has been associated with cardiac dysfunction [7], particularly when combined with anthracycline-containing chemotherapy at higher doses [7,8]. The phase II TRYPHAENA study was conducted to evaluate the overall safety and cardiac toxicity of pertuzumab plus trastuzumab in combination with both anthracycline-containing and anthracycline-free regimens in neoadjuvant treatment of HER2-positive early breast cancer (EBC) [9]. In the TRYPHAENA study, neoadjuvant pertuzumab plus trastuzumab plus chemotherapy was generally well tolerated with low rates of symptomatic left ventricular systolic dysfunction (LVSD; the primary end-point), in patients with HER2-positive, operable, locally advanced or inflammatory breast cancer. All regimens were highly clinically active in terms of pCR, with tpCR rates in the breast and axilla (ypT0/is, ypN0) of 55–64% [9]. We report here the protocol-specified end-points of disease-free survival (DFS), PFS, OS and long-term cardiac safety 5 years after the last patient was randomised.

Previous studies of HER2-targeted therapies, including meta-analyses, have indicated an association between pCR after neoadjuvant treatment and long-term clinical benefits such as DFS, PFS, event-free survival and OS [10–19]. We have therefore also explored this association in TRYPHAENA. Guidelines for the use of pCR as an end-point in clinical trials to support accelerated approval of new drugs has been issued by both the U.S. Food and Drug Administration (FDA) [20] and the European Medicines Agency (EMA) [21], both of which advocate the use of tpCR as the preferred end-point. We therefore focus on associations between tpCR and DFS in the current analysis.

2. Methods

2.1. Study design and participants

TRYPHAENA (NCT00976989) was a randomised, multicentre, open-label study conducted across 44 centres in 19 countries. As previously described [9], eligible patients were women aged ≥18 years with untreated, operable, locally advanced or inflammatory breast cancer, with a primary tumour >2 cm. Patients were HER2-positive by immunohistochemistry (IHC 3+) or by fluorescence *in situ* hybridisation (mandatory for IHC 2+ tumours), with Eastern Cooperative Oncology Group performance status 0 or 1 and left ventricular ejection fraction (LVEF) ≥55% at baseline. Positive HER2 status was assessed locally and centrally confirmed. Oestrogen/progesterone receptor status was assessed locally. Patients were excluded if they had metastatic or bilateral breast cancer, any previous local or systemic breast cancer treatment, inadequate bone