European Journal of Cancer 70 (2017) 146–155

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Bevacizumab plus paclitaxel versus placebo plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer (MERiDiAN): A double-blind placebo-controlled randomised phase III trial with prospective biomarker evaluation☆

David Miles [a,*], David Cameron [b], Igor Bondarenko [c], Lyudmila Manzyuk [d], Juan Carlos Alcedo [e], Roberto Ivan Lopez [f], Seock-Ah Im [g], Jean-Luc Canon [h], Yaroslav Shparyk [i], Denise A. Yardley [j], Norikazu Masuda [k], Jungsil Ro [l], Neelima Denduluri [m], Stanislas Hubeaux [n], Cheng Quah [o], Carlos Bais [o], Joyce O'Shaughnessy [p]

[a] *Mount Vernon Cancer Centre, Rickmansworth Road, Northwood, London, HA6 2RN, UK*
[b] *University of Edinburgh and Cancer Services, NHS Lothian, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU, UK*
[c] *Oncology Department, Dnipropetrovsk Medical Academy, Multiprofile Clinical Hospital, #449102, Blizhnaya Str, Dnipropetrovsk, Ukraine*
[d] *NN Blokhin Cancer Centre, Kashirskoye Schosse 23, Moscow, 115478, Russia*
[e] *Centro Hemato Oncológico Panama, Marbella Edificio Royal Center, 5to. Piso Torre B, Panama City, Panama*
[f] *Medical Oncology Department, National Oncology Institute, Gorgas & Juan de Arco Street, Ancon, PO Box 0816-04433, Panama City, Panama*
[g] *Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 03080, South Korea*
[h] *Oncology and Haematology Service, Grand Hôpital de Charleroi, Grand Rue 3, 6000, Charleroi, Belgium*
[i] *Lviv State Oncological Regional Treatment and Diagnostic Center, 2a Hashek Str, Lviv, 79031, Ukraine*
[j] *Sarah Cannon Research Institute and Tennessee Oncology, PLCC, 3322 West End Avenue, Suite 900TN, Nashville, TN, 37203, USA*
[k] *Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, 2-1-14, Hoenzaka, Chuou-ku, Osaka, 540-0006, Japan*
[l] *Center for Breast Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 10408, South Korea*
[m] *Virginia Cancer Specialists Research Institute, US Oncology, 1635 N. George Mason, Suite 170, Arlington, VA, 22205, USA*
[n] *Biostatistics Oncology, Pharma Development, F. Hoffmann-La Roche, Building 670, Malzgasse 30, 4070 Basel, Switzerland*

DOI of original article: http://dx.doi.org/10.1016/j.ejca.2016.11.002.
☆ The MERiDiAN trial was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland, which also provided third-party writing assistance (Jennifer Kelly, Medi-Kelsey Limited, Ashbourne, UK).
* *Corresponding author*: Fax: +44 1923 844840.
E-mail address: david.miles@doctors.org.uk (D. Miles).

http://dx.doi.org/10.1016/j.ejca.2016.09.024

[o] Global Development BioOncology, Genentech Inc., 1 DNA Way, South San Francisco, CA, 94080, USA
[p] Baylor Charles A. Sammons Cancer Center, US Oncology and Texas Oncology, 3410 Worth Street, Suite 400, Dallas, TX, 75246, USA

Received 31 May 2016; received in revised form 26 September 2016; accepted 28 September 2016
Available online 4 November 2016

KEYWORDS
Bevacizumab;
Metastatic breast cancer;
Predictive;
Biomarker;
Double-blind;
VEGF-A;
Weekly paclitaxel;
Prospective

Abstract ***Aim:*** MERiDiAN evaluated plasma vascular endothelial growth factor-A (pVEGF-A) prospectively as a predictive biomarker for bevacizumab efficacy in metastatic breast cancer (mBC).
Methods: In this double-blind placebo-controlled randomised phase III trial, eligible patients had HER2-negative mBC previously untreated with chemotherapy. pVEGF-A was measured before randomisation to paclitaxel 90 mg/m^2 on days 1, 8 and 15 with either placebo or bevacizumab 10 mg/kg on days 1 and 15, repeated every 4 weeks until disease progression, unacceptable toxicity or consent withdrawal. Stratification factors were baseline pVEGF-A, prior adjuvant chemotherapy, hormone receptor status and geographic region. Co-primary endpoints were investigator-assessed progression-free survival (PFS) in the intent-to-treat and pVEGF-A$_{high}$ populations.
Results: Of 481 patients randomised (242 placebo–paclitaxel; 239 bevacizumab–paclitaxel), 471 received study treatment. The stratified PFS hazard ratio was 0.68 (99% confidence interval, 0.51–0.91; log-rank $p = 0.0007$) in the intent-to-treat population (median 8.8 months with placebo–paclitaxel versus 11.0 months with bevacizumab–paclitaxel) and 0.64 (96% confidence interval, 0.47–0.88; log-rank $p = 0.0038$) in the pVEGF-A$_{high}$ subgroup. The PFS treatment-by-VEGF-A interaction p value (secondary end-point) was 0.4619. Bevacizumab was associated with increased incidences of bleeding (all grades: 45% versus 27% with placebo), neutropenia (all grades: 39% versus 29%; grade ≥3: 25% versus 13%) and hypertension (all grades: 31% versus 13%; grade ≥3: 11% versus 4%).
Conclusion: The significant PFS improvement with bevacizumab is consistent with previous placebo-controlled first-line trials in mBC. Results do not support using baseline pVEGF-A to identify patients benefitting most from bevacizumab.
Clinical trials registration: ClinicalTrials.gov NCT01663727.

1. Introduction

In three randomised phase III trials, adding bevacizumab to first-line chemotherapy for HER2-negative metastatic breast cancer (mBC) significantly improved progression-free survival (PFS) and overall response rate, but not overall survival (OS) [1–3]. Regulatory approval of bevacizumab in mBC was based on the open-label randomised phase III E2100 trial, which demonstrated median PFS of 11.3 months with bevacizumab–paclitaxel versus 5.8 months with paclitaxel alone (hazard ratio [HR] 0.48) [4]. In two subsequent randomised phase III trials combining bevacizumab with alternative chemotherapies, PFS HRs were more modest [2,3]. Possible explanations for this apparent difference include synergistic anti-angiogenic activity of weekly paclitaxel and bevacizumab [5] and methodological differences between the trials. The open-label design and unblinded investigator assessment of PFS in E2100 attracted criticism, although retrospective Independent Review Facility (IRF)-assessed PFS showed similar results [4].

Numerous *post hoc* retrospective subgroup analyses according to clinical and disease characteristics suggest that no specific subgroup derives substantially greater benefit from bevacizumab [6]. Following reassessment of available bevacizumab data, a post-approval commitment was made to the European health authorities to continue attempts to identify a predictive biomarker for bevacizumab efficacy in mBC.

As angiogenesis is a highly complex process, the bevacizumab biomarker programme included a range of candidate biomarkers involved in known pathways of angiogenesis, tumorigenesis and activation of alternative pathways. Following extensive exploration of various sample types across multiple trials and tumour entities, plasma vascular endothelial growth factor (pVEGF)-A was considered the most promising candidate biomarker [7,8]. Initial analyses in lung, colorectal and renal cancers identified a prognostic but not predictive effect of pVEGF-A [9].