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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[☆]

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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.

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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].

However, retrospective analyses of phase III trials in HER2-negative mBC, gastric and pancreatic cancers using a novel immunologic multi-parameter chip technology (IMPACT) enzyme-linked immunosorbent assay suggested potential predictive and prognostic effects of pretreatment pVEGF-A in bevacizumab-treated patients [10–12]. The randomised phase III MERiDiAN trial was designed to investigate pVEGF-A prospectively as a predictive biomarker for bevacizumab effect on PFS in mBC.

2. Methods

2.1. Study design

This double-blind placebo-controlled two-arm randomised phase III trial (ClinicalTrials.gov, NCT01663727) was conducted at 132 centres in the United States of America, Ukraine, Japan, Russia, Korea, United Kingdom, Republic of Panama, Romania, Belgium, South Africa, Argentina, Bulgaria, Italy, Chile and Germany. Each participating institution's Institutional Review Board or Ethics Committee provided ethical approval.

2.2. Patients

Eligible patients had locally assessed HER2-negative locally recurrent or mBC (LR/mBC) and Eastern Cooperative Oncology Group performance status ≤2. Key exclusion criteria were: prior chemotherapy for LR/mBC; prior hormonal therapy <2 weeks before randomisation; prior (neo)adjuvant chemotherapy <12 months before randomisation; prior VEGF pathway-targeted therapy; New York Heart Association Class ≥2 congestive heart failure; left ventricular ejection fraction <55%; history of myocardial infarction, stroke or transient ischaemic attack within 6 months before randomisation; persistent grade ≥3 sensory neuropathy; baseline neutrophil count $<1.5 \times 10^9$/L; or known central nervous system disease. Patients with treated brain metastases were eligible if they had no evidence of disease progression (PD) or haemorrhage after treatment, no ongoing corticosteroid requirement and >3 months had elapsed since local therapy. Additional bevacizumab-specific exclusion criteria included: inadequately controlled hypertension; significant vascular disease; proteinuria at screening; previous hypertensive crisis or hypertensive encephalopathy; history of abdominal fistula or gastrointestinal perforation within 6 months before randomisation; or major surgical procedure within 28 d before randomisation. All patients provided written informed consent.

Before randomisation, pVEGF-A was measured in all patients using an IMPACT assay (version 7.01; Appendix Table A1). Baseline pVEGF-A level was used to classify patients as VEGF-A$_{high}$ (≥5.05 pg/mL) or VEGF-A$_{low}$ (<5.05 pg/mL). The 5.05 pg/mL cut-off represents the median pVEGF-A concentration in

retrospective biomarker analyses of AVADO (Appendix Fig. A1) [10].

Patients were randomly assigned (1:1) to receive first-line paclitaxel with either placebo or bevacizumab, stratified by: baseline pVEGF-A concentration (<5.05 versus ≥5.05 pg/mL); prior adjuvant chemotherapy (yes versus no); progesterone and oestrogen receptor status (either or both positive versus both negative); and geographic region (Asia versus North America/Europe versus other).

2.3. Procedures

Patients received intravenous paclitaxel 90 mg/m^2 on days 1, 8 and 15 with either placebo or bevacizumab 10 mg/kg intravenously on days 1 and 15, all repeated every 4 weeks until PD, unacceptable toxicity or withdrawal of consent. If one drug was discontinued for any reason except PD, the remaining agent could be continued until PD, unacceptable toxicity or withdrawal of consent. Investigators assessed tumours by physical examination and computed tomography, magnetic resonance imaging or nuclear bone scans using Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) every 8 weeks until PD, regardless of whether the patient remained on study treatment. Survival follow-up and post-progression cancer therapy data were collected every 3 months until death, loss to follow-up or study termination. Adverse events (AEs) were recorded at every cycle.

An IRF reviewed scans and patient materials at regular intervals throughout the study. PFS according to IRF assessment was a prespecified sensitivity analysis.

2.4. Outcomes

The co-primary end-points were investigator-assessed PFS in the intent-to-treat (ITT) population and investigator-assessed PFS in the pVEGF-A$_{high}$ subgroup. PFS was defined as the interval between randomisation and first recorded PD (or death, if earlier). Secondary end-points were: VEGF-A-by-treatment interaction test for PFS in the ITT population; investigator-assessed objective response rate (ORR) in patients with measurable disease at baseline (RECIST version 1.1); duration of objective response in responding patients with measurable disease at baseline; OS; 1-year OS rate; and safety (treatment-emergent AEs graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0).

2.5. Statistical analysis

It was planned to randomise approximately 480 patients. The primary PFS analysis was prespecified after PFS events had been recorded both in 326 patients in the ITT
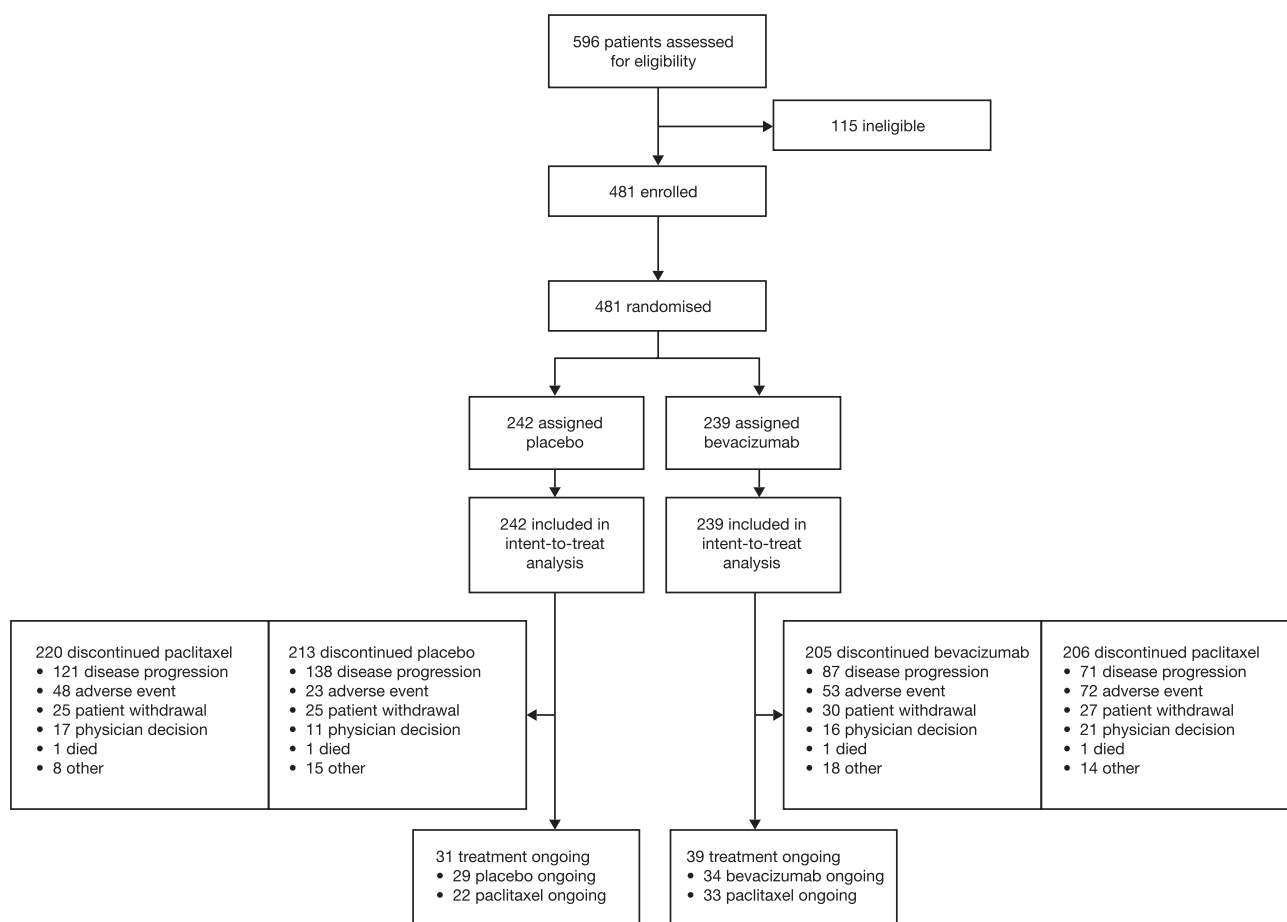
Fig. 1. Trial profile.

population, which allowed 85% power to detect a PFS HR of 0.67 (median PFS increase from 8 to 12 months) at a 1% significance level, and in 146 patients in the $pVEGF-A_{high}$ population, which allowed 85% power to detect a HR of 0.60 (median PFS increase from 6 to 10 months) at a 4% significance level. PFS was compared between treatment groups using two-sided stratified log-rank tests.

Efficacy analyses were performed on all randomised patients within the relevant populations (ITT or $pVEGF-A_{high}$). Safety was analysed in all patients who received at least one dose of study medication. SAS (version 9.2; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

The final OS analysis will occur after deaths in approximately 309 patients in the ITT population and approximately 170 patients in the $VEGF-A_{high}$ sub-group. An interim OS analysis was conducted at the time of the primary PFS analysis; however, as the pre-specified number of OS events had not occurred, a second interim OS analysis was conducted after this number was reached.

An independent Data Monitoring Committee regularly reviewed the unblinded safety data to monitor overall patient safety.

3. Results

Between 27 August 2012 and 26 December 2013, 481 patients were randomised (Fig. 1), of whom 471 received at least one dose of study treatment. Baseline characteristics were generally balanced between treatment groups (Table 1). The median baseline pVEGF-A concentration in the pooled population was 5.27 pg/mL (range, 0.5–90.5 pg/mL). Baseline characteristics according to baseline pVEGF-A level are shown in Appendix Table A2.

At the data cut-off date for the primary PFS analysis (30 November 2014), 13% of the patients in the placebo–paclitaxel group and 16% in the bev-acizumab–paclitaxel group remained on study treatment. In both treatment groups, the median duration of placebo/bevacizumab treatment was slightly longer (approximately 1 month) than that of paclitaxel and some patients continued single-agent therapy (with either placebo/bevacizumab or paclitaxel) for several months (Table 2). In both treatment groups the reasons for discontinuing paclitaxel and discontinuing placebo/bev-acizumab were generally similar, except for a slightly increased proportion discontinuing paclitaxel because of AEs and a correspondingly slightly decreased proportion

Table 1
Baseline characteristics.

Characteristic	Placebo−paclitaxel (n = 242)	Bevacizumab−paclitaxel (n = 239)
Age, years		
Median (range)	56 (28−77)	55 (28−85)
Age group, years, n (%)		
<40	21 (8.7)	17 (7.1)
≥40 to 64	175 (72.3)	165 (69.0)
≥65	46 (19.0)	57 (23.8)
Region, n (%)		
Asia	45 (18.6)	47 (19.7)
North America/Europe	111 (45.9)	108 (45.2)
Other	86 (35.5)	84 (35.1)
ECOG PS, n (%)		
0	141 (58.5)	123 (51.5)
1	100 (41.5)	116 (48.5)
Missing	1	0
Median baseline plasma VEGF-A level, pg/mL (range)	5.31 (0.5−90.5)	5.24 (0.9−66.2)
Hormone receptor status, n (%)		
ER and/or PgR positive	203 (83.9)	200 (83.7)
ER and PgR negative	39 (16.1)	39 (16.3)
Measurable disease at baseline	214 (88.4)	202 (84.5)
No. of metastatic sites, n (%)		
<3	112 (46.3)	117 (49.0)
≥3	130 (53.7)	122 (51.0)
Previous adjuvant chemotherapy, n (%)	118 (48.8)	116 (48.5)
Previous (neoadjuvant or adjuvant) taxane therapy, n (%)	76 (31.4)	81 (33.9)
Previous (neoadjuvant or adjuvant) anthracycline therapy, n (%)	125 (51.7)	115 (48.1)
Previous adjuvant hormonal therapy, n (%)	105 (43.4)	92 (38.5)
Previous hormonal therapy for LR/mBC, n (%)	42 (17.4)	38 (15.9)
Disease-free interval, months, n (%)		
0	79 (32.6)	68 (28.5)
>0 to ≤24	88 (36.4)	80 (33.5)
>24	75 (31.0)	91 (38.1)

ECOG PS = Eastern Cooperative Oncology Group performance status; ER = oestrogen receptor; LR/mBC = locally recurrent or metastatic breast cancer; PgR = progesterone receptor; VEGF-A = vascular endothelial growth factor-A.

Table 2
Treatment exposure.

Treatment exposure	Placebo−paclitaxel (n = 233)	Bevacizumab−paclitaxel (n = 238)
Median number of cycles (range)		
Paclitaxel	6 (1−28)	7 (1−28)
Bevacizumab/placebo	7.5 (1−28)	8 (1−24)
Mean number of cycles		
Paclitaxel	8.1	8.5
Bevacizumab/placebo	8.6	8.8
Median duration, months (range)		
Paclitaxel	5.2 (<0.1−25.3)	5.9 (<0.1−25.5)
Bevacizumab/placebo	6.4 (<0.1−25.3)	6.9 (<0.1−21.6)
Median cumulative dose (range), mg/kg		
Paclitaxel	2720 (3−15,770)	2907 (135−12,557)
Bevacizumab/placebo	9644 (420−55,880)	9598 (520−35,360)
Mean dose intensity, % (SD)		
Paclitaxel	92.7 (12.7)	89.0 (14.6)
Bevacizumab/placebo[a]	105.5 (17.5)	103.3 (19.2)
Paclitaxel continued for ≥1 year, n (%)	40 (17.2)	51 (21.4)
Patients continuing single-agent bevacizumab/placebo after discontinuing paclitaxel, n (%)	31 (13.3)	39 (16.4)
Mean duration of single-agent bevacizumab/placebo, months (SD)	4.3 (3.2)	4.0 (3.3)
Patients continuing single-agent paclitaxel after discontinuing bevacizumab/placebo, n (%)	11 (4.7)	24 (10.1)
Mean duration of single-agent paclitaxel, months (SD)	4.7 (5.6)	3.7 (5.3)

SD = standard deviation.

[a] Calculated as actual dose in mg divided by planned dose in mg at the time of randomisation. Although bevacizumab dose changes were not permitted according to the protocol, in a few cases, doses were recalculated according to weight changes, resulting in dose intensities exceeding 100%.

discontinuing paclitaxel because of PD in the experimental arm (Appendix Table A3).

At the primary PFS analysis, the median duration of follow-up for efficacy was 14.8 and 15.0 months in the placebo−paclitaxel and bevacizumab−paclitaxel groups, respectively.

Both co-primary objectives were met (Fig. 2). In the ITT population, the stratified PFS HR was 0.68 (99% confidence interval [CI], 0.51−0.91; log-rank $p = 0.0007$). Median PFS was 8.8 months with placebo−paclitaxel and 11.0 months with bevacizumab−paclitaxel. In the VEGF-A$_{high}$ subgroup, the stratified PFS HR was 0.64 (96% CI, 0.47−0.88; log-rank $p = 0.0038$). Median PFS

was 7.3 months with placebo−paclitaxel and 9.6 months with bevacizumab−paclitaxel.

Results of the sensitivity analysis of IRF-assessed PFS supported the investigator-assessed PFS results (stratified HR 0.68; 95% CI, 0.53−0.88). Median PFS was 9.7 (95% CI, 7.8−11.3) months in the placebo−paclitaxel group versus 12.9 (95% CI, 11.1−14.4) months in the bevacizumab−paclitaxel group (Appendix Fig. A2). An additional sensitivity analysis censoring for non-protocol therapy before PD was consistent with findings from the primary analysis (stratified HR 0.61; 95% CI, 0.48−0.78). The effect of bevacizumab on PFS was consistent across all subgroups analysed (Fig. 3).
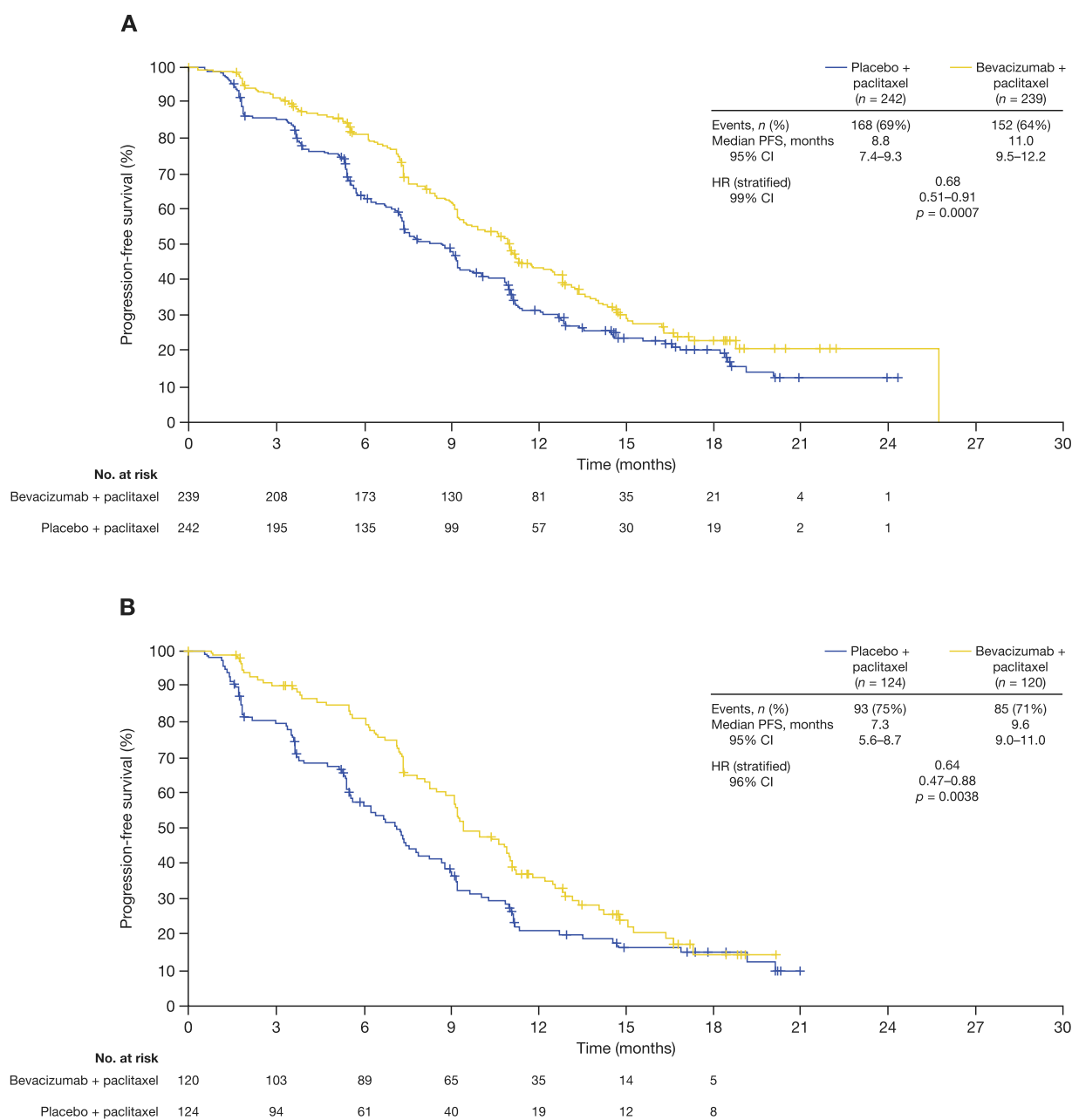

Fig. 2. Investigator-assessed progression-free survival: (A) intent-to-treat population—the 99% CI reflects 1% alpha; (B) VEGF-A$_{high}$ subgroup—the 96% CI reflects 4% alpha. HR = hazard ratio; VEGF-A = vascular endothelial growth factor-A.

Factor	Subgroup	No. of patients		Median PFS, months		Bevacizumab + paclitaxel better ← / → Placebo + paclitaxel better	Hazard ratio (95% CI)[a]
		Placebo + paclitaxel	Bevacizumab + paclitaxel	Placebo + paclitaxel	Bevacizumab + paclitaxel		
All		242	239	8.8	11.0		0.68 (0.54–0.85)
Age, years	<40	21	17	5.4	8.5		0.32 (0.13–0.83)
	≥40–64	175	165	9.2	11.0		0.71 (0.54–0.93)
	≥65	46	57	7.8	10.6		0.73 (0.44–1.21)
ECOG PS	0	141	123	9.3	10.7		0.80 (0.59–1.10)
	1	100	116	7.2	11.3		0.52 (0.37–0.73)
Hormone receptor status	Negative	39	39	6.3	8.8		0.64 (0.37–1.11)
	Positive	203	200	9.1	11.2		0.69 (0.54–0.88)
No. of metastatic sites	<3	112	117	9.3	10.6		0.87 (0.62–1.22)
	≥3	130	122	7.3	11.4		0.53 (0.39–0.73)
Prior adjuvant chemotherapy	No	124	123	9.2	11.0		0.73 (0.53–0.99)
	Yes	118	116	7.6	11.2		0.63 (0.46–0.88)
Prior taxane therapy	No	166	158	9.2	11.2		0.67 (0.51–0.89)
	Yes	76	81	7.5	9.7		0.67 (0.45–1.01)
Prior anthracycline therapy	No	117	124	10.9	11.4		0.79 (0.57–1.09)
	Yes	125	115	7.3	10.0		0.57 (0.41–0.78)
Geographic region	Asia	45	47	9.2	11.3		0.75 (0.42–1.31)
	North America/ Europe	111	108	7.4	10.6		0.62 (0.44–0.88)
	Other	86	84	9.2	11.0		0.78 (0.53–1.15)

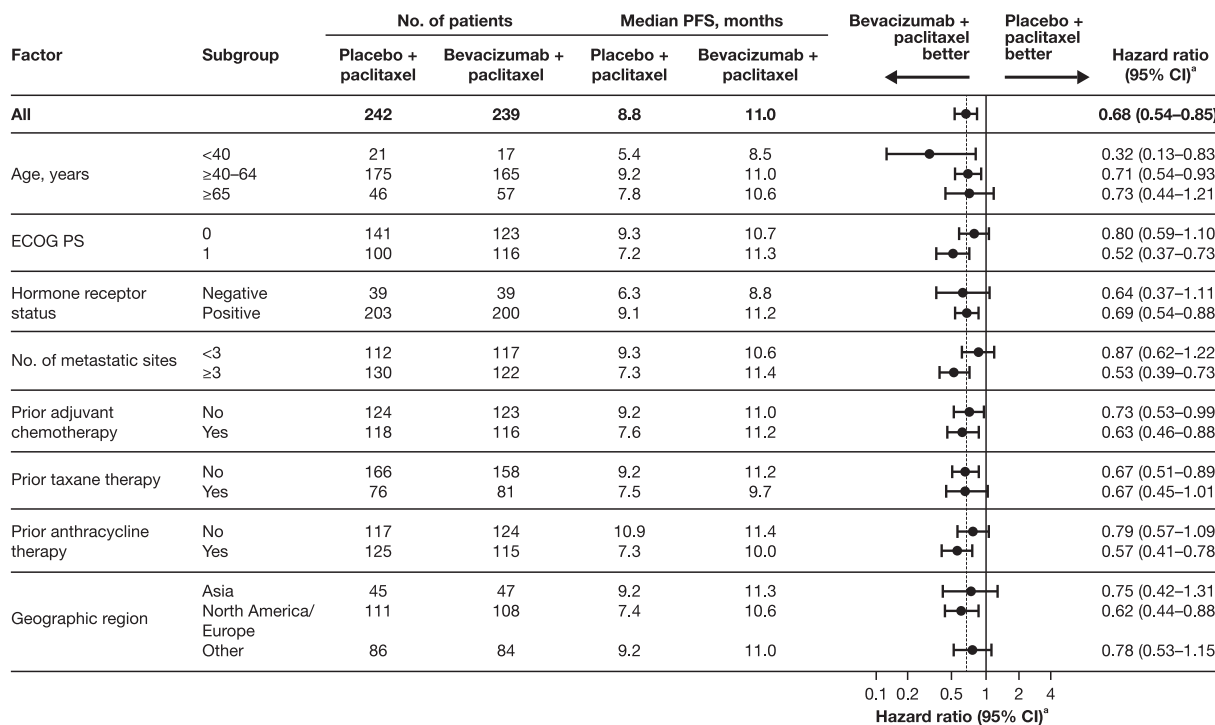Hazard ratio (95% CI)[a] — scale: 0.1 0.2 0.5 1 2 4

Fig. 3. Subgroup analysis of investigator-assessed PFS. [a]Stratified analysis, Wald confidence interval. ECOG PS = Eastern Cooperative Oncology Group performance status; PFS = progression-free survival.

The VEGF-A-by-treatment interaction test ($p = 0.4619$) for PFS in the ITT population did not support a predictive effect of pVEGF-A (Fig. 4).

The ORR was 33.2% (95% CI, 26.9%–39.5%) in the placebo–paclitaxel group versus 54.0% (95% CI, 47.1%–60.8%) in the bevacizumab–paclitaxel group ($p < 0.0001$). The median duration of response in responding patients was 9.2 (95% CI, 7.4–11.5) versus 9.5 (95% CI, 7.8–12.4) months, respectively. OS data are immature; the second interim OS analysis after deaths in 196 patients (41%) showed no significant difference between treatment arms (Fig. 5). Appendix Table A4 summarises post-progression therapy.

The most common all-grade AEs were alopecia, nausea, epistaxis and peripheral sensory neuropathy with bevacizumab–paclitaxel and alopecia and peripheral sensory neuropathy with placebo–paclitaxel (Appendix Table A5). Bevacizumab was associated with higher incidences of all-grade bleeding, neutropenia and associated complications (all grades and grade ≥3) and hypertension (all grades and grade ≥3; Table 3).

All but six deaths in each treatment group were due to PD. In the placebo–paclitaxel group, there were two deaths from dyspnoea, one from pneumonia, one sudden death, one hip fracture and one unexplained death (on day 278 after one cycle of study therapy). In the
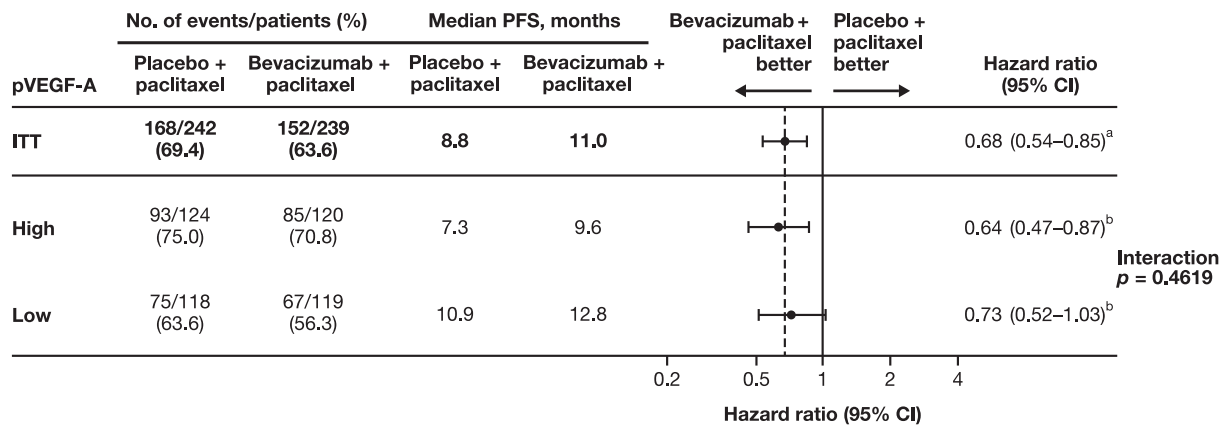
pVEGF-A	No. of events/patients (%)		Median PFS, months		Bevacizumab + paclitaxel better ← / → Placebo + paclitaxel better	Hazard ratio (95% CI)
	Placebo + paclitaxel	Bevacizumab + paclitaxel	Placebo + paclitaxel	Bevacizumab + paclitaxel		
ITT	168/242 (69.4)	152/239 (63.6)	8.8	11.0		0.68 (0.54–0.85)[a]
High	93/124 (75.0)	85/120 (70.8)	7.3	9.6		0.64 (0.47–0.87)[b]
Low	75/118 (63.6)	67/119 (56.3)	10.9	12.8		0.73 (0.52–1.03)[b]

Interaction $p = 0.4619$

Hazard ratio (95% CI) — scale: 0.2 0.5 1 2 4

Fig. 4. Investigator-assessed PFS according to baseline pVEGF-A level. [a]Stratified by prior adjuvant chemotherapy, baseline pVEGF-A and ER/PgR status. [b]Stratified by prior adjuvant chemotherapy and ER/PgR status. ER = oestrogen receptor; ITT = intent-to-treat; PFS = progression-free survival; PgR = progesterone receptor; pVEGF-A = plasma vascular endothelial growth factor-A.
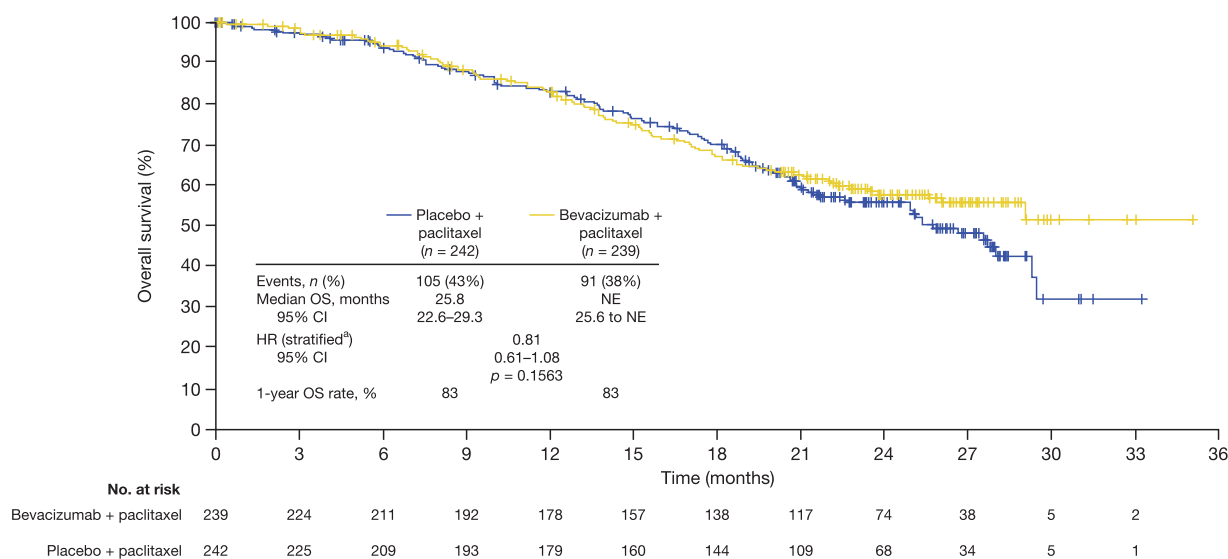
Fig. 5. Overall survival (data cut-off 31 July 2015; median OS follow-up: 20.2 months in the placebo−paclitaxel arm versus 20.7 months in the bevacizumab−paclitaxel arm). [a]Stratified by prior adjuvant chemotherapy, baseline pVEGF-A and oestrogen/progesterone receptor status. NE = not evaluable; pVEGF-A = plasma vascular endothelial growth factor-A.

Table 3
Summary of adverse events of special interest.

Adverse event, n (%)	Placebo−paclitaxel (n = 233)	Bevacizumab−paclitaxel (n = 238)
Bleeding	62 (26.6)	106 (44.5)
Grade ≥3	2 (0.9)	2 (0.8)
Neutropenia and associated complications	68 (29.2)	92 (38.7)
Grade ≥3	30 (12.9)	59 (24.8)
Febrile neutropenia	1 (0.4)	5 (2.1)
Hypertension	31 (13.3)	74 (31.1)
Grade ≥3	10 (4.3)	26 (10.9)
Proteinuria	26 (11.2)	25 (10.5)
Grade ≥3	1 (0.4)	1 (0.4)
Venous thromboembolic events	11 (4.7)	11 (4.6)
Grade ≥3	3 (1.3)	9 (3.8)[a]
Arterial thromboembolic events	5 (2.1)	4 (1.7)
Grade ≥3	0	0
Wound-healing complication	0	7 (2.9)
Grade ≥3	0	1 (0.4)
Gastrointestinal perforation	0	5 (2.1)
Grade ≥3	0	3 (1.3)[b]
Congestive heart failure	2 (0.9)	3 (1.3)
Grade ≥3	1 (0.4)	1 (0.4)

[a] Pulmonary embolism in 7 patients.
[b] Abdominal wall abscess, colonic abscess and peritonitis (each n = 1).

bevacizumab−paclitaxel group, there were two deaths from hepatic failure, one from hyperbilirubinaemia, one from sepsis and two unexplained deaths (on days 11 and 94, respectively, after one cycle of study therapy).

AEs led to discontinuation of any study treatment (paclitaxel, placebo or bevacizumab) in 23% of patients receiving placebo−paclitaxel and 32% receiving bevacizumab−paclitaxel. Placebo or bevacizumab were discontinued because of AEs in 10% of patients receiving placebo−paclitaxel and 22% receiving

bevacizumab−paclitaxel (most commonly due to hypertension [2.5%], peripheral neuropathy [1.7%] and peripheral sensory neuropathy [1.7%]). Paclitaxel was discontinued because of AEs in 22% of the patients receiving placebo−paclitaxel versus 29% receiving bevacizumab−paclitaxel, the predominant AEs being nervous system disorders including peripheral sensory neuropathy in 5% and 6%, respectively.

4. Discussion

The MERiDiAN trial met both of its co-primary objectives, demonstrating a significant improvement in PFS with the addition of bevacizumab to paclitaxel in both the ITT and the pVEGF-A$_{high}$ populations. Median PFS with bevacizumab−paclitaxel was consistent with previously reported randomised phase III trials evaluating this regimen (11.0 months in MERiDiAN, 11.4 months in E2100 [4], 11.0 months in CALGB 40502 [13] and TURANDOT [14]). The 8.8-month median PFS with weekly paclitaxel in MERiDiAN was longer than in the open-label E2100 trial and two earlier studies (median 5−6 months) [15,16] but similar to more recent randomised trials [17,18]. In MERiDiAN, the observed HR met the target HR specified in the trial design and is consistent with previous first-line placebo-controlled trials of bevacizumab in mBC [2,3]. The magnitude of bevacizumab effect on PFS (measured by HR) was less pronounced in MERiDiAN than E2100.

The median baseline pVEGF-A concentration in MERiDiAN (5.27 pg/mL in the pooled population) was similar to the 5.05 pg/mL cut-off from AVADO [10] used to stratify patients at randomisation in MERiDiAN. Therefore the VEGF-A$_{high}$ and VEGF-A$_{low}$ subgroups in MERiDiAN were of almost equal size. As in several

previous analyses [9–12], patients with high pVEGF-A levels appeared to have a worse prognosis than those with low levels, as indicated by the higher event rate and shorter median PFS in both treatment arms for the VEGF-A$_{high}$ versus VEGF-A$_{low}$ subgroups. There was no evidence of a predictive effect of baseline pVEGF-A level (PFS VEGF-A-by-treatment interaction $p = 0.4619$).

MERiDiAN is the first trial prospectively evaluating a candidate biomarker for bevacizumab efficacy, representing a major strength over previous retrospective biomarker analyses [7,9–12,19,20]. With the given sample size, the data do not support pVEGF-A as a predictive marker. This may be because of a true lack of effect or an effect that is too weak to be of clinical utility. Given the complexity and multifactorial nature of the underlying angiogenic mechanisms, it is perhaps unrealistic to expect a single biomarker to predict benefit from anti-VEGF therapy. Further analyses undertaken since the MERiDiAN trial was designed did not support a straightforward relationship between pVEGF-A and bevacizumab efficacy. The potential predictive effect of pVEGF-A suggested in AVADO, AViTA and AVA-GAST [10–12] was not replicated in retrospective analyses of nine further trials in various tumour types [19]. Furthermore, in reassessment of available samples from the AVADO trial using a different version of the assay, the potential predictive effect of pVEGF-A levels was not statistically significant [19,21]. Collectively, available data suggest a low likelihood of pVEGF-A predicting bevacizumab efficacy. Despite an extensive search for a biomarker for bevacizumab efficacy and mandatory biomarker sampling in MERiDiAN, there is no evidence suggesting that factors other than clinical reasons should influence patient selection for bevacizumab.

The secondary efficacy end-point of ORR and sensitivity analyses of PFS supported the primary end-point results. Final OS results are anticipated in 2017.

The tolerability of bevacizumab–paclitaxel in MERiDiAN was consistent with the established safety profile of bevacizumab-containing therapy for mBC [1–3]. Bevacizumab was associated with increased incidences of bleeding, neutropenia and hypertension but discontinuations for these AEs were uncommon. Furthermore, consistent with a published meta-analysis [22], incidences of arterial thromboembolic events and fatal events were not increased with bevacizumab-containing therapy. The incidence of grade ≥3 AEs classified as gastrointestinal perforation appeared slightly higher with bevacizumab-containing therapy, but this classification grouped together a broad range of AEs, including abdominal wall abscess, colonic abscess and peritonitis (each of which occurred in one patient receiving bevacizumab–paclitaxel). There were more patients with grade ≥3 venous thromboembolic events in the bevacizumab arm than in the placebo arm (nine versus three, respectively), the major contributing event being pulmonary embolism in seven bevacizumab-treated patients.

In conclusion, the significant PFS benefit from adding bevacizumab to paclitaxel is consistent with previous first-line placebo-controlled trials of bevacizumab in mBC. MERiDiAN results did not support baseline pVEGF-A as a predictive marker for bevacizumab PFS benefit. Based on these findings and previous retrospective analyses, pVEGF-A does not appear to identify patients deriving the most substantial benefit from bevacizumab. In the overall MERiDiAN population, median PFS with bevacizumab–paclitaxel replicates that in three previous randomised phase III trials evaluating this combination.

Conflict of interest statement

David Miles has received honoraria from and acted in a consulting/advisory role for Roche/Genentech. David Cameron has received research funding and travel expenses from Roche. Juan Carlos Alcedo has acted in a consulting/advisory role and is a member of the speakers' bureau for Roche and Novartis. Seock-Ah Im has acted in a consulting/advisory role for Novartis and Hanmi, has received research funding from AstraZeneca and has received travel expenses from Roche, Novartis, AstraZeneca and Asofarma. Jean-Luc Canon's institution received a grant from Roche to support clinical research staff. Denise A. Yardley is a member of the speakers' bureau for Genentech. Norikazu Masuda has received honoraria from Chugai, Eisai and AstraZeneca. Neelima Denduluri's institution has received research funding from Amgen, Genentech and Novartis. Stanislas Hubeaux is an employee of and holds shares in F. Hoffmann-La Roche. Cheng Quah is an employee of and holds shares in Roche/Genentech. Carlos Bais is a former employee of Genentech Inc./Roche and is currently an employee of Medimmune/AstraZeneca. Joyce O'Shaughnessy has acted in a consulting/advisory role for Genentech. Igor Bondarenko, Lyudmila Manzyuk, Roberto Ivan Lopez, Yaroslav Shparyk and Jungsil Ro declare that they have no conflicts of interest.

Monitoring Committee (Vicento Valero, Chair; Gunter von Minckwitz; Stephen George) and Sanne de Haas (F. Hoffmann-La Roche, Basel, Switzerland).

Appendix A. Supplementary data

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