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Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer

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Purpose: To assess the long-term impact of adding bevacizumab to adjuvant chemotherapy for early triple-negative breast cancer (TNBC).

Methods: Patients eligible for the open-label randomized phase III BEATRICE trial had centrally confirmed triple-negative operable primary invasive breast cancer (pT1a–pT3). Investigators selected anthracycline- and/or taxane-based chemotherapy for each patient. After definitive surgery, patients were randomized 1:1 to receive ≥4 cycles of chemotherapy alone or with 1 year of bevacizumab (5 mg/kg/week equivalent). Stratification factors were nodal status, selected chemotherapy, hormone receptor status, and type of surgery. The primary end point was invasive disease-free survival (IDFS; previously reported). Secondary outcome measures included overall survival (OS) and safety.

Results: After 56 months' median follow-up, 293 of 2591 randomized patients had died. There was no statistically significant difference in OS between treatment arms in either the total population (hazard ratio 0.93, 95% confidence interval [CI] 0.74–1.17; $P = 0.52$) or pre-specified subgroups. The 5-year OS rate was 88% (95% CI 86–90%) in both treatment arms. Updated IDFS results were consistent with the primary IDFS analysis. Five-year IDFS rates were 77% (95% CI 75–79%) with chemotherapy alone versus 80% (95% CI 77–82%) with bevacizumab. From 18 months after first study dose to study end, new grade ≥3 adverse events occurred in 4.6% and 4.5% of patients in the two arms, respectively.

Conclusion: Final OS results showed no significant benefit from bevacizumab therapy for early TNBC. Late-onset toxicities were rare in both groups. Five-year OS and IDFS rates suggest that the prognosis for patients with TNBC is better than previously thought.

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Key words: breast cancer, triple negative, chemotherapy, bevacizumab, survival

Key Message: Final overall survival results of the open-label randomized phase III BEATRICE trial showed no significant benefit from the addition of 1 year of bevacizumab therapy to standard adjuvant chemotherapy for triple-negative breast cancer. These results are consistent with the previously reported analyses of the primary endpoint (invasive disease-free survival).

introduction

In HER2-negative breast cancer, combining bevacizumab with chemotherapy significantly improves progression-free survival (PFS) in the metastatic setting [1–6] and the pathologic complete response (pCR) rate in the neoadjuvant setting [7–11]. However, accumulating phase III data in the adjuvant setting in both colon and breast cancers have shown no benefit from adding 1 year of bevacizumab therapy to standard chemotherapy [12–17]. Similarly, recently published data for another anti-angiogenic approach – vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibition – showed no benefit as adjuvant therapy for high-risk renal cell carcinoma [18]. Primary efficacy results from the BEATRICE trial in early triple-negative breast cancer (TNBC) showed no significant difference in invasive disease-free survival (IDFS; primary outcome measure) between adjuvant bevacizumab and non-bevacizumab regimens after first events in 393 (15%) of the 2591 randomized patients [15]. The stratified hazard ratio (HR) for IDFS was 0.87 (95% confidence interval [CI] 0.72–1.07; $P = 0.18$). Interim overall survival (OS) results at the time of the primary analysis were immature, with events in 107 patients (8%) in the chemotherapy-alone group and 93 patients (7%) in the bevacizumab-containing group. Here we report extended follow-up data from the pre-specified OS analysis of BEATRICE at 56 months' median follow-up.

patients and methods

study design

BEATRICE was an open-label international randomized phase III trial. As described previously [15], eligible patients had operable primary invasive breast cancer (T1b–

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T3 or T1a with ipsilateral axillary node involvement) centrally confirmed as HER2-negative and with hormone receptor status that was either negative (total Allred score of 0 or 2) or low (total Allred score of 3 [intensity score 1, proportion score 2]). Definitive surgery (breast conserving or mastectomy) had to be completed 4–11 weeks before randomization. Patients were aged ≥18 years with an Eastern Cooperative Oncology Group performance status of 0 or 1 and a left ventricular ejection fraction of ≥55% measured up to 3 months before randomization.

Before randomization, investigators selected chemotherapy for each patient from a pre-specified suite of standard chemotherapy regimens. After surgical resection, eligible patients were stratified by axillary nodal status (0 versus 1–3 versus ≥4 positive lymph nodes), selected chemotherapy (anthracycline versus taxane versus anthracycline and taxane), hormone receptor status (negative versus low), and type of surgery (breast conserving versus mastectomy). Patients were randomized to receive either chemotherapy followed by observation or the same chemotherapy combined with bevacizumab and followed by single-agent bevacizumab. Patients who underwent breast-conserving surgery received loco-regional adjuvant radiotherapy according to local guidelines. Bevacizumab was given at a dose equivalent to 5 mg/kg every week (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) with the selected chemotherapy. After completing chemotherapy, patients underwent clinical and laboratory assessments every 3 weeks for the first year after randomization. Thereafter, all patients had annual mammography and clinical review every 3 months for 2 years, then every 6 months for 2 years, and subsequently annual clinic visits coinciding with mammography. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) and recorded at every clinic visit. Safety reporting in the post-

treatment period (from 18 months after the first dose of study drug until end of study) was limited to newly occurring grade ≥3 adverse events, serious adverse events, and adverse events of special interest.

All patients provided written informed consent. The study was approved by the institutional review board at each participating center and was conducted according to the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations.

statistical analysis

The primary objective was to compare IDFS in patients treated with chemotherapy alone versus chemotherapy plus bevacizumab. The sample size was calculated based on assumptions relating to the primary outcome measure (IDFS), as described previously [15].

Secondary end points included OS, breast cancer-free interval, disease-free survival (DFS), distant DFS, and safety. The interim OS analysis and additional secondary end points were reported with the primary end point. The final OS analysis was planned to be performed after a median follow-up of approximately 5 years or after 340 deaths, whichever occurred first. A total of 340 deaths would provide 75% power to detect an OS HR of 0.75 with a two-sided log-rank test at 5% alpha.

Efficacy end points were tested using a two-sided stratified log-rank test. Kaplan-Meier estimates were plotted by treatment group. Treatment effects were estimated by HRs with 95% CIs based on Cox regression models. Unstratified and stratified analyses (applying the stratification factors used at randomization) were performed. Subgroups of interest were pre-specified in the statistical analysis plan and included

the stratification factors as well as other disease- and patient-related prognostic factors. SAS (version 8.2; SAS Institute Inc., Cary, NC) was used for all statistical analyses.

results

patient population

Between December 3, 2007, and March 8, 2010, 2591 patients were randomized; of these, 2559 received treatment (Supplementary Figure S1). Baseline characteristics and investigator-selected adjuvant chemotherapy regimens are summarized in Supplementary Table S1.

efficacy

At the time of data cutoff for the final OS analysis (June 30, 2014), the median duration of follow-up from randomization was 56 months in both treatment groups. All patients had discontinued or completed study therapy. Overall, 293 patients had died (86% of the 340 estimated OS events for the final analysis). Most deaths were from breast cancer recurrence (131 of 147 [89%] deaths in patients treated with chemotherapy alone, 136 of 144 [94%] deaths in bevacizumab-treated patients, and one of two deaths in patients who received no study therapy). Causes of death in the remaining patients are summarized in Supplementary Table S2.

There was no statistically significant difference in OS between the two treatment groups either in the intent-to-treat population (stratified HR = 0.93, 95% CI 0.74–1.17; log-rank $P = 0.52$; Figure 1) or in any of the pre-specified subgroups (Figure 2).

The unstratified analysis of OS showed similar results (unstratified HR = 0.94, 95% CI 0.75–1.18; log-rank $P = 0.61$).

Results of an exploratory analysis updating IDFS at the time of this final OS analysis were very consistent with those of the primary analysis (Supplementary Figure S2). The stratified HR was 0.87 (95% CI 0.73–1.03). The 5-year IDFS rates in this updated exploratory analysis were 76.9% (95% CI 74.4–79.4%) with chemotherapy alone and 79.6% (95% CI 77.2–81.9%) with bevacizumab-containing therapy.

At the time of data cutoff, bevacizumab therapy had been recorded after an IDFS event in 34 patients (2.6%) in the chemotherapy-alone arm and 13 patients (1.0%) in the bevacizumab-containing arm (12.6% versus 5.3%, respectively, of those with IDFS events).

safety

In the post-treatment safety reporting period there were relatively few grade ≥3 adverse events in either arm (4.6% and 4.5% in the chemotherapy-alone and bevacizumab-containing arms, respectively) and no relevant differences between treatment arms were observed (Table 1). The only grade ≥3 adverse events occurring in more than two patients in either treatment group were hypertension and deep vein thrombosis, which occurred in 0.3% and 0.2% of patients, respectively, in the chemotherapy-alone group but were absent in the bevacizumab-containing group. The incidences of adverse events of special interest occurring from 18 months after the first dose of study drug until the end of the study were very similar between the two treatment arms (Supplementary Table S3). Detailed cardiac safety analyses based on the final data cutoff described here will be reported separately.

discussion

The final OS analysis of the BEATRICE trial after 293 deaths showed no statistically significant benefit from adding bevacizumab to standard adjuvant chemotherapy for patients with early TNBC. Results of exploratory updated analyses of IDFS were similar to those from the primary IDFS analysis, showing no difference between the treatment arms (Supplementary Table S4). No new safety signals were identified with long-term follow-up and the safety profile was consistent with the established safety profile of bevacizumab in metastatic breast cancer [19] and the primary analysis of the BEATRICE trial [15].

Since the publication of the primary results from BEATRICE, two additional phase III trials evaluating bevacizumab as adjuvant therapy for early breast cancer have been reported: the BETH trial ($N = 3509$) in HER2-positive disease [16] and the E5103 trial ($N = 4994$) in lymph node-positive or high-risk node-negative HER2-negative disease [17]. None of these three randomized phase III trials (BEATRICE, BETH, and E5103; combined $N = 11,094$) provides evidence of efficacy of bevacizumab in the post-operative adjuvant setting. One additional trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-40, evaluated adjuvant bevacizumab but uniquely in this trial, patients received bevacizumab with neoadjuvant chemotherapy as well as post-operatively. Intriguingly, final results from the NSABP B-40 trial demonstrated a significant OS benefit with neoadjuvant and adjuvant bevacizumab versus neoadjuvant chemotherapy alone, although the improvement in DFS did not reach statistical significance [20]. The benefit from bevacizumab was more pronounced in patients with hormone receptor-positive disease, whereas in other neoadjuvant trials (GeparQuinto, ARTemis, and S0800) [8, 9, 11, 21] and the E5103 adjuvant trial [17],

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a greater effect was observed in patients with TNBC. Specifically in TNBC, the Cancer and Leukemia Group B (CALGB) 40603 (Alliance) neoadjuvant trial demonstrated a significantly improved pCR rate with 18 weeks of bevacizumab added to chemotherapy for stage II or III disease, but the effect on DFS or OS is as yet unknown [10]. Taken together, none of these results support the use of bevacizumab in the primary breast cancer setting.

The lack of effect of bevacizumab as adjuvant therapy (in contrast to improved pCR rate with bevacizumab in the neoadjuvant setting or PFS benefit in the metastatic setting) is perhaps not surprising when considering the absence of macroscopic disease in patients receiving adjuvant treatment and recent results in preclinical models mimicking adjuvant therapy [22]. A vascular supply is required for tumor growth beyond a few millimeters [23, 24] and it is unclear what proportion of the subgroup of patients ultimately destined to relapse will have had micrometastic disease of this size during bevacizumab exposure in the BEATRICE trial (1 year) [25]. Proposed mechanisms by which VEGF blockade could influence disease recurrence in the adjuvant setting include prolonging the dormancy of micrometastatic tumor cell aggregates, preventing 'awakening' of dormant micrometastases by blocking new vessel formation, and inhibiting tumor dissemination [26], but there is currently no evidence to suggest that these postulated mechanisms translate into a clinically useful effect of adjuvant bevacizumab therapy for 1 year. A longer duration of adjuvant bevacizumab administration may be hypothesized to improve efficacy [25], especially when considering the transient benefit from bevacizumab seen in the two phase III trials in colon cancer [12, 14]. On the other hand, results from the AVANT trial [12] may be used to argue against indefinite use of VEGF blockade in the adjuvant setting [26].

Recently published preclinical data suggest that the effect of VEGF inhibition on host vasculature depends not only on the class of agent (antibody versus multi-targeted tyrosine kinase inhibition) but also on co-administration with chemotherapy [27]. The researchers concluded that the benefit of an anti-angiogenic therapy can be improved by chemotherapy as well as the efficacy of chemotherapy being increased by combining with anti-angiogenic therapy (i.e. a mutual bidirectional effect). If this holds true in the clinical setting, better outcomes would be achieved by administering all of the bevacizumab in combination with a tolerable chemotherapy in the adjuvant setting, rather than as a single agent for most of the duration. This strategy has been shown to be beneficial in the metastatic setting, where the addition of capecitabine to maintenance bevacizumab in patients with response or stable disease following initial therapy with bevacizumab plus a taxane significantly improved both PFS and OS compared with bevacizumab alone in the randomized phase III IMELDA trial [28]. However, in early breast cancer this approach has been tested only in the ECOG 5103 trial, in which bevacizumab treatment duration was limited to the duration of the standard chemotherapy in one of the treatment arms. There was no evidence that this approach was more effective, but the possibility that a longer duration of concomitant chemotherapy and bevacizumab could be effective remains untested in the adjuvant setting. However, while these may all be interesting hypotheses for exploration, the feasibility, likelihood of success, and priority for conducting further trials of bevacizumab in the adjuvant breast cancer setting are extremely low when considering all available data and emerging research on new strategies, such as the use of capecitabine in patients with residual disease after neoadjuvant therapy [29] or novel agents [30].

Although results of the BEATRICE trial do not help in identifying a targeted treatment option for early TNBC, they provide valuable information that may help in the design of future trials. Firstly, they serve to remind us that treatments demonstrating efficacy in the macrometastatic setting cannot simply be extrapolated to the adjuvant setting, which is biologically very different from the neoadjuvant and metastatic settings. Secondly, results from the BEATRICE trial indicate that the prognosis for patients with early TNBC is better than previously thought. Data from retrospective series suggest that most recurrences occur within 3–5 years of TNBC diagnosis [31]. However, after a median follow-up of 56 months in BEATRICE, the 5-year IDFS rates were 77% in the chemotherapy-alone arm and 80% in the chemotherapy plus bevacizumab arm. These event rates should inform the statistical design of future studies in TNBC. In addition, ongoing gene expression analyses in the pooled dataset from BEATRICE have already yielded fascinating preliminary results in relation to immune signatures [32], which may guide future research in TNBC. Thus, although BEATRICE failed to confirm its primary hypothesis, it has provided the first randomized phase III data on systemic therapy in early TNBC, as well as interesting translational findings, all of which will inform future trial designs in this patient population.

A Wardley, D Wheatley, C Wilson (United Kingdom); D Amadori, D Amoroso, M Bari, S Barni, A Bernardo, L Bilancia, F Cappuzzo, G Cavazzini, S Cinieri, A Contu, E Cortesi, G Cruciani, A de Censi, M Faedi, F Ferrau, V Gebbia, D Grasso, A Jirillo, V Lorusso, MD Magri, E Maiello, R Mattiolim, F Montemurro, M Nicolini, P Papaldo, L Pavesi, A Ravaioli, S Salvagni, A Santoro, E Simoncini, C Tondini, A Tienghi (Italy); H Assi, N Califaretti, J Chang, R Dent, B Dingle, P Dube, D Grenier, C Hamm, K Laing, J Latreille, C Lohrisch, J Mackey, Y Madarnas, R Myers, L Panasci, G Pansegrau, L Provencher, D Rayson, A Sami, K Sridhar, S Verma, J Wilson, S Young (Canada); S-A Im, Y-H Im, S-B Kim, SY Kim, J Ro (Korea); L Ahmadullina, I Bulavina, O Gladkov, E Gotovkin, V Kallistov, V Khartchenko, R Khasanov, M Kopp, O Lipatov, A Luft, V Semiglazov, S Tjulandin (Russia); MA Ackerman, JT Beck, M Berkowitz, T Butler, R Carroll, B Daniel, J Goodman, K Hagan, J Hon, J Hopkins, CM Jones, M Karwal, A Landis, M McKenzie, M Ogaily, Y Ottaviano, R Patel, G Reznikoff, R Roble, N Shah, A Shwaiki, J Singh, B Sleckman, S Swain, C Truica, N Vrindavanam, F Volterra, J Wallmark, D Waterhouse, D Yardley (USA); Y Cheng, Z Jiang, D Liu, X Ouyang, Z Shen, Q Sun, M Tao, L Teng, Z Tong, X Wang, B Xu, J Yang, S-Y Yu, H Zheng (China); K Aogi, Y Fujiwara, Y Ito, H Iwata, K Kuroi, N Masuda, S Ohno, T Saeki, T Ueno, H Yamauchi (Japan); R Andres, A Avella, N Batista Lopez, F Carabantes, E Ciruelos, R Cubedo, E Espinosa, M Godes Sanz De Bremond, P Gomez Pardo, A Gonzalez Martin, S Gonzalez, B Hernando, P Lianes, A Marques, N Martinez, I Pelaez, I Tusquets, G Viñas (Spain); C Cheng-Shyong, H Chiun-Sheng, C Hong-Tai, T Ling-Ming, H Ming-Feng, C Shin-Cheh, C Tsai-Wang, C Tsu-Yi (Taiwan); M Fridrik, R Greil, A Lang, C Marth, L Melbinger-Zeinitzer, H Samonigg, B Schneeweiss, P Sevelda, C Singer, G Steger, J Thaler (Austria); M Blasinska-Morawiec, E Brewczynska, W Polkowski, I Ryniewicz-Zander, E

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disclosure

references

1. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666–2676.

2. Miles DW, Chan A, Dirix LY et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2010;28:3239–3247.

3. Miles D, Cameron D, Bondarenko I et al. First results from the double-blind placebo (PL)-controlled randomised phase III MERiDiAN trial prospectively evaluating plasma (p)VEGF-A in patients (pts) receiving first-line paclitaxel (PAC) ± bevacizumab (BV) for HER2-negative metastatic breast cancer (mBC). Eur J Cancer 2015; 51(Suppl S3):S287 (abstract 1866).

4. Robert NJ, Diéras V, Glaspy J et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative locally recurrent or metastatic breast cancer. J Clin Oncol 2011;29:1252–1260.

5. Brufsky AM, Hurvitz S, Perez E et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 2011;29:4286–4293.

6. von Minckwitz G, Puglisi F, Cortes J et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-

negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1269–1278.

7. Bear HD, Tang G, Rastogi P et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012;366:310–320.

8. von Minckwitz G, Eidtmann H, Rezai M et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012;366:299–309.

9. Earl HM, Hiller L, Dunn JA et al. Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. Lancet Oncol 2015;16:656–666.

10. Sikov WM, Berry DA, Perou CM et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13–21.

11. Nahleh ZA, Barlow WE, Hayes DF et al. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat 2016;158:485–495.

12. de Gramont A, Van Cutsem E, Schmoll HJ et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer

(AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012;13:1225–1233.

13.   Allegra CJ, Yothers G, O'Connell MJ et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29:11–16.

14.   Allegra CJ, Yothers G, O'Connell MJ et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. J Clin Oncol 2013;31:359–364.

15.   Cameron D, Brown J, Dent R et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol 2013;14:933–942.

16.   Slamon DJ, Swain SM, Buyse M et al. Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab ± bevacizumab in patients with HER2-positive, node-positive or high risk node-negative breast cancer. Cancer Res 2013;73(abstract S1-03).

17.   Miller K, O'Neill AM, Dang CT et al. Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: final results from Eastern Cooperative Oncology Group E5103. J Clin Oncol 2014;32(Suppl 5s):(abstract 500).

18.   Haas NB, Manola J, Uzzo RG et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016;387:2008–2016.

19. Cortes J, Calvo V, Ramírez-Merino N et al. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Ann Oncol 2012;23:1130–1137.

20. Bear HD, Tang G, Rastogi P et al. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial. Lancet Oncol 2015;16:1037–1048.

21. von Minckwitz G, Loibl S, Untch M et al; GBG/AGO-B study groups. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto). Ann Oncol 2014;25:2363–2372.

22. Kerbel RS, Guerin E, Francia G et al. Preclinical recapitulation of antiangiogenic drug clinical efficacies using models of early or late stage breast cancer metastasis. Breast 2013;22 (Suppl 2):S57–S65.

23. Spill F, Guerrero P, Alarcon T et al. Mesoscopic and continuum modelling of angiogenesis. J Math Biol 2015;70:485–532.

24. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285:1182–1186.

25. Perez-Garcia J, Cortes J. Adjuvant bevacizumab: positive data from a negative trial. Lancet Oncol 2013;14:910–911.

26. Mountzios G, Pentheroudakis G, Carmeliet P. Bevacizumab and micrometastases: revisiting the preclinical and clinical rollercoaster. Pharmacol Ther 2014;141:117–124.

27. Paez-Ribes M, Man S, Xu P, Kerbel RS. Potential proinvasive or metastatic effects of preclinical antiangiogenic therapy are prevented by concurrent chemotherapy. Clin Cancer Res 2015;21:5488–5498.

28. Gligorov J, Doval D, Bines J et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:1351–1360.

29. Toi M, Lee S-J, Lee ES et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04). Cancer Res 2016;76(4 Suppl):(abstract S1-07).

30. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 2016;13(11):674–690.

31. Dent R, Trudeau M, Pritchard KI et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–4434.

32. Molinero L, Yu J, Li C et al. Analysis of molecular prognostic factors associated with tumor immune and stromal microenvironment in BEATRICE, an open-label phase 3 trial in early triple-negative breast cancer (eTNBC). Cancer Res 2016;76(4 Suppl):(abstract S1-01).

figure legends

Figure 1. Final OS (intent-to-treat population). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival.

Figure 2. Subgroup analyses of final overall survival. BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HR, hazard ratio; PgR, progesterone receptor.

Supplementary figure legends

Supplementary Figure S1. CONSORT flow diagram.

*Violation of at least one inclusion or exclusion criterion.

Supplementary Figure S2. Updated IDFS results (intent-to-treat population, exploratory analysis after a median follow-up of 56 months). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; IDFS, invasive disease-free survival.