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Final results of the TANIA randomised phase III trial of bevacizumab after progression on first-line bevacizumab therapy for HER2-negative locally recurrent/metastatic breast cancer

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Background: The randomised phase III TANIA trial demonstrated that continuing bevacizumab with second-line chemotherapy for locally recurrent/metastatic breast cancer (LR/mBC) after progression on first-line bevacizumab-containing therapy significantly improved progression-free survival (PFS) compared with chemotherapy alone (hazard ratio [HR] = 0.75, 95% confidence interval [CI] 0.61–0.93). We report final results from the TANIA trial, including overall survival (OS) and health-related quality of life (HRQoL).

Patients and methods: Patients with HER2-negative LR/mBC that had progressed on or after first-line bevacizumab plus chemotherapy were randomised to receive standard second-line chemotherapy either alone or with bevacizumab. At second progression, patients initially randomised to bevacizumab continued bevacizumab with their third-line chemotherapy but those randomised to chemotherapy alone were not allowed to cross over to receive third-line bevacizumab. The primary end point was second-line PFS; secondary end points included third-line PFS, combined second- and third-line PFS, OS, HRQoL and safety.

Results: Of the 494 patients randomised, 483 received second-line therapy; 234 patients (47% of the randomised population) continued to third-line study treatment. The median duration of follow-up at the final analysis was 32.1 months in the chemotherapy-alone arm and 30.9 months in the bevacizumab plus chemotherapy arm. There was no statistically significant difference between treatment arms in third-line PFS (HR = 0.79, 95% CI 0.59–1.06), combined second- and third-line PFS (HR = 0.85, 95% CI 0.68–1.05) or OS (HR = 0.96, 95% CI 0.76–1.21). Third-line safety results showed increased incidences of proteinuria and hypertension with bevacizumab, consistent with safety results for the second-line treatment phase. No differences in HRQoL were detected.

Conclusion: In this trial, continuing bevacizumab beyond first and second progression of LR/mBC improved second-line PFS but no improvement in longer-term efficacy was observed. The second-line PFS benefit appears to be achieved without detrimentally affecting quality of life.

ClinicalTrials.gov: NCT01250379.

Key words: metastatic breast cancer, bevacizumab, anti-angiogenesis, re-treatment, quality of life

Key Message: Final results from the randomised phase III TANIA trial in bevacizumab-pretreated metastatic breast cancer showed that although adding bevacizumab to second- and third-line chemotherapy significantly improved second-line progression-free survival (PFS) versus chemotherapy alone, third-line PFS and overall survival (secondary end points) were not significantly improved with continued bevacizumab.

introduction

Several randomised phase III trials have demonstrated that combining bevacizumab with chemotherapy improves progression-free survival (PFS) in patients with locally recurrent/metastatic breast cancer (LR/mBC) treated in either the first-line or the second-line setting [1–5]. The open-label randomised phase III TANIA trial (NCT01250379) evaluated second-line bevacizumab-containing therapy in patients with bevacizumab-pretreated LR/mBC [6]. As described previously [6], the biological and preclinical rationale for sustained inhibition of vascular endothelial growth factor (VEGF) is based on the crucial role of VEGF throughout the angiogenic pathway. Furthermore, two randomised trials in colorectal cancer indicated significant improvements in efficacy with bevacizumab re-exposure after progression on previous bevacizumab-containing therapy [7, 8]. The primary end point (second-line PFS) of the TANIA trial was reported together with second-line safety results at the time of the primary PFS analysis (data cut-off 20 December 2013) [6]. The primary objective was met: second-line PFS was statistically significantly improved in patients receiving further bevacizumab (hazard ratio [HR] = 0.75, 95% confidence interval [CI] 0.61–0.93; $P = 0.0068$; median: 6.3 months [95% CI 5.4–7.2] with bevacizumab versus 4.2 months [95% CI 3.9–4.7] with chemotherapy alone). Efficacy and safety results relating to the third-line treatment period and overall survival (OS) were not mature at the time of primary end point disclosure. Here we report third-line PFS, third-line safety and OS results at the final analysis, as well as health-related quality of life (HRQoL).

patients and methods

study design

The trial design has previously been described in detail [6]. Briefly, patients with HER2-negative LR/mBC whose disease had progressed on or after first-line bevacizumab combined with chemotherapy were randomised to receive standard second-line

chemotherapy either alone or in combination with bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the selected chemotherapy schedule. The stratification factors were hormone receptor status (triple negative versus oestrogen and/or progesterone receptor positive), first-line PFS (<6 versus ≥6 months), choice of chemotherapy (taxane versus non-taxane versus vinorelbine) and lactate dehydrogenase concentration at baseline (≤ 1.5 versus $> 1.5 \times$ upper limit of normal). At second tumour progression according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, patients initially randomised to chemotherapy alone received third-line chemotherapy without bevacizumab (crossover not permitted), whereas patients initially randomised to bevacizumab plus chemotherapy received third-line chemotherapy with continued bevacizumab.

end points and statistics

The primary end point was investigator-assessed second-line PFS (published previously). Secondary end points included third-line PFS, combined second- and third-line PFS (from randomisation until third progression/death), OS (from randomisation until death from any cause), HRQoL and safety. PFS and OS were compared between treatment groups with a two-sided log-rank test, stratified by the four stratification factors mentioned above. Median values in each treatment arm were estimated using the Kaplan-Meier method. A stratified Cox proportional hazards model was used to estimate the HR with 95% CIs.

Tumours were assessed by investigators (based on limited RECIST version 1.1) every 8 or 9 weeks, coinciding with patients' treatment visits according to the chosen chemotherapy (every-3-week or every-4-week schedule) to minimise inconvenience to patients. There was no independent review of PFS. HRQoL was assessed using the Functional Assessment of Cancer Therapy – Breast (FACT-B) administered at baseline, every 8/9 weeks (depending on treatment schedule) during second-line therapy, and at the time of second progression. HRQoL analyses included differences between treatment arms

in mean change from baseline for each FACT-B subscale; when designing the HRQoL analyses, physical and functional wellbeing subscales were considered prospectively to be the most relevant subscales in this setting [9]. Subscale scores were calculated only if at least 50% of items in the subscale were not missing. FACT-B Trial Outcome Index (TOI), FACT-General and FACT-B total scores were calculated only if at least 80% of the corresponding items were not missing. Missing questionnaires were imputed at every timepoint before or at the 'end of QoL reporting period' date to which no questionnaires were assigned. In exploratory responder analyses based on methods and cut-offs described in the literature [10, 11], patients were categorised as having 'improved' (≥ 3 -point improvement), 'worsened' (≥ 3 -point deterioration) or 'stable' (change of < 3 points) HRQoL and the proportions of patients in each category at each timepoint were calculated.

Third-line efficacy analyses were based on the third-line efficacy population, comprising all patients who received at least one dose of third-line study therapy. Third-line safety was analysed according to the treatment actually received in the third-line treatment phase (bevacizumab versus no bevacizumab) rather than by the treatment to which each patient was randomised for second-line treatment. Analyses of combined second- and third-line PFS and OS were based on the intent-to-treat population.

The final analysis was performed as planned, when all patients had been followed for at least 24 months since randomisation (or died, withdrawn consent or been lost to follow-up).

results

patient population and follow-up

Of the 494 patients randomised to second-line therapy, 234 (47%) received at least one dose of third-line therapy (Figure 1 and Appendix Table S1, online only). At the time of data cut-off for the final analysis (30 April 2015), the median duration of follow-up was

32.1 months (interquartile range [IQR] 25.1–36.9 months) in the chemotherapy-alone arm and 30.9 months (IQR 26.4–37.1 months) in the bevacizumab-containing arm.

treatment exposure

All patients had stopped all study treatment by the time of data cut-off for this analysis.

The median duration of chemotherapy in the second-line safety population was 3.9 months (range <0.1–36.3 months) in the chemotherapy-alone arm and 4.4 months (range <0.1–33.2 months) in the bevacizumab-containing arm. Median second-line bevacizumab exposure in the combination arm was 4.5 months (range <0.1–33.1 months).

In the third-line setting, the chemotherapy regimens most commonly selected by the investigators were vinorelbine (33% of the chemotherapy-alone arm versus 31% of the bevacizumab-containing arm), capecitabine (10% versus 15%, respectively) and non-pegylated liposomal doxorubicin (16% versus 13%, respectively). The median duration of third-line chemotherapy was shorter than second-line chemotherapy in both treatment arms: 2.1 months (range <0.1–20.0 months) in the chemotherapy-alone arm and 2.6 months (range 0.2–14.3 months) in the bevacizumab-containing arm. The median duration of third-line bevacizumab was 2.1 months (range <0.1–22.1 months).

The extent and type of post-study therapy administered were quite similar in the two treatment arms. In the chemotherapy-alone arm, 68% of patients in the third-line population had received further chemotherapy after tumour progression, most commonly eribulin (31%), cyclophosphamide (17%), vinorelbine (15%), gemcitabine (13%) or doxorubicin (12%). In the bevacizumab-containing arm, 61% of patients in the third-line population had received further chemotherapy after progression, most commonly eribulin (30%), doxorubicin (16%), vinorelbine, cyclophosphamide or gemcitabine (each 12%). Endocrine therapy was administered after third-line progression in 26% of the chemotherapy-alone arm versus 29% of the bevacizumab-containing arm. Everolimus was administered in 10% versus 3%, respectively.

efficacy

There was no statistically significant difference in third-line PFS between the two treatment arms (Figure 2A). No differences between treatment arms were observed for either combined second- and third-line PFS (Figure 2B) or OS (Figure 2C).

The Kaplan-Meier curve for third-line PFS showed that in both treatment arms, almost half the patients entering third-line therapy experienced a PFS event within the first 3 months of therapy. The subgroup of patients with early progression on third-line therapy included higher proportions of patients with triple-negative disease, first-line PFS of <6 months and no prior endocrine therapy than the overall population randomised to second-line therapy. However, this comparison was based on patient and disease characteristics before randomisation to second-line therapy rather than immediately before third-line therapy.

Results of subgroup analyses of third-line PFS, combined second- and third-line PFS, and OS (which were not adjusted for multiple testing) were generally consistent with those in the overall population (Appendix Figure S1, online only). An exploratory analysis of second-line PFS (at the time of final data cut-off rather than the prespecified primary analysis cut-off) indicated that the PFS benefit from bevacizumab observed at the primary PFS analysis was sustained with longer follow-up (HR = 0.79; 95% CI 0.65–0.97; $P = 0.0204$). Median second-line PFS was 6.3 months (95% CI 5.5–7.6 months) with bevacizumab-containing therapy versus 4.2 months (95% CI 3.9–5.3 months) with chemotherapy alone.

safety

Seventeen patients initially randomised to and treated with bevacizumab in the second-line setting received no bevacizumab with their third-line chemotherapy (predominantly because of adverse events preventing continuation of bevacizumab [persistent proteinuria or

hypertension, grade 2/3 venous embolism, osteonecrosis of the jaw]), and were therefore included in the chemotherapy-alone arm for safety analyses.

Third-line safety results were consistent with observations in the second-line safety population reported at the time of the primary analysis [6]. Adverse events (all grades) were more common with bevacizumab-containing therapy than chemotherapy alone (81% versus 63%, respectively), driven mainly by higher incidences of proteinuria (23% versus 13%, respectively) and hypertension (20% versus 4%) (Appendix Table S2, online only). Grade ≥ 3 adverse events were reported in 62% versus 43%, respectively, including grade ≥ 3 hypertension in 10% versus 2%, respectively. During third-line therapy there were three fatal adverse events: two in the chemotherapy-alone arm (cardiac failure in one patient, ischaemic cardiomyopathy in the other; both treated with second-line capecitabine and third-line doxorubicin) and one in the bevacizumab-containing arm (multi-organ failure in a patient treated with second-line capecitabine and third-line vinorelbine). In the third-line safety follow-up period, there were two further fatal adverse events (mitral valve incompetence; congestive heart failure), both in the chemotherapy-alone arm.

HRQoL

Compliance with questionnaire completion was similar in the two treatment arms and was 68%–75% between weeks 8/9 and 24/27 (Appendix Figure S2, online only). Mixed-model repeated-measures analyses of change from baseline at week 8/9 and overall showed no meaningful differences between treatment arms for any of the subscales (Appendix Table S3, online only).

For functional wellbeing, the change from baseline across all timepoints was almost identical in the two treatment arms (Figure 3A). For physical wellbeing, 95% CIs were overlapping at almost all timepoints and numerical differences were not clinically meaningful (Figure 3B).

Exploratory responder analyses of the Breast Cancer subscale, FACT-B composite TOI total score, FACT-General TOI total score and FACT-B total score showed no difference between the treatment arms (data not shown). Exploratory analysis of the best response for physical wellbeing over time also showed no difference between treatment arms (Appendix Table S4, online only).

discussion

Although patients treated with bevacizumab after progression on first-line bevacizumab-containing therapy benefited in terms of second-line PFS compared with patients treated with chemotherapy alone [6], no significant improvement in third-line PFS or OS (secondary end points) was observed with longer continuation of bevacizumab. The concept of treatment beyond progression is well established in LR/mBC: for many years, before the availability of alternative anti-HER2 therapies, a standard approach at the time of progression on trastuzumab-containing therapy for HER2-positive mBC was to continue trastuzumab and switch to a different chemotherapy regimen [12]. An important difference between the TANIA trial and the GBG26 trial (which evaluated trastuzumab treatment beyond progression [13]) was the control of third-line as well as second-line therapy in TANIA, prohibiting crossover to bevacizumab from the chemotherapy-alone arm at second progression. This feature of the trial design was implemented to try to limit the confounding effect of subsequent lines of therapy. Nevertheless, as 150 (64%) of the 234 patients who entered the third-line portion of the TANIA trial subsequently received further chemotherapy or targeted therapy, the likely impact of subsequent lines of treatment is not negligible.

Another challenge when assessing longer term outcomes, such as third-line PFS, is the substantial attrition between second progression and third-line therapy. Of the 494 patients randomised, 483 received second-line study therapy but only 234 (47% of all randomised patients) received third-line study therapy. When interpreting OS, it should be noted that more than half of the population did not receive third-line study therapy and 13%

of those entering the third-line bevacizumab treatment phase did not receive bevacizumab. Consequently, in effect the trial tested continuation of bevacizumab into third-line treatment in only 112 (45%) of the 247 patients initially randomised to bevacizumab-containing therapy.

As with many other contemporary trials in HER2-negative LR/mBC, including previous trials evaluating the addition of bevacizumab to chemotherapy, the PFS benefit did not translate into an OS improvement. The challenges of demonstrating an OS benefit in mBC and other tumour types with long post-progression survival have been discussed extensively in the literature [14, 15]. Furthermore, the TANIA trial was not powered to demonstrate differences in secondary efficacy endpoints. Additional limitations include the open-label trial design and investigator assessment of PFS.

None of the analysed subgroups appeared to derive a particularly large or small benefit from bevacizumab consistently across end points, although these analyses were limited by their exploratory nature and dependence on characteristics defined before second-line progression. Analysis of plasma biomarker concentrations at baseline also failed to identify subgroups of patients who may benefit most or least from bevacizumab [16]. Analysis of tissue markers is ongoing.

The proportion of patients completing HRQoL questionnaires was quite high at the start of the study, although at later timepoints only a small proportion of patients completed questionnaires (explained in part by attrition due to progressive disease). HRQoL analyses showed no detectable differences between treatment arms during second-line therapy, suggesting that the second-line PFS benefit with bevacizumab is achieved with maintained HRQoL. The main limitations of the HRQoL analyses were the open-label design of the trial, the lack of questionnaire collection after progression and, arguably, the choice of questionnaire. In addition, there was no prespecified hypothesis relating to HRQoL. Acknowledging the limitations of analyses based solely on comparing mean values or mean changes from baseline, which may mask meaningful benefit to individual patients, we performed responder analyses to determine the proportion of patients with a substantial

improvement in given symptoms. These exploratory analyses also showed no differences between treatment arms.

The safety profile of bevacizumab plus chemotherapy in the third-line treatment period was consistent with the safety profile previously reported for second-line therapy in the TANIA trial [6] and from extensive experience with bevacizumab-containing therapy in earlier treatment settings reported in the literature [1–4, 17]. Of note, even in the third-line setting, hypertension was more common in patients receiving bevacizumab than in those receiving chemotherapy alone. The association between bevacizumab therapy and hypertension might be expected to diminish in later treatment lines, as patients with uncontrollable hypertension would typically discontinue treatment, leaving a population enriched with those able to tolerate bevacizumab. However, bevacizumab-containing therapy was associated with increased risk of hypertension even after prolonged exposure in three treatment lines. Reassuringly there was no evidence of increased cardiac toxicity with multiple lines of bevacizumab.

The results described here should be considered alongside those of the primary PFS analysis. The TANIA trial demonstrated that in patients with bevacizumab-pretreated LR/mBC, continued bevacizumab significantly improved second-line PFS, thus meeting the primary objective of the trial. However, further bevacizumab after second progression did not significantly improve third-line PFS or OS. In one of the first trials of bevacizumab in heavily pretreated disease [18], it was suggested that the lack of bevacizumab treatment effect on PFS was perhaps due to increased redundancy of angiogenic pathways in later stages of the disease. This may partially explain the lack of detectable effect in the third-line setting in TANIA. Alternative treatments are required in this setting. Although few agents have been evaluated specifically in chemotherapy- and bevacizumab-pretreated disease, promising emerging options include CDK4/6 inhibitors, which have demonstrated efficacy in earlier treatment lines for hormone receptor-positive disease [19] and immunotherapeutic approaches, PARP inhibitors and approaches targeting the androgen receptor in triple-negative breast cancer [20, 21]. Overall, results from the TANIA trial demonstrate the

efficacy of second-line bevacizumab in bevacizumab-pretreated patients; however, further bevacizumab in the third-line setting does not appear to improve outcomes further.

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disclosure

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Figure legends

Figure 1. Patient disposition and analysis populations.

^aIntent-to-treat population.

^bOne patient re-randomised by mistake, one patient had HER2-positive disease.

BEV, bevacizumab; CT, chemotherapy.

Figure 2. Final efficacy results (stratified by hormone receptor status, first-line PFS, choice of chemotherapy and lactate dehydrogenase level). (A) Third-line PFS from start of third-line therapy (third-line efficacy population); (B) Combined second- and third-line PFS from randomisation (intent-to-treat population); (C) Final OS (intent-to-treat population).

BEV, bevacizumab; CI, confidence interval; CT, chemotherapy. HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Figure 3. Mean change from baseline in Functional Assessment of Cancer Therapy – Breast subscales: (A) Functional wellbeing; (B) Physical wellbeing.

Numbers above plots represent between-treatment group comparisons for each timepoint with corresponding 95% CIs.

BEV, bevacizumab; CI, confidence interval; CT, chemotherapy.

Appendix figure legends

Appendix Figure S1. Subgroup analyses by stratification factor (at the time of randomization): (A) Third-line PFS; (B) OS.

^aExcluding vinorelbine.

BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; ER, oestrogen receptor; HR, hazard ratio; LDH, lactate dehydrogenase; PFS, progression-free survival; PgR, progesterone receptor; OS, overall survival; TNBC, triple-negative breast cancer; ULN, upper limit of normal.

Appendix Figure S2. Questionnaire completion.

Timepoints beyond week 64/72 are not presented as there were <10 patients in the chemotherapy-alone arm.

BEV, bevacizumab; CT, chemotherapy.