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Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer

Gunter von Minckwitz [a,b,], Kathrin Schwedler [b], Marcus Schmidt [c], Jana Barinoff [d], Christoph Mundhenke [e], Tanja Cufer [f], Eduard Maartense [g], Felix E. de Jongh [h], Klaus H. Baumann [i], Joachim Bischoff [j], Nadia Harbeck [k], Hans-Joachim Lück [l], Nicolai Maass [m], Christoph Zielinski [n,o], Michael Andersson [p], Robert C. Stein [q], Valentina Nekljudova [a], Sibylle Loibl [a,b], On behalf of the GBG 26/BIG 03-05 study group and participating investigators [r]*

[a] *German Breast Group, GBG ForschungsGmbH, Martin-Behaim Str. 12, 63263 Neu-Isenburg, Germany*
[b] *University Women's Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany*
[c] *University Women's Hospital, Mainz, Germany*
[d] *HSK Breast Unit, Dr. Horst Schmidt Klinik, Wiesbaden, Germany*
[e] *University Women's Hospital, Breast Unit, UK SH, Kiel, Arnold-Heller-Str. 3, 24105 Kiel, Germany*
[f] *Institute of Oncology, Ljubljana, Slovenia*
[g] *Reinier de Graaf Gasthuis, Delft, The Netherlands*
[h] *Ikazia Ziekenhuis, Rotterdam, The Netherlands*
[i] *University Women's Hospital, Marburg, Germany*
[j] *University Women's Hospital, Magdeburg, Germany*
[k] *Breast Center, University of Cologne, Germany*
[l] *Gynaecological Praxis, Hannover, Germany*
[m] *University Women's Hospital, Aachen, Germany*
[n] *Clinical Division of Oncology, Department of Medicine I, Medical University Vienna, Austria*
[o] *Central European Cooperative Oncology Group (CECOG), Austria*
[p] *Rigshospitalet University Hospital, Copenhagen, Denmark*
[q] *University College London Hospitals, 250 Euston Road, London NW1 2PG, United Kingdom*

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ABSTRACT

Background: Continuation of trastuzumab plus capecitabine (XH) showed a significantly improved overall response rate and time to progression compared with capecitabine (X) alone in women with HER2-positive breast cancer progressing during trastuzumab treatment. Here, we report the final analysis on overall survival.

Patients and methods: Patients with HER2-positive, advanced breast cancer who progressed during treatment with trastuzumab with or without 1st-line metastatic chemotherapy were prospectively randomised to X (2500 mg/m^2 on days 1–14, q3w) or XH (6 (8) mg/kg, q3w). Overall survival was a pre-specified secondary end-point.

* *Corresponding author at:* c/o GBG ForschungsGmbH, Martin-Behaim-Str. 12, 63263 Neu-Isenburg, Germany. Tel.: +49 (0)6102 7480 411; fax: +49 (0)6102 7480 111
E-mail address: Gunter.vonMinckwitz@germanbreastgroup.de (G. von Minckwitz).
[r] See list of investigators in Appendix.

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Results: Median follow-up at June 2010 was 20.7 months. Fifty nine of 74 and 60 of 77 patients died in the X and XH arm, respectively. Median overall survival was 20.6 and 24.9 months with X and XH, respectively (HR = 0.94 [0.65–1.35]; $p = 0.73$). Performance status and metastatic site were independent prognosticators for overall survival. No difference between treatment arms was observed for patients who achieved clinical response or clinical benefit, respectively. Patients who continued/restarted anti-HER2 treatment (trastuzumab or lapatinib) after 2nd progression ($N = 52$) had a post-progression survival of 18.8 compared with 13.3 months for those who did not receive 3rd line treatment with anti-HER2 agents ($N = 88$) (HR 0.63; $p = 0.02$).

Conclusions: Final overall survival analysis of the GBG-26 study did not demonstrate a significant survival benefit for treatment beyond progression with trastuzumab. However, in a *post-hoc* analysis, patients receiving anti-HER2 treatment as 3rd line therapy showed a better post-progression survival than those not receiving this targeted treatment.

1. Introduction

Trastuzumab (Herceptin, Roche), a humanised monoclonal antibody against the extracellular domain of human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu or ErbB-2) has shown high clinical efficacy especially in combination with cytotoxic agents in patients with breast cancer over-expressing HER2. Prognosis of HER2 -positive advanced disease when treated with trastuzumab has now become more favourable than ER2-negative disease today.[1]

There is increasing clinical evidence that continued blockade of HER2 beyond tumour progression can improve patient outcomes. This has been shown not only by various retrospective analyses[2–5] but was also the result of the GBG 26/BIG 3-05 phase III study comparing 2nd line chemotherapy treatment with or without continuation of trastuzumab in patients who had progressed during 1st line trastuzumab treatment for metastatic HER2 positive breast cancer.[6] Comparable results were reported for the EGF100151 study comparing capecitabine with or without lapatinib, a small molecule inhibiting both tyrosine kinases, HER2 as well as epidermal growth factor receptor type 1 (EGFR, HER1, ErbB-1) in trastuzumab pre-treated patients.[7] Further evidence is derived from a phase III trial in heavily chemotherapy and trastuzumab pretreated breast cancer patients who received either lapatinib or lapatinib in combination with trastuzumab.[8] The combination of the two anti-HER2 agents (which can also be considered as treatment with trastuzumab beyond progression) achieved a significant prolongation of progression-free survival and a marginal prolongation of overall survival. A comparable observation was made when pertuzumab, an antibody that inhibits the dimerisation of HER2 with other receptors of the HER family, was given in one cohort alone and in a second cohort in combination with trastuzumab and a clinical benefit rate of 50% was observed for the combined treatment.[9]

Since GBG 26 is still the only randomised trial investigating the efficacy of trastuzumab beyond progression in combination with chemotherapy, we prospectively collected further data from the participants of the GBG 26 trial with regard to subsequent treatments and overall survival.

2. Patients and methods

2.1. Study design

The German Breast Group (GBG) 26/Breast International Group (BIG) 03-05 trial was an international, intergroup, open-label, phase III randomised trial. Participants were assigned in a 1:1 ratio to continue trastuzumab with the start of capecitabine or to receive capecitabine as single agent therapy. Randomisation was stratified by pre-treatment (taxanes and trastuzumab as adjuvant treatment ($N = 3$), taxanes and trastuzumab as 1st-line treatment for metastatic disease ($N = 111$), trastuzumab alone or in combination with cytotoxic agents other than capecitabine or taxanes as 1st-line treatment ($N = 42$) and participating center.

Overall survival was a predefined secondary end-point of the trial and was defined as the time period between randomisation and death of any cause. Patients who withdrew consent or were lost to follow-up were censored at the date of last contact.

2.2. Selection of patients

Women with pathologically confirmed, HER2-positive, locally advanced or metastatic breast cancer were enrolled. HER2-status was considered positive if over-expression was detected in either the primary or metastatic tumour tissue by local immunohistochemistry (score 3+ staining intensity) or by fluorescence in situ hybridisation (FISH). Duration of previous trastuzumab treatment had to be $\geqslant$12 weeks and the time since the end of the last trastuzumab cycle <6 weeks. Patients could have received up to one chemotherapy for metastatic disease.

2.3. Treatment

Patients received either capecitabine 2500 mg/m^2 (1250 mg/m^2 semi-daily) on days 1 through 14 followed by 1 week of rest or the same capecitabine regimen plus trastuzumab 6 (8) mg per kilogram body weight as a 30 min infusion every 3 weeks until disease progression, unacceptable toxicity, or disease progression. Trastuzumab treatment could be

continued at the investigator's discretion while capecitabine was being withheld.

Participants were assessed clinically for signs of progression every 3 weeks during treatment and every 3 months thereafter. Treatment after progression was not defined by the protocol but treatment was recorded.

Further information on the study design has been published previously.[6]

2.4. Statistical methods

The time to event outcome parameters were estimated using the Kaplan–Meier product-limit method and the log-rank test was used to compare between treatment groups. The study was powered to detect an absolute difference in time to progression of 1.1 months between the treatment arms with a target sample size of 482 patients. However, recruitment to the trial was slow and was stopped with 156 participants when lapatinib was registered in the EU for this indication. The primary end-point analysis showed that the absolute difference in median progression-free survival was 2.6 months in favour of continuing trastuzumab which was significant with a *p*-value of 0.034. Apart from the protocol-defined analysis for overall survival, four further analyses were planned at the time of preparation of the statistical analysis plan with the knowledge of previously reported results[6] (referred to as *post-hoc* analyses):

- To compare overall survival between the two arms in the group of patients with a clinical (complete or partial) response to study treatment,
- To compare overall survival between the two arms in the group of patients with clinical benefit (clinical response or stable disease for at least 24 weeks),
- To compare overall survival between only those patients who continued 3rd line treatment without cross-over of treatment arms,
- To compare post-progression survival (time between progression after study treatment and any death) according to the anti-HER2 treatment after progression on study treatment.

All analyses were performed as an intent-to-treat analyses on all patients who started study treatment ($N = 151$) (Fig. 1). All statistical tests used in these analyses are by default two-sided. The *p*-values are reported explicitly without any adjustment for multiple comparisons. Cox's proportional hazards models for overall survival and for time from disease progression to death were fitted using the same prognostic factors as used in the analysis for time to progression.[6]

The protocol was approved by all responsible local ethics committees. All subjects gave informed consent for participation. The conduct of the trial was supervised by an IDMC.

3. Results

The GBG 26 trial started in September 2003 and included a total of 156 patients during the following 45 months. Baseline characteristics have been published in the initial report.[6]

After a median follow-up of 20.7 months, of the 151 patients who started study treatment, 119 (78.8%) patients had died and 32 were still alive. The median overall survival in the intent-to-treat analysis was not statistically different between the two arms (hazard ratio (HR): 0.94 (95% CI: 0.65–1.3); log-rank $P = 0.734$) (Fig. 2). No significant difference in overall survival between the treatment arms was observed in the subgroup of patients achieving a clinical response (X: 20 patients, 34.7 [95% CI: 18.2–63.3] months; XH: 37 patients, 32.0 [95% CI: 24.9–46.6]; HR:1.08, $P = 0.83$) or a clinical benefit (X: 40 patients, 33.9 [95% CI: 20.7–50.6] months; XH: 58 patients, 28.0 [95% CI: 22.3–36.5]; HR:1.25, $P = 0.35$).

At the time of analysis, 11 patients had not received 3rd line metastatic treatment; five in the capecitabine arm and six in the trastuzumab plus capecitabine arm. The median time of post-progression survival was similar between patients from the capecitabine alone arm and patients from the capecitabine/trastuzumab arm (HR: 1.20, $P = 0.33$) (Fig. 3).

Patients continuing treatment with or without anti-HER2 treatment in the 3rd-line setting according to their initial randomisation showed no statistically different OS (HR 0.70, $P = 0.20$) (Fig. 4).

However, when survival was analysed according to the 3rd line treatment given, post-progression survival was better for those patients receiving trastuzumab compared to those not receiving anti-HER2-treatment as part of their 3rd line treatment (HR 0.63, $P = 0.02$) months (Fig. 5).

Factors independently associated with a more favourable overall survival were a Karnofsky index of $\geqslant 80\%$, positive hormone-receptor-status and non-visceral metastasis (Table 1). Factors independently associated with a longer post-progression survival were Karnofsky index of $\geqslant 80\%$, small pT stage, positive hormone-receptor-status, and anti-HER2 treatment after progression (Supplemental Table).

4. Discussion

Despite a significant improvement of time to progression observed in the analysis of the primary end-point of the GBG 26 study, we were not able to show an overall survival benefit for those patients continuing trastuzumab beyond progression. Post-progression survival was similar for both treatment groups. Almost half of all patients had cross-over of anti-HER2 treatment subsequent to treatment in GBG-26, as expected. Therefore, two further analyses considering 3rd line treatment were performed. The first analysis only included those patients who continued or did not receive anti-HER2 treatment as randomised at 3rd line (no cross-over). The statistical power of this analysis was limited due to the small overall number of patients and specifically the low number of patients ($N = 31$) continuing anti-HER2 treatment; which led to a non-significant difference in overall survival between the two groups. The second analysis compared post-progression survival in patients with anti-HER2 treatment as 3rd line treatment with that of patients receiving chemotherapy alone. With the larger number of patients but also the shorter remaining survival time, the difference was significant in favour of a continued anti-HER2 treatment: patients receiving anti-HER2 treatment at 2nd and at 3rd line showed the longest median overall survival (26.7 months).

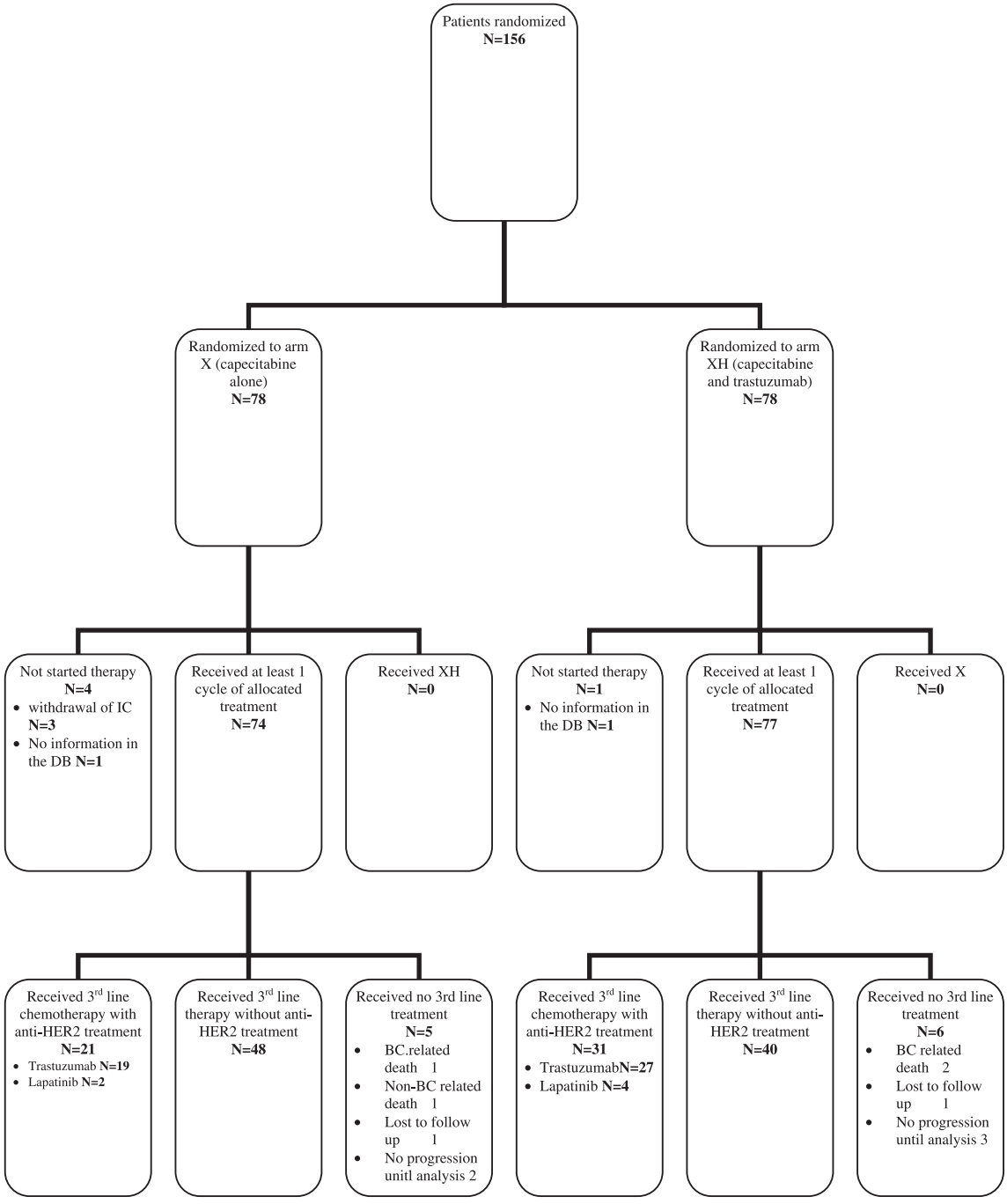

Fig. 1 – Disposition of patients (CONSORT diagram) in the GBG 26/BIG 03-05 study.

There is an intensive debate ongoing about appropriate end-points for patients with advanced breast cancer.[10] Progression-free survival and time to progression are attractive end-points for clinical trials because they are available earlier than overall survival, they are less influenced by competing causes of death than overall survival, and are not influenced by subsequent treatments. The chance to detect a gain in overall survival is strongly correlated with the size of the study. The GBG 26 study is substantially smaller than the reported median 407 patients in trials that showed a gain in overall survival.[9] The chance for a positive result also depends on the duration of overall survival. In 1st line trials, which reported a median of 20.7 (for chemotherapy trials) to 31.1 (for endocrine trials) months, overall survival differences were significantly less frequent compared to 2nd line trials with median overall survival duration of 15.2–23.2 months, respectively. Overall survival in the GBG 26 study with 20.6–24.9 months was considerably long taking into account that patients already received a 2nd line treatment. However, such long overall survival durations increase the risk of bias by subsequent treatments. This potential bias becomes even more relevant if effective salvage treatment options are available for later line treatments. Our analysis on post-progression survival showed a median duration of 13.3–18.8 months

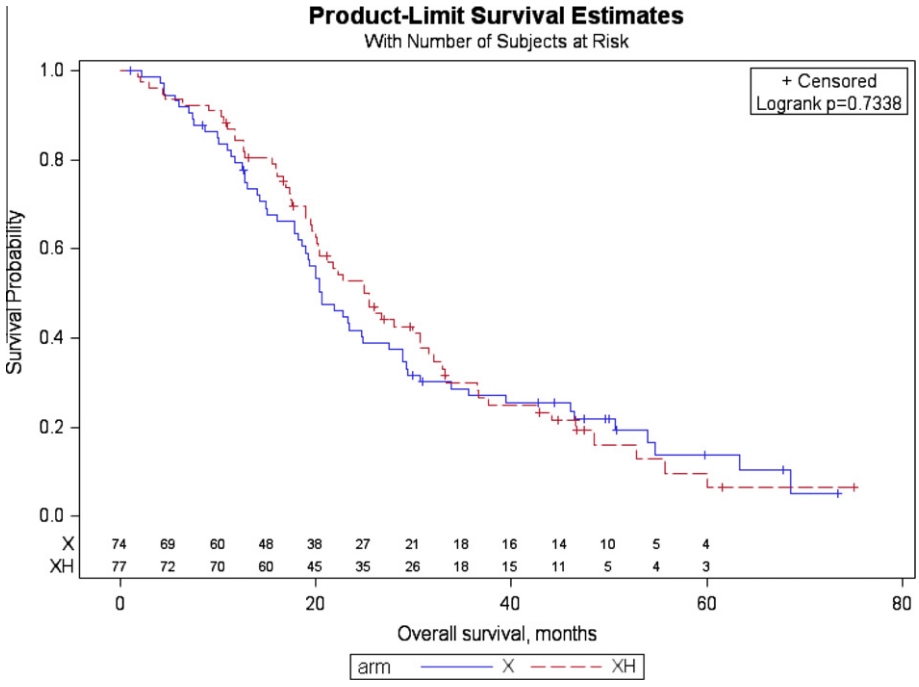

Fig. 2 – Kaplan–Meier curves for median overall survival (OS) of the two randomised treatment groups in the ITT population. Median OS was 20.6 (95% CI: 18.6–27.4) months in the capecitabine group and 24.9 (95% CI: 20.3–30.7) months in the capecitabine plus trastuzumab group (hazard ratio (HR): 0.94 (95% CI: 0.65–1.3); log-rank *P* = 0.734).

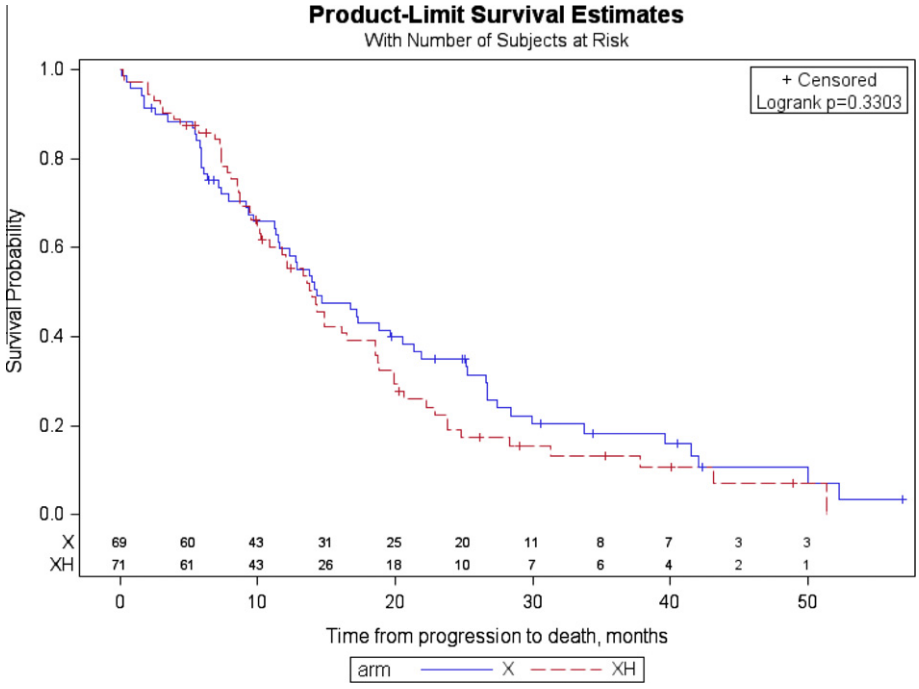

Fig. 3 – Kaplan–Meier curves for post-progression survival of the two randomised treatment groups in the ITT population. The median time of post-progression survival for the 69 patients from the capecitabine alone arm was 14.3 (95% CI: 11.5–21.3) months and for the 71 patients from the capecitabine/trastuzumab arm was 13.9 (95% CI: 10.8–18.6) months in the group (HR: 1.20, *P* = 0.33).

(which appears similar to the reported average for 2nd line chemotherapy trials) and was, therefore, much more likely to show overall survival differences.

Our analysis has the strengths that the dataset can be considered mature enough for survival analysis. Whereas the initial report included only 71 (47.0%) deaths, we now report on

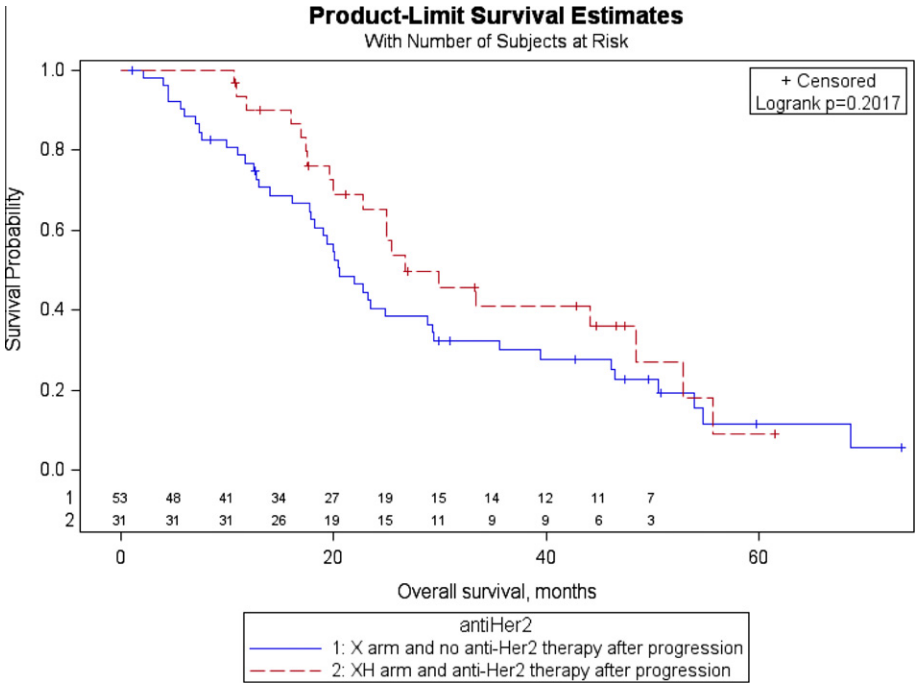

Fig. 4 – Kaplan–Meier curves for OS considering only patients without crossover at 3rd line treatment. Eighty four (55.6%) patients continued with or without anti-HER2 treatment in the 3rd-line setting according to their initial randomisation, 53 in the X arm and 31 in the XH arm. No statistically significant difference in overall survival was observed (X: 20.4 [95% CI: 18.2–24.8); XH: 26.7 [95% CI: 22.8–48.5]; HR 0.70, *P* = 0.20).

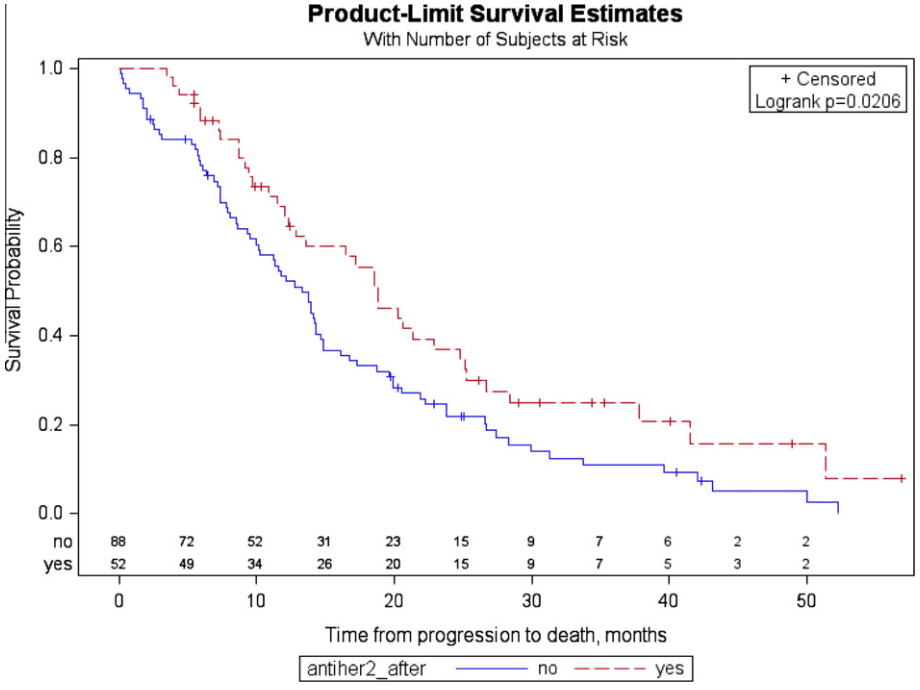

Fig. 5 – Kaplan–Meier curves for post-progression survival (PPS) according to anti-HER2 treatment or not as part of 3rd line treatment. PPS in the 88 patients who received 3rd line chemotherapy without anti-HER2 treatment was 13.3 [95% CI: 10.2–14.7] months and in the 52 patients given 3rd line chemotherapy with anti-HER2 treatment, 18.8 [95% CI: 12.9–24.8] months (HR 0.63, *P* = 0.02) months.

119 (78.8%) deaths. However, due to the small overall number of patients, the study will always lack sufficient power to observe smaller but relevant survival differences. However, it is planned to conduct a meta-analysis with other trials,

Table 1 – Univariate and multivariate (full model) Cox regression analysis for overall survival.

Factor value	Deaths N (%)	HR, univariate	95% CI, univariate	p, univariate	HR, multivariate	95% CI, multivariate	p, multivariate
Age, years							
⩾Median	62 (80.5)						
>Median	57 (77.0)	.918	(.640, 1.32)	.640	.875	(.594, 1.29)	.499
Karnofsky index (%)				.003			.001
⩾80	112 (77.8)						
<80	4 (100)	5.24	(1.86, 14.7)	.002	4.24	(1.32, 13.6)	.015
Not known	3 (100)	2.52	(.795, 7.98)	.116	6.29	(1.63, 24.4)	.008
pT stage at primary diagnosis				.145			.133
pT1-2	84 (80.8)						
pT3-4	26 (76.5)	1.23	(.788, 1.90)	.366	1.59	(.901, 2.81)	.109
Not known	9 (69.2)	.571	(.286, 1.14)	.112	.700	(.293, 1.67)	.423
Tumour grade				.914			.900
III	65 (77.4)						
I or II	46 (82.1)	1.05	(.719, 1.53)	.802	1.05	(.691, 1.60)	.811
not known	8 (72.7)	.898	(.427, 1.89)	.776	1.21	(.512, 2.86)	.664
Nodal status at primary diagnosis				.664			.571
Negative	20 (80.0)						
Positive	91 (79.1)	1.00	(.617, 1.63)	.988	.847	(.480, 1.50)	.568
Not known	8 (72.7)	.720	(.316, 1.64)	.432	.556	(.186, 1.66)	.292
M stage at primary diagnosis				.869			.318
M0	90 (81.1)						
M1	19 (67.9)	.874	(.530, 1.44)	.597	.707	(.401, 1.25)	.230
Not known	10 (83.3)	.962	(.500, 1.85)	.907	1.37	(.623, 3.00)	.434
ER/PgR status at primary diagnosis				.006			.001
ER and PgR negative	51 (82.3)						
ER and/or PgR positive	64 (75.3)	.896	(.619, 1.30)	.561	.712	(.467, 1.08)	.113
Not known	4 (100)	4.97	(1.74, 14.2)	.003	5.60	(1.89, 16.6)	.002
Pretreatment				.663			.421
Trastuzumab plus taxane	86 (79.6)						
Trastuzumab with or without other therapy	31 (77.5)	1.01	(.667, 1.52)	.968	.899	(.559, 1.45)	.660
Adjuvant trastuzumab plus taxane	2 (66.7)	.525	(.129, 2.14)	.368	.378	(.086, 1.66)	.198
Metastatic site							
Low risk (non-visceral)	36 (72.0)						
High risk (visceral)	83 (82.2)	1.52	(1.02, 2.25)	.039	1.70	(1.11, 2.62)	.015
Anti-Her2 treatment after progression							
No	82 (82.8)						
Yes	37 (71.2)	.763	(.517, 1.13)	.174	.744	(.489, 1.13)	.168
Assigned treatment							
X	59 (79.7)						
XH	60 (77.9)	.939	(.654, 1.35)	.734	.985	(.640, 1.51)	.945

ER = oestrogen receptor; PgR = progesterone receptor; HR = hazards ratio; CI = confidence interval; X = capecitabine; XH = capecitabine + trastuzumab.

including especially the study comparing capecitabine + lapatinib versus capecitabine alone[11], which would considerably raise the statistical power. Due to the *post-hoc* character and the potential bias of selecting patients with better prognosis, this post-progression survival analysis is only hypothesis generating and it will be a major aim to confirm this result using such a meta-database.

In conclusion, this final overall survival analysis of the GBG-26 study did not demonstrate a survival benefit for treatment beyond progression with trastuzumab. However, the *post-hoc* analysis on patients receiving or not receiving anti-HER2 treatment as 3rd line therapy still supports current recommendations to continue blockage of HER2 throughout multiple lines.[12,13]

Role of the funding source

Roche was not involved in the conduct and analysis of the trial.

Conflict of interest statement

GvM received speakers honoraria and research funding by Roche and GSK. CM received speakers honoraria by Roche and GSK. JB received honoraria by GSK and Roche, and research funding by GSK. NH received honoraria for consulting and lectures by Roche and GSK. CZ received speakers' honoraria by Roche and has a compensated advisory role for Roche and GSK. MA received honoraria and research

funding from Roche. RCS received honoraria for consulting and lectures by Roche. The trial was supported financially and the drug was supplied by Roche AG, Germany.

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Appendix A. List of participating investigators

Marianne Ewertz, Den Kliniske Forskningsenhed, Aalborg, Denmark, Dr. Dorte Nielsen, Amtssygfehuset I Herlev, Herlev, Denmark, Dr. Georg Heinrich, Schwerpunktpraxis der Gynäkologie und Onkologie, Fürstenwalde, Germany, Prof. Dr. Andreas Schneeweiß, Klinikum der Ruprecht-Karls-Universität Heidelberg, Frauenklinik, Heidelberg, Germany, Prof. Dr. Fritz Jänicke, Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Gynäkologie, Hamburg, Germany, Dr. Doris Augustin, Klinikum Deggendorf, Mammazentrum, Deggendorf, Germany, Dr. Claus Hanusch, Frauenklinik vom Roten Kreuz, Gynäkologie und Geburtshilfe, München, Germany, Prof. Dr. Christoph Thomssen, Martin-Luther-Universität Halle Wittenberg, Universitätsklinik u. Poliklinik f. Gynäkologie, Halle/Saale, Germany, Dr. Albrecht Kretzschmar, Helios Klinikum Berlin, Charité Campus Buch, Robert-Rössle-Klinik, Berlin, Germany, Prof. Dr. Martin Carstensen, Albertinen-Krankenhaus, Gynäkologie und Geburtshilfe, Hamburg, Germany, Dr. Holger Eidtmann, Universitätsklinikum Schleswig-Holstein Campus Kiel, Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany, Dr. Sabine Schnohr, Südharz Krankenhaus, Frauenklinik, Nordhausen, Germany, Prof. Nadia Harbeck, Klinikum rechts der Isar der TU München, Frauenklinik, München, Germany, Dr. Erhardt Schäfer, Onkologische Schwerpunktpraxis Dres. Schäfer/Just/Görner, Bielefeld, Germany, Prof. Dr. Volker Runde, Wilhelm-Anton-Hospital gGmbH, Klinik für Innere Medizin, Hämatologie, internistische Onkologie, Goch, Germany, PD Dr. Gernot Seipelt, Praxis Drs. Seipelt und Koch, Onkologische Schwerpunktpraxis, Bad Soden, Germany, Dr. Christoph Heiss, Klinik am Eichert, Frauenklinik, Göppingen, Germany,Dr. Klaus Rensing/Dr. Matthias Lerch, Universitätsklinikum Münster, Frauenklinik/Josephs-Hospital Warendorf, Gynäkologie und Geburtshilfe, Münster/Warendorf, Germany, Dr. Ingo Thalmann, Klinikum am Steinenberg, Frauenklinik, Reutlingen, Germany, Dr. Ute Bückner, Praxis für Innere Medizin, Hämatologie, internistische Onkologie, Bochum, Germany, Dr. Rainer Lipp, Praxis Lerchenfeld, IORC GmbH, Hamburg, Germany, Dr. Johann Weiss, Schwerpunktpraxis Dr. Weiss, Hämatologie und internistische Onkologie, Weiden, Germany, Dr. Jürgen Kowolik, Praxis Gynaekologie Arabella, München, Germany,Prof. Dr. Henning Kühnle, Medizinische Hochschule Hannover, Zentrum Frauenheilkunde/Brustzentrum, Hannover, Germany, Dr. Arnd Nusch, Gemeinschaftspraxis Drs. Nusch, Kalhori, Hämatologie und Onkologie, Velbert, Germany, Dr. Toralf Reimer, Klinikum Südstadt, Universitätsfrauenklinik, Rostock, Germany, Dr. Ernst Oberlechner, Klinikum Landshut, Frauenklinik, Landshut, Germany, Dr. Joachim Bischoff, Klinikum der Otto-v.-Guericke-Universität, Frauenklinik, Magdeburg, Germany, Dr. Matthias Zaiss, Schwerpunktpraxis Hämatologie und Onkologie, Freiburg, Germany, Dr. Claudia Fischäß, Evangelisches Krankenhaus, Frauenklinik, Gelsenkirchen, Germany, Dr. Beatrice Goldmann, Internistisch-gynäkolog.-onkolog. Schwerpunktpraxis, Lüneburg, Germany, Prof. Dr. Heinz-Gert Höffkes, Klinikum Fulda, Interdisziplinäres Tumorzentrum, Fulda, Germany, Dr. Jörn Kohnke, Onkologische Praxis Remscheid, Remscheid, Germany, Dr. Maik Hauschild, Frauenklinik Rheinfelden, Geburtshilfe, Gynäkologie, Brustzentrum, Rheinfelden, Germany, Dr. Isolde Gröll de Rivera, Kreiskrankenhaus Ebersberg, Gynäkologisch-onkologische Abteilung, Ebersberg, Germany, PD Dr. Dirk Strumberg, Marienhospital Herne, Onkologische/Hämatologische Ambulanz, Herne, Germany, Dr. Angelika Ober, St. Vincenz Krankenhaus, Frauenklinik, Limburg, Germany, Dr. van Riehl, St. Elisabeth Ziekenhuis, Tilburg, The Netherlands, Dr. Van der Hoeven, Amstelland Hospital, Amstelveen, The Netherlands, Prof. Dr. J.W.R. Nortier, Leiden University, Medical Center L.U.M.C., Leiden, The Netherlands, Dr. J.B. Ruit, Vlietland–Ziekenhuis, Schiedam, The Netherlands, Dr. W.A. van Deyk, Haga Ziekenhuis, loc Rode Kruis, Den Haag, The Netherlands, Prof. Dr. Christian Marth, Leopold-Franzens Universitätsklinikum, Abteilung für Gynäkologie, Innsbruck, Austria, Dr. Rosemarie Greul, Allgemeines Krankenhaus der Stadt Linz, Innere Medizin 3/Zentrum f. Häm. u. Med. Onkologie, Linz, Austria, Prof. Dr. Richard Greil, LKH Salzburg, Uni.klinik f. Innere Med. III/Onkol. Amb., Salzburg, Austria, Dr. Andreas Kretschmer, Krankenhaus Waidhofen a.d. Thaya, Interne Abteilung, Waidhofen, Austria, Dr. Hans-Jörg Neumann, Krankenhaus der Barmherzigen Brüder, Interne Abteilung, St. Veit a. d. Glan, Austria, Herr Prof. Dr. Thomas Brodowicz, Universitätsklinikum für Innere Medizin I, Wien, Austria, Dr. Christoph Tinchon, LKH Leoben, Onkologische und Hämatologische Ambulanz, Leoben, Austria, Dr. J. Schüller, Krankenanstalt Rudolfstiftung, Medizinische Abteilung, Wien, Austria, Dr. Johannes Andel, Landeskrankenhaus Steyr, 2. Med. Abt. Onkologie, Steyr, Austria, Dr. Andrew Wardley, Christie Hospital, Withington, Manchester, United Kingdom, Dr. RE Coleman, The University of Sheffield, Sheffield, United Kingdom, Dr. W. Tayler, University Hospital of North Durham, Durham, United Kingdom.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.06.021.

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