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Title: Combination of everolimus with trastuzumab plus paclitaxel as first-line therapy for HER2+ advanced breast cancer (BOLERO-1): primary results of a phase III, randomized, double-blind, multicenter trial

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ABSTRACT

Background: mTOR inhibition has been shown to reverse trastuzumab resistance from hyperactivated the PIK/AKT/mTOR pathway due to PTEN loss, by sensitizing PTEN-deficient tumors towards trastuzumab. The BOLERO-1 study evaluated the efficacy and safety of adding everolimus to trastuzumab and paclitaxel as first-line therapy for HER2+ advanced breast cancer (ABC).

Methods: In this phase III, randomized, double-blind trial, patients were enrolled across 141 sites in 28 countries. Eligible patients were ≥18 years of age, with locally assessed HER2+ advanced breast cancer (ABC), with Eastern Cooperative Oncology Group performance status of 0-1, who had not received prior trastuzumab or chemotherapy for ABC, had measurable disease as per Response Evaluation Criteria in Solid Tumors or bone lesions in the absence of measurable disease, without prior systemic therapy for advanced disease except endocrine therapy. The patients were randomized 2:1 (with an interactive voice and web response system) to receive either daily everolimus (10 mg/day) orally or placebo plus weekly trastuzumab intravenously at 4 mg/kg loading dose on Day-1 with subsequent weekly doses of 2 mg/kg of each 4-week cycle plus paclitaxel intravenously at a dose of 80 mg/m^2 on days 1, 8, and 15 of each 4-week cycle. Randomization was stratified according to prior use of trastuzumab and visceral metastasis. Patients and investigators were blinded to the assigned treatments. Identity of experimental treatments was concealed by use of everolimus and placebo that were identical in packaging, labelling, appearance, and administration schedule. The two primary objectives were investigator-assessed progression-free survival (PFS) in the full study population and in the subset of patients with hormone receptor-negative (HR−) breast cancer at baseline; the latter was added during the course of the study, prior to unblinding based on new clinical and biological findings from other studies. All efficacy analyses were based on the intention-to-treat population. Enrolment for this trial is closed and results of the final PFS analyses are presented here. Clinicaltrials.gov identifier: NCT00876395.

Findings: Between 10-Sep-2009 and 16-Dec-2012, 719 patients were randomized to receive everolimus (n=480) or placebo (n=239). Median follow-up was 41.3 months (IQR: 35.4 – 46.6 months). The primary objective in the full population was not met; median PFS was 15.0 months with everolimus vs 14.5 months with placebo (hazard ratio, 0.89; 95% CI, 0.73-1.08; p=0.1166). In the HR− subpopulation (n=311), median PFS with everolimus was 20.3 months vs 13.1 months with placebo (hazard ratio, 0.66; 95% CI, 0.48-0.91; p=0.0049), however, the protocol-specified statistical significance threshold (p=0.0044) was not crossed. The most common adverse events (AEs) with everolimus vs placebo were stomatitis (314 [66.5%] vs 77 [32.4%] patients), diarrhea (267 [56.6%] vs 111 [46.6%] patients), and alopecia (221 [46.8%] vs 125 [52.5%]). The most frequently reported grade 3/4 AEs in the EVE arm vs PBO arm were neutropenia (117 [24.8%] of 472 patients vs 35 [14.7%] of 238 patients), stomatitis (59 [12.5%] of 472 patients vs 3 [1.3%] of 238 patients), anemia (46 [9.7%] of 472 patients vs 6 [2.5%] of 238 patients) and diarrhea (43 [9.1%] of 472 patients vs 10 [4.2%] of 238 patients) On-treatment AE-related deaths were reported in 17 [3.6%] vs 0% of patients respectively.

Interpretation: The primary objective of PFS was not met. However, consistent with the preliminary observations from BOLERO-3, everolimus prolonged median PFS by 7.2 months in patients with HR–, HER2+ ABC, which warrants further investigation. The safety profile was generally consistent with what was previously reported in BOLERO-3. Proactive monitoring and early management of AEs in patients treated with everolimus and chemotherapy is critical..

Funding: Novartis Pharmaceuticals Corporation.

Introduction

Human epidermal growth factor receptor-2 (HER2) is overexpressed in approximately, 20%-25% of breast cancers.[1] Before the introduction of targeted therapies, HER2+ breast cancer was characterized by its aggressive proliferation, and poor prognosis.[2–4] Trastuzumab has dramatically improved the outcomes in both early and metastatic HER2+ breast cancer,[5,6] however, resistance to trastuzumab (de novo or acquired) presents a significant clinical challenge that warrants identification of novel treatment strategies.[7,8]

Constitutive activation of PI3K/AKT/mTOR signaling due to PTEN loss can lead to trastuzumab resistance.[9,10] mTOR inhibition sensitizes PTEN-deficient tumors to trastuzumab thereby suggesting that the combination of everolimus, an mTOR inhibitor, and trastuzumab may have a role in the treatment of HER2-overexpressing breast cancer.[11,12] The addition of everolimus, an mTOR inhibitor, to trastuzumab and chemotherapy showed clinical benefit in heavily pretreated patients with HER2+ advanced breast cancer (ABC) progressing on prior trastuzumab and taxane therapy.[13–15] Thus, two phase III studies, BOLERO-1 and BOLERO-3, were developed to evaluate whether adding an mTOR inhibitor to trastuzumab-based therapy would circumvent treatment resistance and improve patient outcomes in HER2+ ABC. The recently reported BOLERO-3 trial demonstrated a small but statistically significant improvement of 1.2 months in progression free survival (PFS) benefit with the addition of everolimus to trastuzumab plus vinorelbine (7.0 months vs 5.78 months; hazard ratio, 0.78; p=0.0067) in patients with HER2+ ABC progressing on prior trastuzumab and a taxane.[16] The present BOLERO-1 study evaluated the addition of everolimus to trastuzumab and taxane as first-line therapy for HER2+ ABC.

Data from multiple clinical trials in HER2+ breast cancer indicate that hormone receptor (HR) co-expression impacts tumor behavior and response to systemic therapy.[17–21] In particular, a subset analysis from BOLERO-3 showed patients with HR− tumors tend to derive more benefit when everolimus is added to vinorelbine/trastuzumab compared with those with HR+ tumors (hazard ratio [HR], 0.65 vs 0.93, respectively).[16] Due to this compelling biological rationale, and to validate the hypothesis of differential efficacy in HR− patients, BOLERO-1 was amended to prospectively evaluate the impact of everolimus on PFS in both the full patient population and the HR− subpopulation.

Methods

Study design and participants

BOLERO-1 was a phase III, international, randomized, double-blind, placebo-controlled trial. Women aged ≥18 years with locally assessed HER2+, locally recurrent invasive breast cancer unamenable to resection with curative intent or metastatic disease, with Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, were eligible. Patients had measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) or bone lesions in the absence of measurable disease. No prior systemic therapy for advanced disease was allowed, except endocrine therapy that required discontinuation due to disease progression before randomization. Prior (neo)adjuvant trastuzumab and chemotherapy were discontinued at least 12 months before randomization. There were no restrictions on the number of lines of prior endocrine therapy in the metastatic setting. Patients had to meet the routine hematology and biochemistry laboratory criteria at baseline and Left Ventricular Ejection Fraction (LVEF) ≥LLN within four weeks prior to randomization. Patients were excluded if they had previously received an mTOR inhibitor or had inadequate liver, renal, cardiac or bone marrow functions (additional information in supplementary material).

Written informed consent was obtained from all patients. The study was performed in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by an independent ethics committee or institutional review board at each site.

Randomization and masking

Enrolled patients were randomly assigned in 2:1 ratio to receive either everolimus (EVE arm) or placebo (PBO arm) in addition to weekly trastuzumab plus paclitaxel, using a centralized patient screening and randomization system. Randomization was stratified according to visceral metastases and prior (neo)adjuvant trastuzumab therapy. An interactive voice and web response system was used to gather screening information and randomly allocate treatment (IDDI, Louvain-la-Neuve, Belgium). Patients and investigators (including local radiologists) remained blinded to the assigned treatments until final PFS analyses. Premature unblinding of study drug assignment was only allowed in case of emergency. Identity of experimental treatments was concealed by use of everolimus and placebo that were identical in packaging, labelling, appearance, and administration schedule.

Procedures

Everolimus (Novartis Pharmaceuticals Corporation, USA) or matching placebo was self-administered by patients as 10 mg/day orally. Trastuzumab was administered intravenously at a 4 mg/kg loading dose on Day-1 with subsequent weekly doses of 2 mg/kg of each 4-week cycle. Paclitaxel was administered intravenously at a dose of 80 mg/m^2 on days 1, 8, and 15 of each 4-week cycle. Endocrine therapy was not allowed. Study treatment continued until disease progression, intolerable toxicity, or withdrawal of consent. Standard premedication before administration of paclitaxel and trastuzumab was allowed. G-

CSF prophylaxis was not required, but was allowed in line with the ASCO guidelines.[22] A baseline tumor assessment was performed within 28 days prior to randomization. After treatment start, tumor assessments (CT/MRI of chest, abdomen and pelvis) according to RECIST were made every 8 weeks (+/- 1 week) until disease progression. An independent review of imaging assessments was conducted by an Independent Imaging CRO. Results of the local review were used for analysis of all efficacy endpoints. A central review was used as secondary supportive analyses of efficacy endpoints. Safety assessments included recording of all adverse events (AEs) at each visit and serious AEs (SAEs) continuously throughout the study period. The severity of AEs were graded as per National Cancer Institute Common Terminology Criteria for AEs v3.0 on a scale of grade 1–4 and assessments were made to identify potential relationship to study treatment. Safety monitoring included hematology and biochemistry assessments and ECOG performance status at baseline or ≤7 days of protocol treatment start through each treatment cycle until the follow-up phase. Specific guidelines for the management of stomatitis, non-infectious pneumonitis, neurotoxicity, pulmonary, metabolic, and hematological toxicities, hepatitis B and C, were provided in the protocol (Supplementary table 1 presents Pneumonitis management guidelines). Dose adjustments for everolimus (10 mg daily; 5 mg daily; 5 mg every other day), and paclitaxel (80 mg/m^2; 60 mg/m^2) were permitted to manage treatment-related toxicities.

Outcomes

The primary efficacy endpoint, investigator-assessed PFS as per Response Evaluation Criteria In Solid Tumors v1.0 criteria was tested in the full population (all randomized patients) and HR– subpopulation (randomized patients with HR– disease).

The second primary objective of comparing PFS between the treatment arms in the HR– subpopulation was introduced prior to unblinding via protocol amendment in March 2014, based on the observation from BOLERO-3 which showed patients with HR– tumors tend to derive more benefit when everolimus is added to vinorelbine/trastuzumab compared with those with HR+ tumors (hazard ratio, 0.65 vs 0.93, respectively). PFS was defined as time from randomization to first radiological tumor progression or death from any cause.

The key secondary endpoint was overall survival (OS) assessed in the full population and the HR– subpopulation. Other secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR), and safety.

Statistical analysis

The primary efficacy analyses were planned after at least 420 PFS events were documented in the full population. Patients were analyzed according to their assigned treatment and stratum at randomization. All efficacy analyses were based on the intention-to-treat principle, i.e. including all randomized patients. The safety analyses included patients who received at least one dose of any of the study treatments with at least one post-baseline safety evaluation.

For the primary analysis of PFS, patients were censored at the last adequate tumor assessment if one of the following occurred: absence of event; the event occurred after a new anticancer therapy was given; the event occurred after two missing tumor assessments. Several sensitivity analyses were conducted. Notably, as advised by the study steering committee, prior to unblinding the study, a strict intention-to-treat sensitivity analysis without censoring patients at the start of new antineoplastic therapy was performed. As secondary supportive analysis of PFS, central radiology assessment was performed.

PFS was estimated using the Kaplan-Meier method; comparison of PFS between the treatment arms was performed using a stratified log-rank test (with baseline stratification factors used at randomization). A stratified Cox regression model was used to estimate the hazard ratio of PFS, along with 95% confidence interval (CI). This stratified Cox model did not include any covariates other than randomized treatment. For sample size calculation, it was hypothesized that trastuzumab plus paclitaxel would result in a median PFS of at least 7 months, and the addition of everolimus to this regimen would result in a 26.3% reduction in the hazard ratio, leading to a clinically meaningful 36% improvement in median PFS from 7 to 9.5 months. The assumption of median PFS of 7 months in the control arm in the study design was based on available information at the time of designing the study. Data from pivotal trials with trastuzumab plus standard taxane chemotherapy showed median PFS ranging between 6.9 months and 7.1 months.[23,24] The overall Type I error rate (α=0.025) for testing two primary statistical tests for PFS was controlled via weighted Hochberg procedure with unequal weights (80% for the full population and 20% for the HR− subpopulation). Multiplicity arising from group sequential study design was addressed using two independent Lan and DeMets (1983) with O'Brien-Fleming type alpha spending functions for the full population and the HR− subpopulation, each at the overall alpha level as allocated by weighted Hochberg. The corresponding simulated powers were 82% and 47%, respectively. Note that simulated power for the second primary comparison in the HR− subpopulation was 47% assuming HR= 0.737. However, it was expected that the treatment effect would be much stronger in the subgroup which would result in higher power.

All reported p-values are one-sided as the study was designed to test one-sided alternative hypotheses of an improved treatment effect of everolimus as compared with placebo in combination with trastuzumab and paclitaxel. As per Hochberg procedure, under group sequential design, statistical significance could be claimed in both populations simultaneously if the corresponding observed p-values for full and HR− subpopulations were below 0.0216 and 0.0214, respectively. If either both or one of the above conditions were not satisfied, statistical significance could also be claimed in either only the full population or HR− subpopulation if the observed p-values were below 0.0174 in full population or below 0.0044 in HR− subpopulation. Please note that in the results section, we refer to p-value threshold from the second step of Hochberg procedure as the study did not cross the p-value boundaries for both populations in the first step.

EAST 5.4 was used in the calculation of sample size and in the implementation of the group sequential design and SAS version 9.3 was used for the statistical analyses.

Role of the funding source

The study was designed by the sponsor in collaboration with TRIO-Global, with input from academic investigators, and the study steering committee. The sponsor provided study drugs, participated in regulatory and ethics approvals, site level study monitoring and performed statistical analyses. TRIO-Global in collaboration with the sponsor performed data management and safety monitoring. A study steering committee supervised scientific conduct and integrity of the trial. Safety was monitored by an independent data monitoring committee. All authors had full access to the data for interpretation and analysis, were involved in development and approval of the manuscript, and had the final responsibility for the decision to submit for publication.

This trial was registered with ClinicalTrials.gov, number NCT00876395.

Results

Between 10-September-2009 and 16-December-2012, 719 patients were enrolled at 141 centers in 28 countries (study site details are provided in supplementary material); 480 were randomly assigned to the EVE arm, and 239 to the PBO arm (Figure 1). All patients (N=719) were included in the efficacy analysis, and 710 patients were included in the safety analysis. Nine patients who were not included in the safety analysis had not received any study treatment. Supplementary Table 2 presents data on those patients who did not meet the protocol-specified eligibility criteria.

At the data cut-off date (May 30, 2014), after a median study follow-up of 41.3 months (IQR: 35.4 – 46.6 months), there were 425 PFS events in the full population; 73 patients were continuing study treatments, 46 (9.6%) in the EVE arm and 27 (11.3%) in the PBO arm. Baseline and disease characteristics in the full population were generally balanced between the two treatment arms (Table 1). Overall, median age was 53 years, 507 [70.5%] patients had visceral metastases, and 311 [43.3%] patients had HR− disease; prior therapy included an anthracycline (298 patients; 41.4%), taxane (179 patients; 24.9%), and trastuzumab (78 patients; 10.8%). Baseline characteristics by treatment arm for the HR− subpopulation are displayed in Table 1.

In the safety set, the median treatment duration was 40.8 weeks for everolimus, and 48.1 weeks for placebo. The most frequently reported reasons for treatment discontinuation (all three drugs) were disease progression (245 patients [51.0%] in the EVE arm vs 155 patients [64.9%] in the PBO arm), consent withdrawal (62 [12.9%] vs 31 [13%]) patients, and AEs (59 [12.3%] vs 10 [4.2%] patients).

Treatment with everolimus plus trastuzumab and paclitaxel did not improve PFS in the full population; investigator-assessed median PFS, 15.0 months [271 events] vs 14.5 months [154 events] in the PBO arm (HR=0.89; 95% CI, 0.73-1.08; p=0.1166 vs protocol pre-specified statistical significance threshold p=0.0174) (Figure 2A). Independent central radiological reviews corroborated the treatment effect as assessed by the local assessments (Figure 2B); median PFS (EVE arm vs PBO arm) was 20.4 months vs 18.3 months; HR=0.86 (95% CI, 0.68-1.09). In the HR− patients, a 7.2-month benefit in median PFS was observed by investigator review (20.3 months [97 events] vs 13.1 months [66 events] in the PBO arm; HR=0.66 (95% CI, 0.48-0.91; p=0.0049). However, the p-value of p=0.0049 was close to but did not cross the protocol-specified threshold of statistical significance (p=0.0044) (Figure 2C). Pre-specified sensitivity analysis of PFS without censoring patients at the start of new antineoplastic therapy yielded a HR consistent with the primary analysis (HR=0.66; 95% CI, 0.48-0.90) with a p-value=0.0043 (additional information on sensitivity analysis is available in the supplementary material). Furthermore, independent central assessments showed prolongation of median PFS by 8.3 months; median PFS was 23.1 months vs 14.8 months; HR=0.61 (95% CI, 0.42-0.87; p=0.0030) (Figure 2D). The number of PFS events in the HR+ subpopulation was 173 in the EVE arm vs 88 in the PBO arm; the hazard ratio for the comparison of PFS was 1.06 (95% CI, 0.82−1.37). The p-value for the interaction between treatment effect and HR status was 0.0206.

The ORRs in the full population were high and comparable between the EVE vs PBO arms (322 [67.1%] vs 165 [69.0%] patients), with corresponding CBRs of 364 (75.8%) vs 194 (81.2%) patients, respectively; in the HR− subpopulation, the ORRs were reported in 152 (73.1%) vs 73 (70.9%) patients and CBR was reported in 164 (78.8%) vs 82 (79.6%) patients (p=0.6382) in the EVE and PBO arms, respectively (Table 2). Data on differences in site of relapse or brain metastasis are currently not available.

The median everolimus relative dose intensity was 0.54 in this trial (vs 0.96 in the PBO arm), which may be explained by the dose adjustments necessitated due to toxicity encountered from the combination of everolimus with chemotherapy. A similar trend was observed in the HR− subpopulation (0.53 vs 0.95). Dose interruptions and/or reductions in the full population were 86.0% vs 73.5% in the EVE arm vs PBO arm, respectively (Table 3). The most frequently reported non-hematologic AEs reported in the EVE vs PBO arms were stomatitis (314 [66.5%] vs 77 [32.4%] patients), diarrhea (267 [56.6%] vs 111 [46.6%] patients), and alopecia (221 [46.8%] vs 125 [52.5%] patients); neutropenia (177 [37.5%] vs 59 [24.8%] patients) was the most frequently reported hematologic AE (Table 4). The majority of AEs were of grade 1/2 severity. The most frequently reported grade 3/4 AEs were neutropenia, stomatitis, diarrhea, and anemia, all of which were more common in the EVE arm than in the PBO arm (Table 4). Pneumonitis was reported in 77 (16.3%) vs 10 (4.2%) patients in the EVE vs PBO arms, respectively. The majority of these were of grade 1/2 severity; in the EVE arm, 19 (4.0%) patients experienced grade 3 pneumonitis and 4 (0.8%) patients experienced grade 4 pneumonitis vs 1 (0.4%) patient in the PBO arm experienced grade 3 pneumonitis. AEs leading to treatment discontinuation of the any of three drugs suspected to be study treatment related were reported for 234 patients (49.6%) in the EVE arm vs 91 patients (38.2%) in the PBO arm. AEs leading to treatment discontinuation irrespective of relationship to any of the three study treatments were reported in 260 (55.1%) vs 96 (40.3%) patients in the EVE vs PBO arms, respectively, the most frequent being peripheral neuropathy (36 [7.6%] vs 18 [7.6%] patients), neurotoxicity (29 [6.1%] vs 18 [7.6%] patients), and pneumonitis (27 [5.7%] vs 1 [0.4%] patient), respectively. SAEs were reported in 169 (35.8%) vs 36 (15.1%) patients in the EVE vs PBO arms. The most frequent SAEs irrespective of relationship to any of the study treatments reported in the EVE arm were pneumonitis in 21 (4.4%), pneumonia in 19 (4%) and pyrexia 12 (2.5%) patients, and in the PBO arm were cellulitis and infusion-related reaction in 3 (1.3%) patients.

As of the data cut-off date, 263 deaths (approximately 60%; 179 patients [37.3%] and 84 patients [35.1%] in the EVE and PBO arms, respectively) of the pre-specified 438 OS events were recorded in the full study population. Overall, 22 (4.7%) patients in the EVE arm and 2 (0.8%) patients in the PBO arm died while on treatment. Of these, 17 (3.6%) deaths were attributed to AEs, all in the EVE arm. The causes of death included respiratory and thoracic disorders for 8 patients (1.7%), infections (including respiratory) for 5 patients (1.1%), cardiac disorders, cerebrovascular accidents, injury, metabolic acidosis for 1 patient each (Table 5). All but one of these deaths occurred within the first 2.3 years of enrollment (median time from randomization to death was 78 days). There appeared to be a higher rate of on-treatment deaths in regions with limited experience with everolimus (data not presented); in some cases, the protocol-defined

AE management guidelines were not followed.

The safety in the HR– subpopulation was generally consistent with that observed in the full population (data not presented).

Antineoplastic therapies since discontinuation of study treatment are presented in Supplementary table 3.

Discussion

The present BOLERO-1 study results show that the addition of everolimus to trastuzumab and paclitaxel did not improve clinical outcomes as first-line therapy in HER2+ ABC (median PFS HR=0.89; 95% CI, 0.73-1.08; p=0.1166). In contrast, HR− patients derived a 7.2-month median PFS benefit; the p-value did not cross the statistical boundary by a very small margin. To be noted that based on the statistical design (in particular, use of weighted Hochberg procedure combined with group sequential design), the threshold for statistical significance in the HR− subpopulation was rather stringent (p=0.0044). Sensitivity analysis of PFS in the HR− subpopulation without censoring patients at the start of new anti-cancer therapy yielded HR=0.66 (95% CI, 0.48-0.90) and a one-sided p=0.0043. Likewise, the PFS analysis in the HR− subpopulation based on central radiology review yielded HR=0.61 (95% CI, 0.42-0.87) and a one-sided p=0.0030. The PFS effect observed in the HR− subpopulation, therefore might be considered as clinically relevant. This result in the HR− patients is consistent with the previously reported predefined subgroup analysis in BOLERO-3 wherein patients with HR−, HER2+ ABC derived more benefit when everolimus was added to HER2-targeted therapy in the absence of hormonal treatment (HR=0.65 vs 0.93 in HR− patients).[16] It may be acknowledged here that the PFS effect observed in the HR− subpopulation was neither reflected by ORR nor by CBR. However, ORR is not necessarily a reliable surrogate marker for PFS.[25,26] The median PFS observed in the PBO arm for the full population and the HR− subpopulation (14.5 months and 13.1 months by local assessment, respectively) were longer than what was anticipated at the time of study design (7 months). This substantial prolongation of the median PFS is likely attributed to the improvement in clinical management (including toxicity management) of HER2+ ABC since early 2000. Recently reported trials for HER2+ metastatic breast cancer in the first-line setting have shown a median PFS between 12.4 months and 13.7 months in the control arm patients who received trastuzumab and a taxane.[27,28]

BOLERO-1 is the first study that prospectively evaluated the efficacy of a HER2-targeted combination regimen in HR− patients as one of its primary objectives and may serve as a benchmark for future studies. Data from BOLERO-1 support the preliminary observation from BOLERO-3 that treatment effect of EVE differs depending on the presence/absence of ER expression in patients with HER2+ ABC not receiving hormonal therapy.[16,19] Exploration of the HER2+, HR− subsets with the PI3K/mTOR inhibitor is of great scientific interest. A review of at least seven neoadjuvant trials of HER2-targeted agents given with or without chemotherapy (none of which included hormonal therapy) has consistently shown higher pCR rates in HR− patients.[29] The interaction between HER2-directed therapy and hormone receptors has been described and extensive crosstalk between the ER and HER2 pathways may act as an escape mechanism for HER2-directed agents.[29] Thus, the efficacy of everolimus and trastuzumab might be enhanced if the estrogen pathway is inhibited concomitantly. Therefore, data from these two trials support further investigation of the benefits of adding an PI3K/mTOR inhibitor to endocrine and HER2-targeted therapy in HER2+, HR+ ABC.

The combination of everolimus, trastuzumab, and paclitaxel was associated with a higher incidence of AEs, although most AEs were of grade 1/2 intensity. The incidence of hematologic AEs, including neutropenia and anemia (all grade 177 patients [37.5%] and 146 patients [30.9%], respectively) were higher in the EVE arm; however no new safety signals were identified. Treatment discontinuation of all three drugs due to disease progression was lower with everolimus vs placebo (245 patients [51.0%] vs 155 patients [64.9%], respectively), while treatment discontinuation of all three drugs due to AEs showed a reverse trend (59 patients [12.3%] for everolimus vs 10 patients [4.2%] placebo). AEs leading to treatment discontinuation suspected to be related to any of the three drugs were reported for 234 patients (49.6%) in the EVE arm vs 91 patients (38.2%) in the PBO arm. The most frequently reported AEs in the EVE arm were consistent with those reported in previous trials of everolimus in breast cancer when combined with chemotherapy and included non-hematologic AEs such as stomatitis, diarrhea, pneumonitis, rash, pyrexia, and headache, and hematologic toxicities such as neutropenia and anemia.[14,16,30]

The rate of on-treatment deaths due to AE in the EVE arm (EVE arm: 17 [3.6%]; PBO arm: 0%) appears to be high when using the combination of everolimus with trastuzumab and paclitaxel. Lower rates were observed in other everolimus studies in patient populations with metastatic breast cancer (BOLERO-2; 1.7%) and (BOLERO-3; 0.7%).[16,31] This may be due to the limited experience with everolimus when used with paclitaxel and trastuzumab. Other unknown factors could have contributed to this observation. To that end, after safety review of the data, based on recommendations from the independent data monitoring committee, a communication was sent to the investigators underlining the importance of management of specific everolimus-related AEs. Subsequently, until the data analysis in 2014, only one on-treatment death due to AE was reported. This reinforces the importance of proactive monitoring, early detection and appropriate management of AEs following everolimus plus chemotherapy regimens. Available standardized AE management protocols and education of both healthcare providers and patients regarding the class-effect AEs of mTOR inhibitors like everolimus can facilitate optimal treatment exposure and clinical benefit.[32–34]

The initial dose of everolimus in this study was 10 mg/day, however, the median RDI of everolimus was 0.54 when administered in combination with trastuzumab and paclitaxel due to toxicity related dose interruptions and reductions. Based on this, we could speculate whether 5 mg/day might be a more appropriate dose for everolimus when combined with chemotherapy and trastuzumab. In fact, 5 mg/day was the everolimus dose used in the BOLERO-3 trial, when combined with another chemotherapy and trastuzumab).[16] It should be noted however that, these observations do not necessarily apply to other settings such as the HR+, HER2– ABC setting, where an everolimus 10 mg/day dose has been established as an effective treatment option in combination with an aromatase inhibitor and approved by health authorities worldwide.[35,36]

Genetic biomarker analysis and overall survival analyses are ongoing and will be presented/published

when available.

There were a few limitations in the BOLERO-1 study that should be considered while interpreting these results. Firstly, the study was not stratified by HR status resulting in some imbalances in the baseline disease characteristics in HR– subpopulation. The inability to implement this stratification at the onset was due to the fact that the second primary objective of comparing PFS between the two treatment arms in the HR– subpopulation was introduced during the course of the trial, prior to unblinding, at which time the study enrolment was complete. However, the observed imbalances are not believed to have significantly impacted the results of the PFS in this subpopulation Secondly, local HER2 status testing was not confirmed by central testing before the study entry. Finally, very few patients received prior trastuzumab in the neoadjuvant or adjuvant setting (10.6%), although these numbers were similar to that observed in previous studies in a similar setting (10.9%).[27]

Conclusion:

Data from BOLERO-1 support the preliminary observation from BOLERO-3 that treatment effect of everolimus differs based on HR expression in HER2+ ABC in the absence of hormonal therapy. The addition of everolimus to trastuzumab and paclitaxel provided a 7.2 months PFS benefit in HR–, HER2+ ABC. Proactive monitoring and early management of AEs are warranted in patients receiving the combination therapy of everolimus, trastuzumab and paclitaxel. Two ongoing phase I trials are evaluating the benefits of adding PI3K/mTOR inhibitors to endocrine therapy and HER2-targeted therapy in HR+, HER2+ ABC; Mayer, et al are investigating the combination of an α-specific PI3K inhibitor BYL719 plus letrozole and trastuzumab (NCT01791478) and Wheler, et al are evaluating everolimus plus letrozole and trastuzumab (NCT02152943) in patients with HER2+, ER+ ABC. Further investigation of these compounds in the HR– subpopulation is also of interest.

Panel: research in context (Lancet Oncology requirement)

Evidence before this study

Based on PubMed search using the terms "HER2" and either "advanced breast cancer" or "metastatic breast cancer" and "first-line", full text original articles published up to January, 2015 were identified. The review was restricted to phase II and phase III prospective trials reporting progression-free survival (PFS) irrespective of whether it was a primary or secondary objective. Twelve relevant randomized clinical trials (RCTs) and 17 single-arm trials were identified including 12 trials which reported time to progression (TTP) instead of PFS (List of trials included in the systematic review are available in Appendix). Treatment options included single agent HER2-targeted regimens, targeted therapy plus chemotherapy, and TRAS-containing triple regimen with chemotherapy and a targeted agent. Median PFS for all first-line treatment regimens tested in HER2+ ABC ranged between 3.4 months and 20 months. For single agent HER2-targeted regimens, PFS ranged between 3.4 months and 14.2 months; for targeted therapy plus chemotherapy, between 5.6 months and 20 months and for trastuzumab plus chemotherapy and targeted agent, between 9.9 months and 18.7 months. Four trials presented exploratory efficacy data in patients with HR−, HER2+ ABC; treatment regimens included pertuzumab/vinorelbine/capecitabine plus trastuzumab and docetaxel or doxorubicin plus trastuzumab and paclitaxel which led to reduction in the risk of disease progression by 13%−43%. Only two of these trials presented exploratory PFS data; capecitabine plus trastuzumab and docetaxel did not show any benefit in HR− patients (15.2 months vs 14.6 months), while a more recent study reported a PFS benefit of 6.7 months with a non-pegylated liposomal doxorubicin plus trastuzumab and paclitaxel therapy vs trastuzumab and paclitaxel (20.7 months vs 14.0 months; p=0.042). BOLERO-1 is the first RCT to evaluate mTOR inhibitor everolimus, a non-HER2-targeted agent, in this setting. Comparisons drawn across different trials should be interpreted with caution, as there was a high degree of heterogeneity in study designs and patient populations.

Added value of this study

To our knowledge, the present BOLERO-1 study is the first phase 3 trial to systematically and prospectively evaluate the efficacy of adding everolimus to a trastuzumab-taxane chemotherapy regimen as first-line therapy in patients with HR−, HER2+ ABC. The everolimus plus trastuzumab and paclitaxel combination therapy prolonged median PFS to 20.3 months (difference with PBO arm: 7.2 months), though this did not cross our pre-specified threshold of statistical significance. Furthermore, the PBO arm showed a median PFS of 13.1 months which was similar to that reported in other published studies evaluating HER2-targeted therapy plus chemotherapy. This validates the choice of the trastuzumab plus paclitaxel combination therapy as the comparator arm.

Implications of all the available data

Taken together with BOLERO-3 data, these observations from BOLERO-1 suggest that the addition of everolimus to trastuzumab and paclitaxel may provide clinical benefit as first-line therapy in patients with HR−, HER2+ ABC. Proactive monitoring and early management of AEs are warranted in patients receiving this combination regimen.

Contributors

Sara A Hurvitz was responsible for designing the study, patient accrual, clinical care, data collection, data interpretation, drafting, revising, final review and approval of the manuscript
Fabrice Andre was responsible for patient accrual, data interpretation, drafting, revising, final review and approval of the manuscript
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Dennis Slamon was responsible for designing the study, data interpretation, drafting, revising, final review and approval of the manuscript.

Declarations of interests

Sara A Hurvitz reports grants from Novartis during the conduct of the study, grants, personal fees and travel reimbursement from Genentech, Boehringer Ingelheim and Novartis, grants from GSK, PUMA Biotech outside the submitted work.

Fabrice Andre reports grants from Novartis during the conduct of the study and personal fees from Novartis outside the submitted work.

Max S Mano reports grants from Novartis outside the submitted work for lectures, advisory boards and educational activities.

Zefei Jiang, Zhimin Shao, Silvia P Neciosup, Ling-Min Tseng, Qingyuan Zhang, Kunwei Shen, Donggeng Liu declare that they has no competing interests.

Lydia M Dreosti reports personal fees, honoraria for advisory board and congress sponsorship from Novartis, Roche and Pfizer, honoraria for advisory board from Amgen and congress sponsorship from Merck outside the submitted work.

Howard A Burris declares that he has no competing interests.

Masakazu Toi reports research funding from Novartis outside the submitted work.

Marc E Buyse is an employee and shareholder of IDDI S.A.

David Cabaribere is an employee of TRIO-Global which co-designed the study, and co-performed data management and safety monitoring.

Mary-Ann Lindsay is an employee of TRIO-Global which co-designed the study, and co-performed data management and safety monitoring and received grants from Novartis outside the submitted work.

Shantha Rao and Tetiana Taran are employees and stockholders of Novartis Pharmaceutical Corporation.

Lida Bubuteishvili Pacaud is an employee of Novartis Pharmaceutical Corporation.

Dennis Slamon reports grants from Novartis for the submitted work and grants from Genentech/Roche outside the submitted.

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Table and Figure legends

Table 1 Baseline and treatment characteristics (full analysis set and HR– subpopulation)

Characteristic, n (%)	Full Population		HR⁻ subpopulation	
	EVE + TRAS + PAC (N = 480)	PBO + TRAS + PAC (N = 239)	EVE + TRAS + PAC (N = 208)	PBO + TRAS + PAC (N = 103)
Baseline characteristics				
Median age, years (range)	54.0 (23 - 86)	52.0 (19 - 82)	55.5 (29 - 85)	53.0 (24 - 82)
Race				
Caucasian	214 (44.6)	97 (40.6)	95 (45.7)	39 (37.9)
Asian	198 (41.3)	105 (43.9)	85 (40.9)	47 (45.6)
Black	26 (5.4)	12 (5)	11 (5.3)	6 (5.8)
Native American	3 (0.6)	0 (0)	2 (1)	0 (0)
Other	39 (8.1)	25 (10.5)	15 (7.2)	11 (10.7)
ECOG performance status				
0	278 (57.9)	148 (61.9)	126 (60.6)	65 (63.1)
1	202 (42.1)	91 (38.1)	82 (39.4)	38 (36.9)
Extent of disease at study entry				
Locally advanced disease	34 (7.1)	16 (6.7)	17 (8.2)	8 (7.8)
Metastatic disease	446 (92.9)	223 (93.3)	191 (91.8)	95 (92.2)
Hormone receptor status				
HR+ (ER+ and/or PgR+)	271 (56.5)	135 (56.5)	0 (0)	0 (0)
HR– (ER- and PgR-)	208 (43.3)	103 (43.1)	208 (100)	103 (100)
Visceral involvement	338 (70.4)	169 (70.7)	135 (64.9)	72 (69.9)
Lung	217 (45.2)	103 (43.1)	90 (43.3)	42 (40.8)
Liver	117 (36.9)	110 (46.0)	68 (32.7)	50 (48.5)
Lung and liver	72 (15.0)	51 (21.3)	30 (14.4)	21 (20.4)
Bone involvement	210 (43.8)	117 (49.0)	69 (33.2)	46 (44.7)
Prior antineoplastic therapy				
(Neo)adjuvant TRAS	52 (10.8)	26 (10.9)	22 (10.6)	13 (12.6)
(Neo)adjuvant chemotherapy	215 (44.8)	123 (51.5)	81 (38.9)	54 (52.4)

Any taxane	115 (24.0)	64 (26.8)	51 (24.5)	26 (25.2)
Anthracyclines	186 (38.8)	112 (46.9)	71 (34.1)	51 (49.5)
Other chemotherapy	192 (40.0)	110 (46.0)	74 (35.6)	51 (49.5)
Hormonal therapy for HR+ disease	118 (24.6)	56 (23.4)	0 (0)	0 (0)
(Neo)adjuvant	89 (18.5)	48 (20.1)	0 (0)	0 (0)
Metastatic	3 (0.6)	1 (0.4)	0 (0)	0 (0)
Both Neo-/Adjuvant and metastatic	26 (5.4)	7 (2.9)	0 (0)	0 (0)
Radiotherapy	174 (36.3)	98 (41.0)	54 (26.0)	40 (38.8)
Surgery	479 (99.8)	238 (99.6)	208 (100.0)	103 (100.0)

Abbreviations: EVE, everolimus; HR, hormone receptor; PAC, paclitaxel; PBO, placebo; TRAS, trastuzumab.

Table 2 Locally assessed best overall response (full analysis set and HR– subpopulation)

Best Overall Response, , n (%)	Full Population		HR⁻ subpopulation	
	EVE + TRAS + PAC (N = 480)	**PBO + TRAS + PAC (N = 239)**	**EVE + TRAS + PAC (N = 208)**	**PBO + TRAS + PAC (N = 103)**
CR	27 (5.6)	14 (5.9)	16 (7.7)	3 (2.9)
PR	295 (61.5)	151 (63.2)	136 (65.4)	70 (68.0)
SD	104 (21.7)	55 (23.0)	36 (17.3)	23 (22.3)
PD	16 (3.3)	11 (4.6)	3 (1.4)	6 (5.8)
Unknown	38 (7.9)	8 (3.3)	17 (8.2)	1 (1.0)
ORR [CR or PR] (95% CI)	322 (67.1) [62.7 - 71.3]	165 (69.0) [62.8 - 74.8]	152 (73.1) [66.5 - 79.0]	73 (70.9) [61.1 - 79.4]
CBR [CR or PR or SD ≥ 24 wks] (95% CI)	364 (75.8) [71.7 - 79.6]	194 (81.2) [75.6 - 85.9]	164 (78.8) [72.7 - 84.2]	82 (79.6) [70.5 - 86.9]

Abbreviations: CBR, clinical benefit rate; CR, complete response; EVE, everolimus; HR, hormone receptor; OR, overall response; ORR, objective response rate; PAC, paclitaxel; PBO, placebo; PD, progressive disease; PR, partial response; SD, stable disease; TRAS, trastuzumab.

Table 3 Median relative dose intensities and dose interruption and/or reduction (full analysis set and HR– subpopulation)

	Full Population		HR⁻ subpopulation	
	EVE + TRAS + PAC (N = 472)	**PBO + TRAS + PAC (N = 238)**	**EVE + TRAS + PAC (N = 206)**	**PBO + TRAS + PAC (N = 103)**
Median relative dose intensity, %				
Everolimus	0.54	0.96	0.53	0.95
Trastuzumab	0.96	0.97	0.97	0.96
Paclitaxel	0.70	0.81	0.70	0.81
Dose interruption and/or reduction, n (%)	406 (86.0)	175 (73.5)	176 (85.4)	76 (73.8)

Abbreviations: EVE, everolimus; HR, hormone receptor; PAC, paclitaxel; PBO, placebo; TRAS, trastuzumab..

Table 4 **Adverse events of ≥10% incidence in either treatment group or grade 3, 4 AEs of ≥0.5% incidence in either treatment group (Safety set)**

Preferred term	EVE+TRAS+PAC			EVE+TRAS+PAC		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Stomatitis	255 (54.0)	59 (12.5)		74 (31.1)	3 (1.3)	
Diarrhea	224 (47.5)	43 (9.1)		101 (42.4)	10 (4.2)	
Alopecia	220 (46.6)	1 (0.2)		125 (52.5)		
Rash	187 (39.6)	3 (0.6)		48 (20.2)	1 (0.4)	
Cough	187 (39.6)	2 (0.4)		76 (31.9)	2 (0.8)	
Pyrexia	177 (37.5)	7 (1.5)		60 (25.2)	3 (1.3)	
Neutropenia	60 (12.7)	100 (21.2)	17 (3.6)	24 (10.1)	25 (10.5)	10 (4.2)
Fatigue	143 (30.3)	23 (4.9)		79 (33.2)	6 (2.5)	
Epistaxis	157 (33.3)			42 (17.6)		
Edema peripheral	152 (32.2)	4 (0.8)		57 (23.9)	1 (0.4)	
Nausea	150 (31.8)	4 (0.8)		80 (33.6)	2 (0.8)	
Anemia	100 (21.2)	40 (8.5)	6 (1.3)	32 (13.4)	6 (2.5)	
Neuropathy peripheral	118 (25.0)	18 (3.8)		47 (19.7)	11 (4.6)	
Headache	128 (27.1)	3 (0.6)		67 (28.2)	2 (0.8)	
Vomiting	116 (24.6)	5 (1.1)		49 (20.6)	6 (2.5)	
Dyspnea	97 (20.6)	16 (3.4)	2 (0.4)	22 (9.2)	2 (0.8)	
Decreased appetite	104 (22.0)	6 (1.3)		35 (14.7)		
Constipation	101 (21.4)			50 (21.0)		
Weight decreased	92 (19.5)	7 (1.5)		12 (5.0)		

Alanine aminotransferase increased	70 (14.8)	28 (5.9)		32 (13.4)	11 (4.6)	1 (0.4)
Asthenia	84 (17.8)	8 (1.7)		39 (16.4)	2 (0.8)	
Nasopharyngitis	88 (18.6)			45 (18.9)	2 (0.8)	
Hypercholesterolemia	82 (17.4)	5 (1.1)		23 (9.7)		
Pain in extremity	79 (16.7)	5 (1.1)	1 (0.2)	38 (16.0)		
Arthralgia	76 (16.1)	4 (0.8)		39 (16.4)	2 (0.8)	
Insomnia	77 (16.3)			39 (16.4)		
Myalgia	77 (16.3)			44 (18.5)	1 (0.4)	
Pneumonitis	54 (11.4)	19 (4.0)	4 (0.8)	9 (3.8)	1 (0.4)	
Aspartate aminotransferase increased	56 (11.9)	16 (3.4)	2 (0.4)	21 (8.8)	5 (2.1)	1 (0.4)
Dizziness	69 (14.6)	4 (0.8)	1 (0.2)	34 (14.3)	2 (0.8)	
Oropharyngeal pain	74 (15.7)			31 (13.0)		
Back pain	67 (14.2)	5 (1.1)		36 (15.1)	5 (2.1)	
Leukopenia	42 (8.9)	28 (5.9)	2 (0.4)	13 (5.5)	10 (4.2)	1 (0.4)
Abdominal pain	67 (14.2)	4 (0.8)		29 (12.2)		
Hypertension	60 (12.7)	11 (2.3)		22 (9.2)	4 (1.7)	
Hypokalemia	31 (6.6)	30 (6.4)	7 (1.5)	5 (2.1)	3 (1.3)	
Nail disorder	65 (13.8)	3 (0.6)		24 (10.1)	3 (1.3)	
Hypertriglyceridemia	52 (11.0)	13 (2.8)	2 (0.4)	13 (5.5)	4 (1.7)	
Upper respiratory tract infection	62 (13.1)	4 (0.8)		32 (13.4)	1 (0.4)	
Pruritus	62 (13.1)	2 (0.4)		24 (10.1)		
Peripheral sensory neuropathy	60 (12.7)	3 (0.6)		34 (14.3)	2 (0.8)	
Hyperglycemia	33 (7.0)	25 (5.3)	4 (0.8)	10 (4.2)	3 (1.3)	

Hypoesthesia	55 (11.7)	6 (1.3)		33 (13.9)	2 (0.8)	
Mouth ulceration	56 (11.9)	4 (0.8)		13 (5.5)		
Urinary tract infection	55 (11.7)	5 (1.1)		17 (7.1)		
Dysgeusia	59 (12.5)			24 (10.1)		
Abdominal pain upper	54 (11.4)			26 (10.9)		
Dyspepsia	50 (10.6)			25 (10.5)	1 (0.4)	
Erythema	46 (9.7)	3 (0.6)		16 (6.7)		
Thrombocytopenia	38 (8.1)	5 (1.1)	4 (0.8)	6 (2.5)		
Pneumonia	32 (6.8)	11 (2.3)	2 (0.4)	10 (4.2)		
Neutrophil count decreased	14 (3.0)	23 (4.9)	7 (1.5)	8 (3.4)	13 (5.5)	2 (0.8)
Hemoglobin decreased	27 (5.7)	13 (2.8)	1 (0.2)	8 (3.4)		
Neurotoxicity	40 (8.5)			23 (9.7)	1 (0.4)	
Paraesthesia	33 (7.0)	2 (0.4)		24 (10.1)	1 (0.4)	
Hemorrhoids	31 (6.6)	3 (0.6)		7 (2.9)		
Left ventricular dysfunction	29 (6.1)	4 (0.8)		9 (3.8)	1 (0.4)	
White blood cell count decreased	11 (2.3)	21 (4.4)	1 (0.2)	6 (2.5)	8 (3.4)	
Cellulitis	25 (5.3)	5 (1.1)		6 (2.5)	2 (0.8)	
Bone pain	26 (5.5)	3 (0.6)		13 (5.5)		
Hypocalcaemia	19 (4.0)	4 (0.8)	3 (0.6)	3 (1.3)	1 (0.4)	
Aphthous stomatitis	19 (4.0)	6 (1.3)		4 (1.7)		
Gastritis	21 (4.4)	3 (0.6)		8 (3.4)		
Oral pain	18 (3.8)	5 (1.1)		3 (1.3)		
Interstitial lung disease	13 (2.8)	8 (1.7)		1 (0.4)		
Dehydration	12 (2.5)	8 (1.7)		4 (1.7)		
Drug hypersensitivity	18 (3.8)	2 (0.4)		4 (1.7)	2 (0.8)	

Blood triglycerides increased	13 (2.8)	4 (0.8)	2 (0.4)	1 (0.4)		1 (0.4)
Gamma-glutamyltransferase increased	8 (1.7)	11 (2.3)		3 (1.3)	2 (0.8)	
Weight increased	16 (3.4)	2 (0.4)		25 (10.5)	1 (0.4)	
Lymphopenia	10 (2.1)	4 (0.8)	3 (0.6)	2 (0.8)	1 (0.4)	1 (0.4)
White blood cell count	7 (1.5)	8 (1.7)		5 (2.1)	3 (1.3)	
Device related infection	5 (1.1)	9 (1.9)		2 (0.8)	2 (0.8)	
Hepatic enzyme increased	12 (2.5)	2 (0.4)		4 (1.7)	2 (0.8)	
Hemoglobin	6 (1.3)	7 (1.5)		1 (0.4)		
Gingivitis	8 (1.7)	1 (0.2)		3 (1.3)	2 (0.8)	
Hyponatremia	2 (0.4)	6 (1.3)	1 (0.2)		1 (0.4)	
Febrile neutropenia	1 (0.2)	5 (1.1)	2 (0.4)			1 (0.4)
Hypoalbuminemia	5 (1.1)	3 (0.6)			1 (0.4)	
Infusion related reaction	6 (1.3)	1 (0.2)		3 (1.3)	3 (1.3)	
Lethargy	4 (0.8)	3 (0.6)		4 (1.7)	2 (0.8)	
Respiratory failure	1 (0.2)	1 (0.2)	5 (1.1)			1 (0.4)
Blood potassium decreased	5 (1.1)	1 (0.2)			3 (1.3)	
Cataract	3 (0.6)	2 (0.4)	1 (0.2)	2 (0.8)		
Renal failure acute		6 (1.3)			1 (0.4)	
Sepsis		2 (0.4)	4 (0.8)	1 (0.4)		
Hyperkalemia	2 (0.4)	3 (0.6)		1 (0.4)	1 (0.4)	
Hypophosphatemia	2 (0.4)	1 (0.2)	2 (0.4)			
Syncope	1 (0.2)	3 (0.6)	1 (0.2)			
Bronchopneumonia	1 (0.2)	3 (0.6)				
Hepatic function abnormal	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.4)		

Viral infection	1 (0.2)	3 (0.6)		1 (0.4)
Pneumocystis jirovecii pneumonia		2 (0.4)	1 (0.2)	
Hypersomnia	2 (0.4)			2 (0.8)

Abbreviations: EVE, everolimus; HR, hormone receptor; PAC, paclitaxel; PBO, placebo; TRAS, trastuzumab.

Table 5 On-treatment deaths at data cut-off date (May 30, 2014) [Safety set]

Characteristic	Full Population		HR– subpopulation	
	EVE + TRAS + PAC (N = 472) n (%)	**PBO + TRAS + PAC (N = 238) n (%)**	**EVE + TRAS + PAC (N = 206) n (%)**	**PBO + TRAS + PAC (N = 103) n (%)**
On-treatment deaths	22 (4.7)	2 (0.8)	7 (3.4)	2 (1.9)
Due to disease progression	5 (1.1)	2 (0.8)	1 (0.5)	2 (1.9)
Due to AE	17 (3.6)	0 (0)	6 (2.9)	0 (0)
Pneumonitis	3 (0.6)	0 (0)	1 (0.5)	0 (0)
Pulmonary embolism	2 (0.4)	0 (0)	0 (0)	0 (0)
Respiratory failure	2 (0.4)	0 (0)	2 (1)	0 (0)
Pulmonary edema	1 (0.2)	0 (0)	0 (0)	0 (0)
Pneumonia	2 (0.4)	0 (0)	1 (0.5)	0 (0)
Cardio-respiratory arrest	1 (0.2)	0 (0)	0 (0)	0 (0)
Sepsis	3 (0.6)	0 (0)	1 (0.5)	0 (0)
Fall	1 (0.2)	0 (0)	1 (0.5)	0 (0)
Diabetes	1 (0.2)	0 (0)	0 (0)	0 (0)
Cerebrovascular accident	1 (0.2)	0 (0)	0 (0)	0 (0)

Abbreviations: EVE, everolimus; PAC, paclitaxel; PBO, placebo; TRAS, trastuzumab.

Figure 1 Trial profile

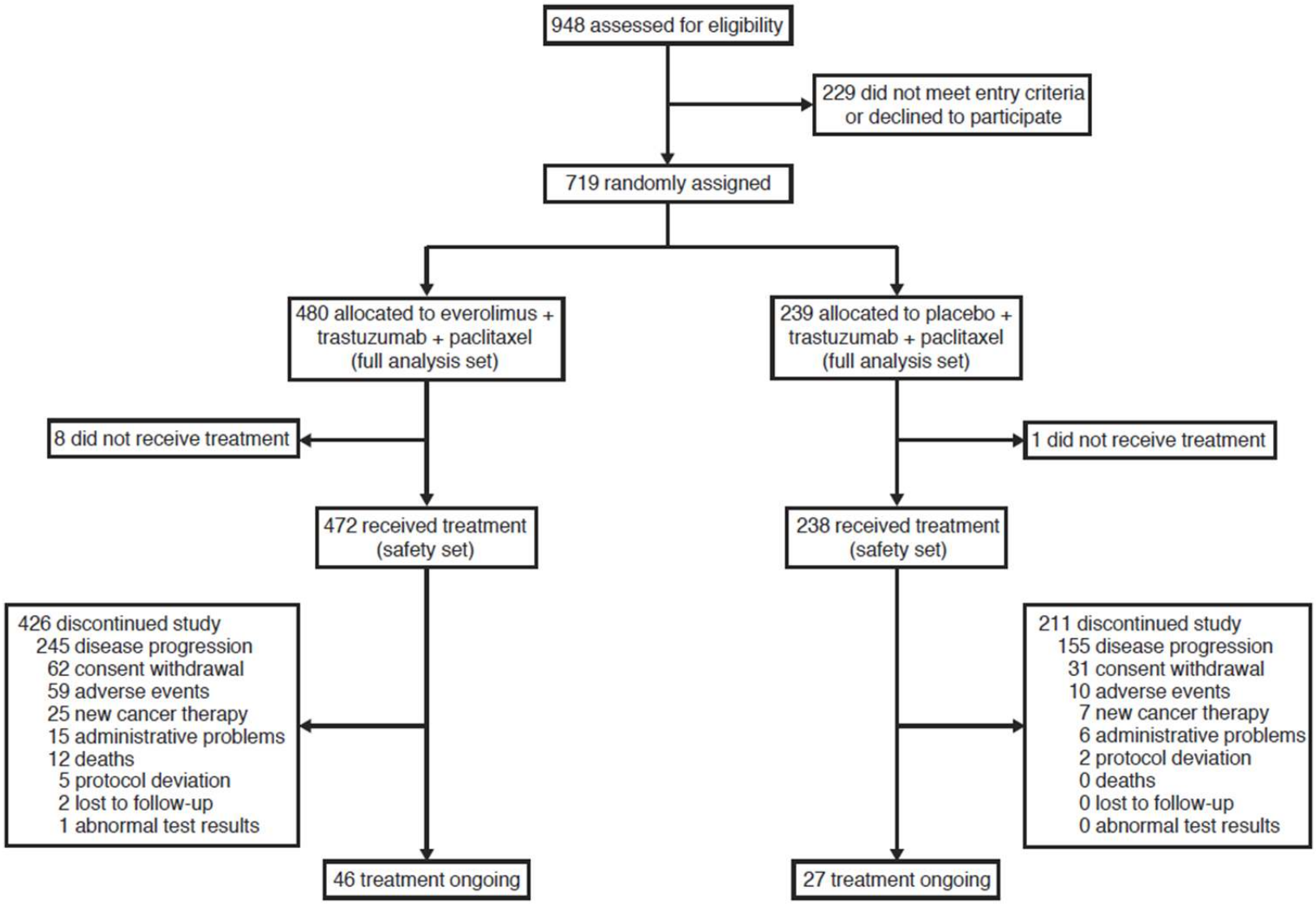
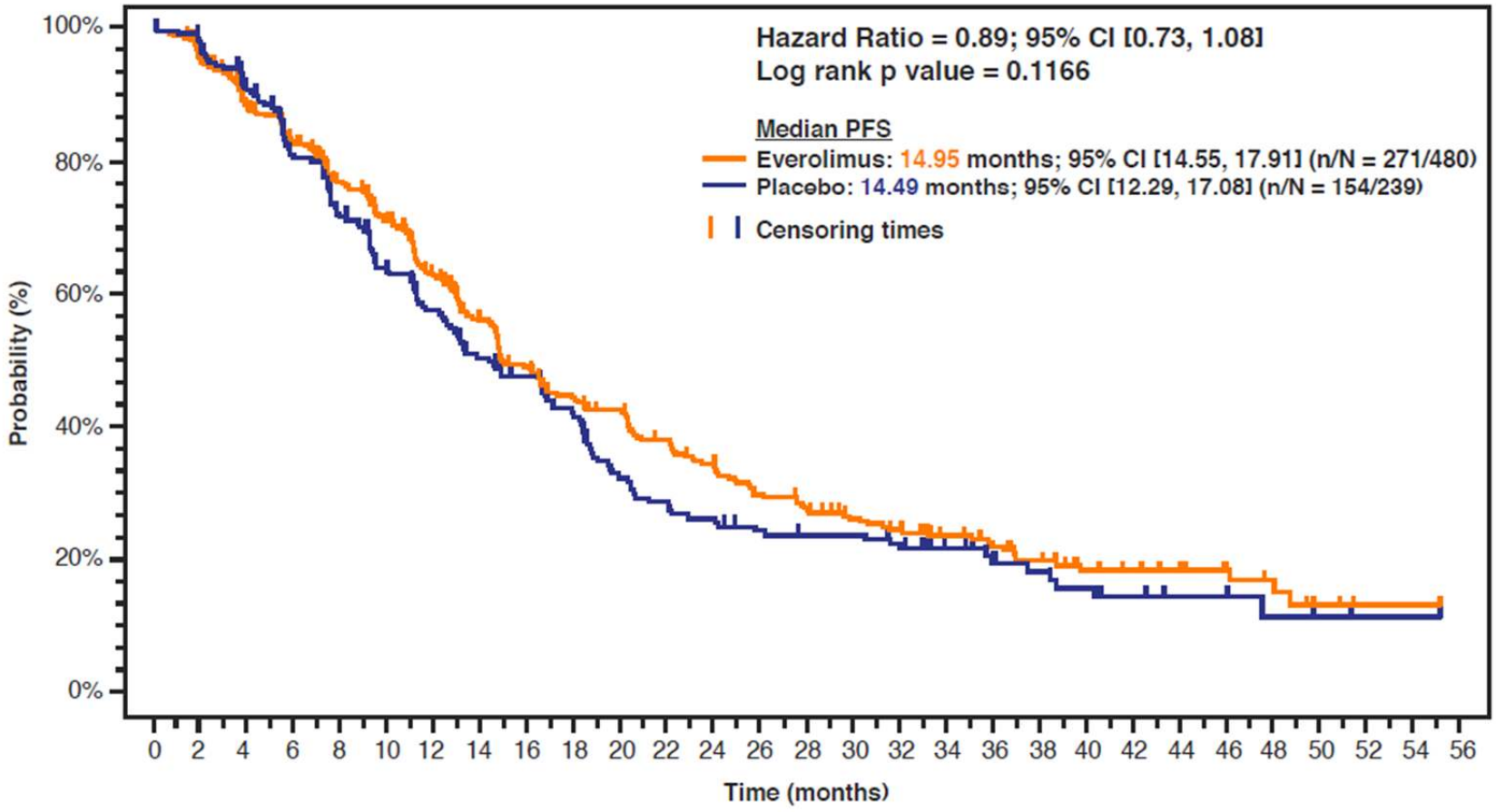


Figure 2 Kaplan-Meier curves for progression-free survival (full analysis set)

(A) Local assessment



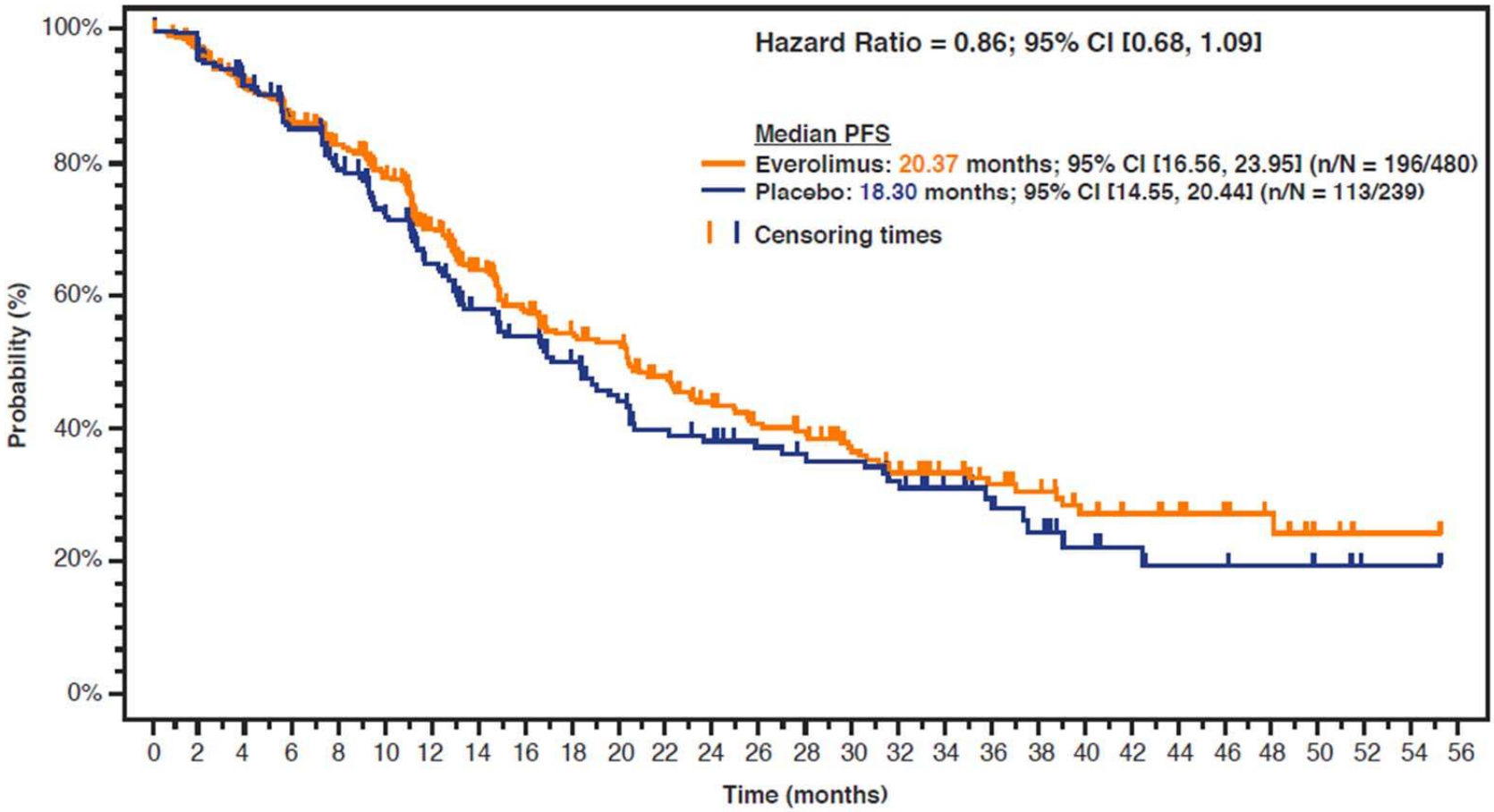
No. of patients still at risk

Everolimus	480	416	365	324	289	260	217	178	151	130	122	107	94	80	72	63	58	48	42	35	26	21	17	13	10	5	3	3	0
Placebo	239	221	199	166	144	123	106	91	80	69	53	47	43	38	36	36	31	24	17	15	12	9	7	6	4	3	1	1	0

-One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

Figure 2 Kaplan-Meier curves for progression-free survival (full analysis set)

(B) Central assessment

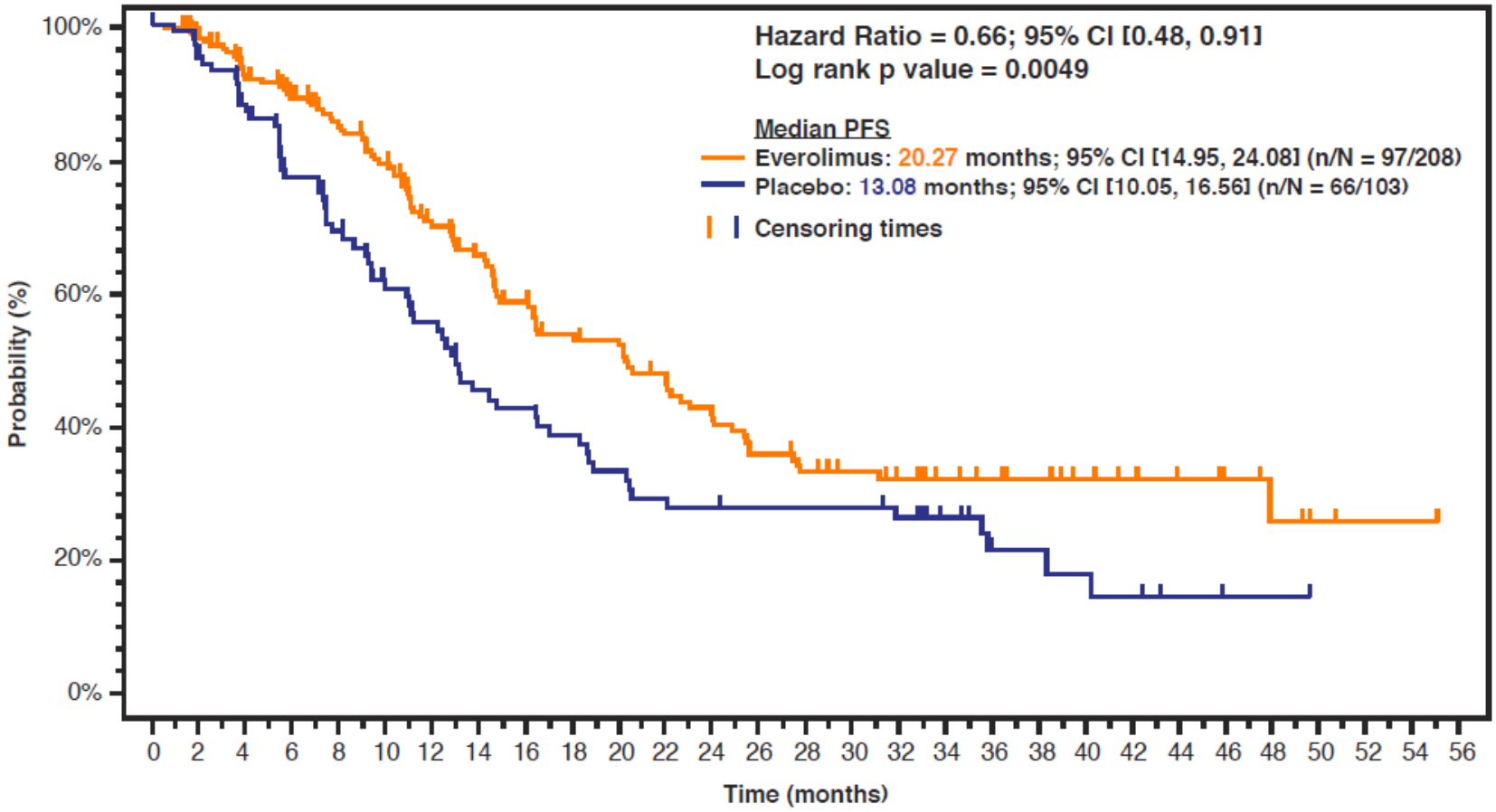


No. of patients still at risk

Everolimus	480	406	352	309	281	252	208	168	140	123	117	100	84	74	68	57	50	40	35	31	24	18	15	11	9	5	3	3	0
Placebo	239	212	189	158	138	120	97	82	73	63	53	46	43	38	35	35	29	23	17	14	10	8	6	6	5	4	1	1	0

Figure 3 Kaplan-Meier curves for progression-free survival (HR– subpopulation)

(A) Local assessment



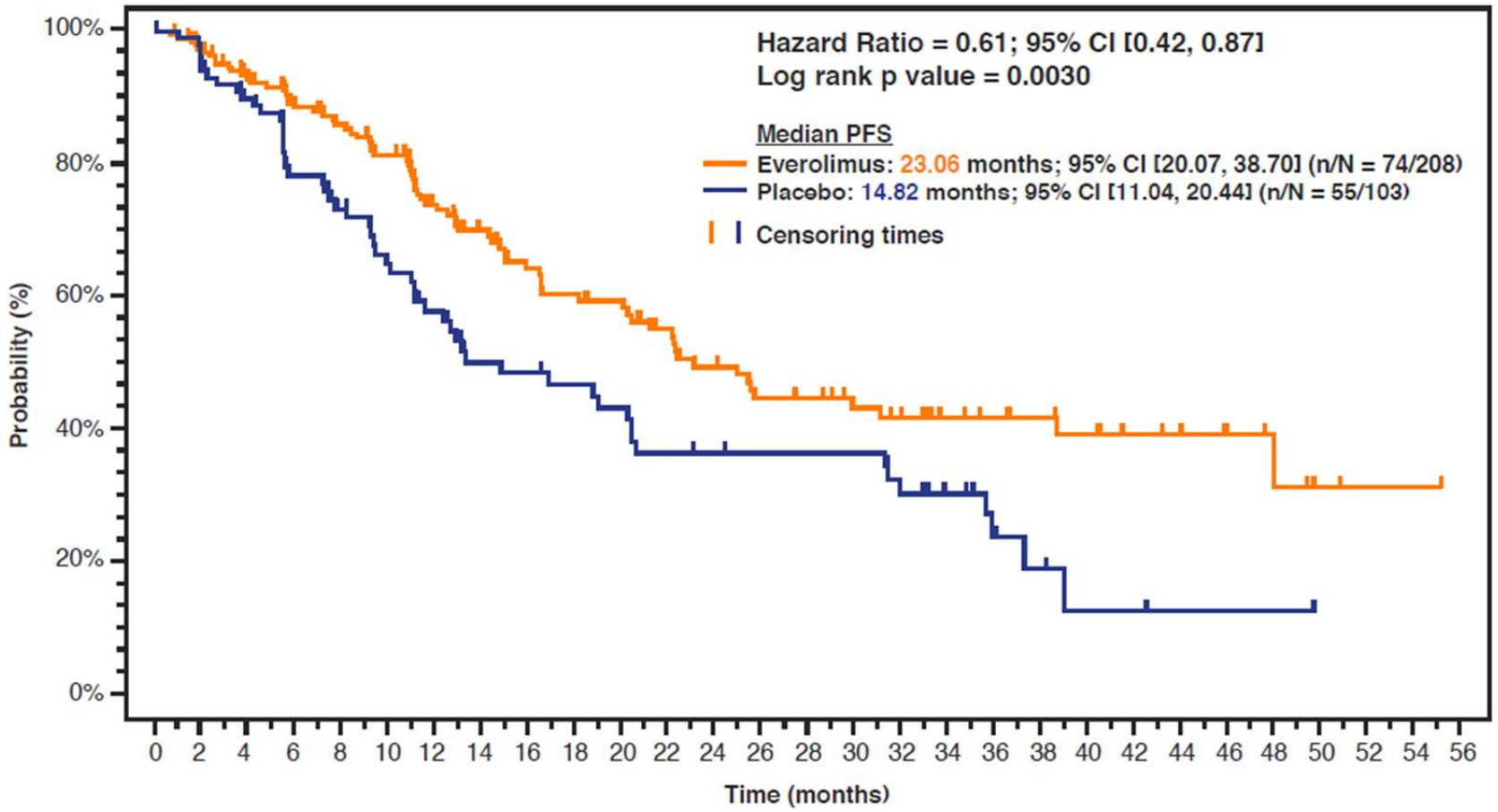
No. of patients still at risk

Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

-One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

Figure 3 Kaplan-Meier curves for progression-free survival (HR– subpopulation)

(B) Central assessment



No. of patients still at risk

Everolimus	208	174	156	139	131	118	96	78	65	60	57	49	42	36	34	30	28	22	20	18	15	10	9	6	5	2	1	1	0
Placebo	103	93	81	63	55	46	39	31	30	27	25	21	20	19	19	19	15	12	6	4	2	2	1	1	1	0	0	0	0

SUPPLEMENTARY MATERIAL TO BE MADE AVAILABLE ONLINE:

Inclusion/exclusion criteria

Women aged 18 years or older with HER2+ (IHC 3+ or FISH+), histologically or cytologically confirmed invasive locally recurrent or radiologically confirmed metastatic breast cancer were eligible to participate. Patients must have had measurable disease or bone lesions (lytic or mixed) as defined by RECIST criteria and an ECOG performance status ≤ 1. Patients were required to have normal laboratory parameters and a LVEF value ≥LLN. No prior systemic therapy for advanced disease was allowed, except endocrine therapy, which must have been discontinued due to disease progression before randomization. Prior neo(adjuvant) trastuzumab and chemotherapy must have been discontinued at least 12 months prior to randomization. Patients were excluded if they had previously received an mTOR inhibitor or had only non-measurable lesions, had a history of CNS metastasis, or if they had inadequate liver, renal, GI, cardiac or bone marrow functions.

Supplementary Table 1 Pneumonitis management guidelines

Worst grade pneumonitis	**Required investigations**	**Management of pneumonitis**	**Required dose adjustment**
Grade 1 Asymptomatic, radiographic findings only	CT scans with lung windows Repeat every 2 cycles until return to normal limits.	No specific therapy is required.	Administer 100% of protocol treatment dose.
Grade 2 Symptomatic, not interfering with ADL	CT scan with lung windows. Consider pulmonary function testing.[1] Repeat every other cycle until return to normal limits. Consider a bronchoscopy with biopsy and/or BAL[3].	Symptomatic only. Consider corticosteroids[2] if symptoms are troublesome.	**Everolimus:** Reduce Everolimus dose by 1 dose level until recovery to ≤ Grade 1. Everolimus administration may also be interrupted if symptoms are to be considered important. Patients will discontinue everolimus if they fail to improve to ≤ Grade 1 within 3 weeks. **Paclitaxel:** Hold until improvement to grade ≤ 1. Reintroduce at same dose level.
Grade 3 Symptomatic, interfering with ADL; O2 indicated	CT scan with lung windows and pulmonary function testing.[1] Repeat every cycle until return to within normal limits. Bronchoscopy with biopsy and / or BAL[3] is recommended.	Short course of corticosteroids[2] to be considered if infective origin is ruled out.	**Everolimus** Hold Everolimus treatment until improvement to ≤ Grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit. **Trastuzumab:** Hold until improvement to grade ≤ 1. **Paclitaxel:** Hold until improvement to grade ≤ 1. Reintroduce at same dose level.
Grade 4 Life-threatening; ventilatory support indicated	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 2 cycles until return to within normal limits. Bronchoscopy with biopsy and / or BAL[3] is recommended if possible.	Short course of corticosteroids[2] to be considered if infective origin is ruled out.	Discontinue protocol treatments.

[1] PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation
Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O2

saturation ≤ 88% at rest on room air.
[2] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.
[3] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.

Supplementary Table 2 Unmet eligibility criteria (Full analysis set)

Unmet eligibility criteria	**EVE+TRAS+PAC N=480 n**	**PBO+TRAS+PAC N=239 n**
Unmet inclusion criteria		
Unconfirmed locally recurrent or metastatic breast cancer	2	1
Unconfirmed measurable disease or bone lesion status per RECIST	2	1
Unconfirmed HER2+ status of tumor	1	1
Received prior (neo)adjuvant trastuzumab or trastuzumab+chemotherapy <12 months prior to randomization	1	0
Pregnancy test not done within 7 days prior to randomization	6	5
Hematology and biochemistry parameters out of pre-specified range within 21 days prior to randomization	2	2
LVEF assessment not performed within 4 weeks prior to randomization	1	0
Unmet exclusion criteria		
Patient either received anti-cancer therapy other than hormone therapy or experienced disease recurrence within 12 months after the end of trastuzumab+chemotherapy	3	5
Patient had a history of CNS metastasis	1	0

Sensitivity analysis of PFS

The following sensitivity PFS analyses were performed to address the impact of missing/unknown tumor assessments and to assess the impact of censoring due to another anti-neoplastic therapy.

Analyses of PFS as per investigator assessment for Full population

			Median PFS (months) 95% CI	
Sensitivity analysis	**p-value***	**Hazard ratio [95% CI]**	**EVE+TRAS+PAC N=480**	**PBO+TRAS+PAC N=239**
Primary Analysis	0.1166	0.89 [0.73 ,1.08]	14.95 [14.55 ,17.91]	14.49 [12.29 ,17.08]
Unstratified log rank test and Cox model	0.1140	0.89 [0.73 ,1.08]	14.95 [14.55 ,17.91]	14.49 [12.29 ,17.08]
Stratified Cox model adjusting for baseline covariates a	0.1036	0.88 [0.72 ,1.07]	14.95 [14.55 ,17.91]	14.49 [12.29 ,17.08]
Including the event whenever it occurred even after ≥2 missing tumor assessments	0.1392	0.9 [0.74 ,1.09]	16.13 [14.65 ,17.94]	14.29 [12.42 ,17.08]
Used the date of the next scheduled assessment for events occurring after ≥1 missing assessment	0.2272	0.93 [0.76 ,1.13]	14.75 [13.14 ,16.53]	13.80 [11.60 ,16.85]
By not censoring patients at start of new antineoplastic therapy	0.1142	0.89 [0.73 ,1.08]	14.78 [14.39 ,17.22]	14.49 [12.29 ,17.87]

***** All p-values are from log rank test except for stratified Cox model adjusting for baseline covariates where p-value is from Cox model

Analyses of PFS as per investigator assessment for HR– population

Sensitivity analysis	p-value*	Hazard ratio [95% CI]	Median PFS (months) 95% CI EVE+TRAS+PAC N=208	Median PFS (months) 95% CI PBO+TRAS+PAC N=103
Primary Analysis	0.0049	0.66 [0.48 ,0.91]	20.27 [14.95 ,24.08]	13.08 [10.05 ,16.56]
Unstratified log rank test and Cox model	0.0031	0.65 [0.47 ,0.89]	20.27 [14.95 ,24.08]	13.08 [10.05 ,16.56]
Stratified Cox model adjusting for baseline covariates a	0.0072	0.67 [0.48 ,0.92]	20.27 [14.95 ,24.08]	13.08 [10.05 ,16.56]
Including the event whenever it occurred even after ≥2 missing tumor assessments	0.0091	0.69 [0.51 ,0.94]	20.07 [16.33 ,22.47]	13.08 [10.05 ,17.05]
Used the date of the next scheduled assessment for events occurring after ≥1 missing assessment	0.0261	0.74 [0.54 ,1]	17.97 [14.72 ,22.11]	12.88 [9.46 ,16.56]
By not censoring patients at start of new antineoplastic therapy	0.0043	0.66 [0.48 ,0.9]	20.27 [14.82 ,24.08]	12.88 [10.94 ,16.56]

***** All p-values are from log rank test except for stratified Cox model adjusting for baseline covariates where p-value is from Cox model

Supplementary Table 3 Antineoplastic therapy since discontinuation of study treatment (Full analysis set)

Antineoplastic therapy since discontinuation of study treatment	EVE+TRAS+PAC N=480 n (%)	PBO+TRAS+PAC N=239 n (%)
Monoclonal antibodies	131 (27.3)	71 (29.7)
Chemotherapy		
Pyrimidine analogues	94 (19.6)	55 (23.0)
Vinca alkaloids and analogues	54 (11.3)	32 (13.4)
Taxanes	37 (7.7)	20 (8.4)
Anthracyclines	28 (5.8)	19 (7.9)
Nitrogen mustard analogues	32 (6.7)	15 (6.3)
Platinum compounds	14 (2.9)	9 (3.8)
Other chemotherapies	7 (1.5)	1 (0.4)
Protein kinase inhibitors	51 (10.6)	34 (14.2)
Hormonal therapy		
Anti-estrogens	26 (5.4)	10 (4.2)
Aromatase inhibitors	26 (5.4)	26 (10.9)
Gonadotropin releasing hormone analogues	4 (0.8)	3 (1.3)
Progestogens	1 (0.2)	1 (0.4)
Surgery/radiotherapy/other non-drug procedures	88 (18.3)	55 (23.0)
Other therapeutic products	9 (1.9)	9 (3.8)
Folic acid analogues	7 (1.5)	1 (0.4)
Other systemic antipsoriatics	7 (1.5)	1 (0.4)
Other gyneacologicals	7 (1.5)	1 (0.4)
Other immunosuppresants	7 (1.5)	1 (0.4)
Other specific antirheumatic agents	7 (1.5)	1 (0.4)
Other antineoplastic agents	1 (0.2)	1 (0.4)
Appetite stimulants	1 (0.2)	1 (0.4)
Other cytotoxic antibiotics	3 (0.6)	0 (0)
Selective immunosuppressants	2 (0.4)	0 (0)
Pregnadiene derivatives	1 (0.2)	1 (0.4)
Antimetabolites	0 (0)	1 (0.4)
Antineoplastic agents	0 (0)	1 (0.4)
Unspecified herbal and traditional medicine	0 (0)	1 (0.4)

Study site details

Center Country	Center Number	Investigator (PI) First name	Investigator (PI) Last name	Center Name	No. of Pts Enrolled
Peru	0192	Silvia	Neciosup	Instituto Nacional de Enfermedades Neoplasicas	25
China	0781	Zhi-Min	Shao	Cancer Hospital of Fudan University	25
Brazil	0127	Max	Mano	Instituto do Câncer de São Paulo Octávio Frias de Oliveira	23
Taiwan	0917	Ling-Ming	Tseng	Taipei Veterans General Hospital	22
China	0790	Qingyuan	Zhang	Tumor Hospital of Harbin Medical University	20
China	0783	Kunwei	Shen	Ruijin Hospital Shanghai Jiao Tong Univ. School of Medicine	19
China	0787	Donggeng	Liu	Sun Yat-san University Cancer Center	19
France	0320	Fabrice	André	Institut Gustave Roussy	18
China	0785	Zefei	Jiang	307 Hospital of PLA	18
South Africa	0875	Lydia	Dreosti	Steve Biko & Pretoria Academic Hospital	18
China	0780	Binghe	Xu	Cancer hospital, Chinese Academy of Medical Sciences	16
China	0782	Jifeng	Feng	Jiangsu Province Cancer Hospital	16
China	0786	Xiaojia	Wang	Zhejiang Cancer Hospital	16
Korea, Republic of	0831	Jung-Sil	Ro	National Cancer Center	16
Russia	0865	Anatoly	Makhson	Moscow Municipal Hospital No. 62	16
Egypt	0002	Amr	Abdel Aziz	Clinical Research Centre	14
Argentina	0113	Guillermo	Lerzo	Sanatorio de la Providencia	10
Hong Kong	0817	Ting Ying	Ng	Department of Clinical Oncology, Tuen Mun Hospital	10
United States	0580	Beth	Hellerstedt	Texas Oncology, P.A.	9
Italy	0400	Francesco	Nuzzo	IRCCS Fondazione G. Pascale	8
United States	0541	Denise	Yardley	Sarah Cannon Research Institute	8
Korea, Republic of	0834	Joohyuk	Sohn	Severance Hospital	8
Russia	0861	Ludmila	Manzyuk	Russian Cancer Research Centre	8
Italy	0402	Paolo	Bidoli	Nuovo Ospedale S.Gerardo-A.O.S.Gerardo-Univ.Studi Milano	7
United States	0503	Mikhail	Shtivelband	Ironwood Cancer and Research Centers	7
Japan	0705	Hiroji	Iwata	Aichi Cancer Center Hospital	7
Russia	0860	Sergei	Tjulandin	Russian Cancer Research Centre	7
Russia	0862	Rustem	Khasanov	Clinical Oncology Dispensary	7
Taiwan	0915	King-Jen	Chang	National Taiwan University Hospital	7

Egypt	0003	Hamdy	Abdel Azim	ElManial ElGamaei Hospital	6
France	0321	Florence	Dalenc	Institut Claudius Regaud	6
France	0331	Mario	Campone	Centre René Gauducheau	6
United States	0554	Sara	Hurvitz	UCLA/ University of California Los Angeles	6
Ireland	0668	John	Crown	St. Vincents Hospital	6
Korea, Republic of	0833	Younghyuck	Im	Samsung Medical Center	6
Taiwan	0916	Shin-Cheh	Chen	Chang-Gung Memorial Hospital-Linko	6
Argentina	0100	Monica	Rondinon	MIND OUT Research	5
Brazil	0135	Aline	Andrade	Hospital Luxemburgo	5
Colombia	0181	Manuel	Gonzalez	Oncomedica	5
United States	0542	Janice	Eakle	Florida Cancer Specialists	5
Japan	0703	Hirofumi	Mukai	National Cancer Center Hospital East	5
Japan	0714	Norikazu	Masuda	National Hospital Organization Osaka National Hospital	5
Hong Kong	0816	Ava	Kwong	Queen Mary Hospital	5
Korea, Republic of	0832	Yoon Ji	Choi	Korea University Anam Hospital	5
Russia	0864	Vladimir	Semiglazov	N. N. Petrov research Institute of Oncology	5
South Africa	0878	Johann	Jordaan	Westridge Medical Centre	5
South Africa	0882	Michiel	Botha	Department of Oncotherapy	5
Belgium	0962	Luc	Dirix	Sint-Augustinus Ziekenhuis	5
Argentina	0101	Luis	Fein	Centro Oncologico de Rosario	4
Argentina	0110	Beltran	Bosch	Centro Oncologico Integral	4
Argentina	0118	Nora	Mohr	Sanatorio Boratti	4
Brazil	0132	Jose	Bines	Instituto Nacional do Câncer	4
Peru	0191	Roberto	Coello	Instituto Oncologico de Lima	4
France	0324	Francesco	Del Piano	CHI - Les Hôpitaux du Léman	4
France	0330	Dominique	Genet	Clinique François Chénieux	4
United Kingdom	0494	Nicholas	Turner	The Royal Marsden Hospital	4
United States	0506	Joseph	Beck	Highlands Oncology Group	4
United States	0551	William	Lawler	St. Jude Heritage Medical Group	4
United States	0577	John	Pippen	Texas Oncology, P.A.	4
Japan	0704	Yutaka	Tokuda	Tokai University Hospital	4
China	0788	Ning	Liao	Guangdong General Hospital	4
Hong Kong	0815	Wing Ming	Ho	Prince of Wales Hospital	4
Russia	0863	Alexey	Manikhas	City Oncological Dispensary	4
Taiwan	0918	Hwei-Chung	Wang	China Medical University Hospital (Taichung)	4

Taiwan	0919	Ming-Feng	Hou	Kaohsiung Medical University Chang-Ho Memorial Hospital	4
Germany	0935	Thorsten	Kühn	Städt. Kliniken Esslingen	4
Germany	0938	Christoph	Mundhenke	Universitaetsklinikum Kiel	4
Switzerland	0980	Urs	Breitenstein	Onkozentrum Zürich	4
France	0326	Philippe	Gomez	Centre Frédéric Joliot	3
Greece	0432	Meletios	Dimopoulos	Alexandra Peripheral General Hospital	3
United States	0501	Elisabeth	McKeen	Palm Beach Cancer Institute	3
United States	0578	Elsayed	Aly	Central Indiana Cancer Centers	3
United States	0579	Donald	Richards	Tyler Cancer Center	3
Ireland	0666	John	Kennedy	St James Hospital	3
Japan	0706	Hiroshi	Ishiguro	Kyoto University Hospital	3
Japan	0708	Atsushi	Shimomura	Osaka University Hospital	3
Japan	0709	Shinji	Ohno	National Kyushu Cancer Center	3
Japan	0710	Hirotaka	Iwase	Kumamoto University Hospital	3
Australia	0762	Michelle	White	Monash Medical Center Moorabbin	3
Russia	0866	Irina	Selezneva	Central Clinical Hospital #2 n.a. N.A. Semashko	3
Turkey	0903	Erhan	Gokmen	Ege University Medical Faculty Hospital	3
Belgium	0966	Annelore	Barbeaux	CH Peltzer La Tourelle	3
Egypt	0001	Heba	ElZawahry	National Cancer Institute	2
Argentina	0115	Ruben	Kowalyszyn	Clinica Viedma	2
Brazil	0129	Sergio	Simon	Universidade Federal de São Paulo - Núcleo de Pesquisa	2
Venezuela	0202	Nuria	Marrero Chico	Instituto Docente de Urologia	2
Mexico	0252	Flavia	Vasquez	FUCAM	2
France	0325	Jean-Pierre	Bergerat	Hopital de Hautepierre	2
Italy	0403	Francesco	Cognetti	Istituti Fisioterapici Ospitalieri-Polo Oncol. Regina Elena	2
Greece	0436	Dimosthenis	Skarlos	Metropolitan Hospital	2
United Kingdom	0490	Nicholas	Turner	The Royal Marsden Hospital	2
United States	0502	Thomas	Butler	University of South Alabama / Mitchell Cancer Institute	2
United States	0504	Stephen	Malamud	Beth Israel Medical Center	2
United States	0543	Maura	Hagan	Virginia Cancer Institute	2
United States	0555	Ravi	Patel	Comprehensive Blood and Cancer Center	2
United States	0559	Eddie	Hu	Central Hematology Oncology Medical Group	2
United States	0571	Michael	Danso	Virginia Oncology Associates	2
United States	0572	John	Smith	Northwest Cancer Specialists	2

United States	0575	Karen	Tedesco	New York Oncology Hematology, P.C.	2
Canada	0601	Wilson	Miller	McGill University, Dept of Oncology	2
Ireland	0665	Seamus	O'Reilly	Cork University Hospital	2
Japan	0702	Jun	Horiguchi	Gunma University Hospital	2
Japan	0711	Kenichi	Inoue	Saitama Cancer Center Hospital	2
Japan	0712	Hideko	Yamauchi	St Luke's International Hospital	2
Japan	0713	Katsumasa	Kuroi	Tokyo Metropolitan Komagome Hospital	2
Japan	0716	Keisei	Anan	Kitakyushu Municipal Medical Center	2
China	0784	Shukui	Qin	PLA No. 81 Hospital	2
Turkey	0900	Isil	Somali	Dokuz Eylul University Medical Faculty	2
Turkey	0901	Serdar	Turhal	Marmara University Medical Faculty	2
Turkey	0902	Kadri	Altundag	Hacettepe University Medical Faculty	2
Turkey	0904	Berna	Oksuzoglu	Ankara Numune Training and Research Hospital	2
Germany	0936	Petra	Krabisch	Klinikum Chemnitz gGmbH	2
Belgium	0960	Lionel	D'Hondt	Cliniques Universitaires UCL Mont-Godinne	2
Belgium	0965	Jeroen	Mebis	Virga Jesse Ziekenhuis	2
Brazil	0133	Rodrigo	Guimarães	Hospital das Clinicas Universidade Federal de Minas Gerais	1
Colombia	0183	Alexy	(Villadiego) Maza	Fundación Cardiovascular de Colombia	1
Mexico	0250	Manuel	Magallanes	Arké Estudios Clínicos	1
Italy	0401	Gabriele	Luppi	A.O.Univ.Policl.di Modena Univ.Studi Modena e R.Emilia	1
Italy	0404	Fernando	Gaion	Presidio Ospedaliero di Camposampiero	1
Greece	0431	Vassilios	Georgoulias	University General Hospital of Heraklion	1
Greece	0437	George	Fountzilas	Papageorgiou General Hospital of Thessaloniki	1
United Kingdom	0492	Duncan	Wheatley	Royal Cornwall Hospital	1
United States	0513	Luis	Baez-Diaz	University of California San Diego	1
United States	0515	Elizabeth	Reed	University of Nebraska Medical Center	1
United States	0550	Robert	Dichmann	Central Coast Medical Oncology Corporation	1
United States	0553	Frederic	Kass	Santa Barbara Hematolgy Oncology Medical Group	1
United States	0556	Rosemary	McIntyre	Ventura County Hematology and Oncology	1
United States	0573	Richard	McKittrick	Kansas City Cancer Center	1
United States	0574	Devchand	Paul	Rocky Mountain Cancer Centers	1
Canada	0600	Josee-Anne	Roy	Hopital du Sacre-Coeur	1

Canada	0603	Ghislain	Cournoyer	St-Jerome Medical Research Inc.	1
Ireland	0660	Bryan	Hennessy	Cancer Clinical Trials Unit	1
Japan	0701	Hiroko	Yamashita	Hokkaido University Hospital	1
Japan	0707	Hideo	Inaji	Osaka Medical Center for Cancer and Cardiovascular Diseases	1
Australia	0763	Jasotha	Sanmugarajah	Gold Coast Hospital	1
Lebanon	0851	Naji	El-Saghir	American University of Beirut	1
Lebanon	0852	Georges	Chahine	Hotel Dieu de France Hospital	1
Germany	0931	Jan	Eucker	Humboldt-Univ. Charité Campus Mitte	1
Germany	0940	Christian	Lerchenmueller	Onkologische Gem.Praxis Drs. Wehmeyer/Lerchenmueller	1
Belgium	0961	Jean-Luc	Canon	Grand Hôpital de Charleroi	1
Switzerland	0981	Alexandre	Bodmer	Hôpitaux universitaires de Genève	1

List of trials included in the systematic review:

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