Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer

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Abstract

Purpose: To determine the feasible dose and schedule for everolimus, an oral mTOR inhibitor, combined with vinorelbine and trastuzumab for patients with HER2-overexpressing metastatic breast cancer pretreated with trastuzumab.

Methods: In this phase Ib multicenter, Bayesian dose-escalation study, 50 patients received everolimus 5 mg/day, 20 mg/week, or 30 mg/week plus vinorelbine (25 mg/m^2 on day 1 and 8 every 3 weeks) and trastuzumab (2 mg/kg weekly). Endpoints included end-of-cycle-1 dose-limiting toxicity (DLT) rate (primary endpoint), safety, relative dose intensity, overall response rate (ORR), and pharmacokinetics.

Results: Grade 3/4 neutropenia was the most common end-of-cycle-1 DLT and occurred in 10 of 30 and 4 of 14 patients in the 5 mg/day and 30 mg/week cohorts, respectively. Other end-of-cycle-1 DLTs included single cases of febrile neutropenia, grade 3 stomatitis with concomitant fatigue, grade 2 stomatitis, grade 3 anorexia, and grade 2 acneiform dermatitis, all in the 5-mg/day cohort. Based on recorded DLTs and global safety, everolimus 5 mg/day and 30 mg/week were chosen as the optimal dose levels for the daily and weekly arms. Forty-seven patients were evaluable for efficacy. ORR was 19.1%, with a disease control rate of 83.0% and median progression-free survival of 30.7 weeks. No drug interaction was observed between everolimus and vinorelbine.

Conclusion: Everolimus combined with weekly vinorelbine and trastuzumab generally was well tolerated and had encouraging antitumor activity in heavily pretreated patients with HER2-overexpressing metastatic breast cancer that progressed on trastuzumab (NCT00426530).

Introduction

In approximately 14% to 30% of primary breast tumors, the erb-B2 oncogene is amplified, with the percentage of amplification dependent on tumor size and stage, resulting in overexpression of the human epidermal growth factor receptor-2 (HER2) [1, 2]. HER2 activates multiple signal transduction pathways stimulating cell proliferation [2]. Consequently, HER2-overexpressing breast cancer is associated with a poor prognosis [1-3].

Trastuzumab, an anti-HER2 monoclonal antibody, improves outcomes in the metastatic and adjuvant settings [1, 2, 4, 5]. Almost all patients initially responding to trastuzumab become unresponsive [6, 7]. However, patients failing first-line therapy with taxanes and trastuzumab have responded to the combination of capecitabine and trastuzumab or lapatinib, a HER1/2 tyrosine kinase inhibitor [8, 9]. In vitro evidence suggests that activation of Akt/mammalian target of rapamycin (mTOR) caused by PTEN loss or PI3K overexpression is associated with trastuzumab resistance [10, 11]. These observations support the inhibition of mTOR as a therapeutic option for restoring trastuzumab sensitivity in patients with HER2-overexpressing breast cancer.

Recent clinical studies have shown promising antitumor activity of everolimus, an oral mTOR inhibitor, as a monotherapy and in combination therapy in breast cancer [12-15]. In patients with HER2-overexpressing advanced breast cancer, a phase I study of everolimus combined with trastuzumab and paclitaxel showed antitumor activity in patients previously considered refractory to trastuzumab [16].

Vinorelbine, a vinca alkaloid that interferes with microtubule assembly, is effective in combination with trastuzumab as first-line therapy or in heavily pretreated patients with

HER2-overexpressing advanced breast cancer [17-21]. The combination demonstrated similar activity in a randomized study comparing trastuzumab with docetaxel or vinorelbine, demonstrated a more favorable toxicity profile, and could be administered for a longer time than docetaxel at the approved standard dose of 100 mg/m^2 combined with trastuzumab three times per week [22].

This study was conducted to select the dose and schedule of everolimus in combination with weekly trastuzumab and vinorelbine for patients with HER2-overexpressing metastatic breast cancer whose disease progressed with trastuzumab therapy.

Patients and methods

Study design, treatment, and dose escalation

In this multicenter, open-label, nonrandomized, sequential dose-escalation phase Ib study, eligible patients received daily or weekly everolimus combined with trastuzumab and vinorelbine during six treatment cycles of 21 days each (Fig 1). Intravenous (IV) administration of trastuzumab 2 mg/kg was performed on days 1, 8, and 15 of each cycle, and IV administration of vinorelbine 25 mg/m^2 was performed on days 1 and 8 of each cycle. A 4 mg/kg loading dose of trastuzumab was administered on day 1 of cycle 1 if the patient was not on trastuzumab at study entry. The starting dose of everolimus was 5 mg/day in the daily treatment arm and 30 mg/week in the weekly treatment arm, administered starting on day 2 of the first cycle. Patients were given the option to extend treatment beyond six cycles (the core phase) if no disease progression or unacceptable toxicities were observed. During this extension phase, the everolimus regimen of the

core phase was maintained and vinorelbine could be discontinued at the investigator's discretion; trastuzumab was administered either at 2 mg/kg weekly with vinorelbine or at 6 mg/kg every 3 weeks if vinorelbine was discontinued.

The primary endpoint was the end-of-cycle-1 dose-limiting toxicity (DLT) rate, expressed in terms of the probability of falling within fixed toxicity intervals. An adaptive, sequential Bayesian time-to-DLT model was used to guide everolimus dose escalation separately for the daily and weekly arms [23, 24]. The Bayesian model assumes that the time-to-DLT follows a Weibull distribution (Appendix A) from which the probability of a DLT in cycle 1 was derived. Prior information on single-agent everolimus DLT rates was used to set up the model, and the model was continually updated with actual observed times to DLT (Appendix A). A dose level of everolimus was defined as feasible if it maximized the probability of end-of-cycle-1 DLT rate within the targeted toxicity interval (20%–35%). Further, the probability of end-of-cycle-1 DLT rate within the unacceptable toxicity range (60%–100%) had to be less than 5%, and the combined probability within excessive (35%–60%) and unacceptable toxicity intervals had to be less than 25%. The toxicity outcomes were monitored during the study, and dose escalation decisions and toxicity concerns were verbally discussed and made by investigators by teleconference with the sponsor after every DLT that occurred within the first cycle of treatment; after the first 6 patients in a regimen completed cycle 1; or every 2 months. Formal dose selections were based on the estimates provided by the model and the comprehensive safety data review. The Bayesian design was applied separately for the daily and weekly everolimus dosing arms. The relative dose intensity

(RDI) of everolimus and vinorelbine were assessed to confirm that the selected dose of everolimus would allow for an adequate dose of vinorelbine.

Secondary endpoints included safety, RDI of study drugs, overall response rate (ORR), and pharmacokinetics. Study treatment was discontinued in the event of disease progression or unacceptable toxicities.

Eligibility criteria

Patients were ≥ 18 years of age with HER2-overexpressing metastatic breast cancer, verified by immunohistochemistry (score of 3+) or fluorescence in situ hybridization (for most patients, based on analyses of the primary tumor) who progressed during or after treatment with trastuzumab alone or in combination with other anticancer agents; had a World Health Organization performance status score of 0 or 1; had a left ventricular ejection fraction > 50%; and had adequate bone marrow, cardiac, hepatic, and renal functions. Patients with any severe or uncontrolled medical condition and those who previously had received vinorelbine or an mTOR inhibitor were excluded from the study. Any previous anticancer treatment, except trastuzumab, had to be completed at least 4 weeks before enrollment. No immunosuppressants were permitted during the study. All patients provided written informed consent. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

Assessments

Adverse events (AEs) or abnormalities in laboratory test results that were defined as DLTs, if they were considered to be related to study treatment, are listed in Appendix B.

Safety evaluation included regular monitoring of AEs, assessment of vital signs and physical condition, and clinical laboratory tests; AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [25]. Tumor response was assessed at enrollment (baseline) and every 9 weeks using computed tomography, magnetic resonance imaging, bone scan (if indicated), and physical examination according to Response Evaluation Criteria in Solid Tumors [26]. Assessment of complete response (CR) or partial response (PR) included confirmation ≥ 4 weeks after the first documentation.

For pharmacokinetic analysis of everolimus, serial blood samples were collected on days 8 and 15 in cycle 1 before, and 0.5, 1, 2, 4, and 24 hours after dosing. To assess vinorelbine pharmacokinetics, additional blood samples were collected 0.5, 1, 2, 4, and 24 hours after dosing on days 1 and 8 of cycle 1. Whole-blood concentrations of everolimus and vinorelbine were determined by liquid chromatography–mass spectrometry with lower limits of quantification of 0.3 ng/mL for everolimus and 0.5 ng/mL for vinorelbine. Serum concentrations of trastuzumab were determined by enzyme-linked immunosorbent assay with a lower limit of quantification of 20 μg/mL from predose samples collected during each cycle. Pharmacokinetic parameters for everolimus and vinorelbine were derived by standard noncompartmental analysis methods using WinNonlin, Version 5 (Pharsight Corporation, CA). Pharmacokinetic parameters for everolimus and vinorelbine were compared on days 8 and 15 to assess any influence of the combination on individual pharmacokinetics, if any.

Results

Patient characteristics

From February 2007 to March 2009, 49 female patients and 1 male patient were enrolled. Based on Bayesian dose-escalation model predictions and overall safety data, 30 patients received everolimus 5 mg/day, six patients received 20 mg/week, and 14 patients received 30 mg/week. The clinical cutoff date for the present analysis was July 23, 2009, at which point the last participant completed the core phase of the study. At the cutoff date, median follow-up was 4.2 months (range, 0–12.5). All patients were heavily pretreated; prior therapies included trastuzumab, lapatinib, anthracyclines, and taxanes (Table 1).

Study treatment

Thirty-seven patients (74%) completed the core phase and 35 entered the extension phase. Of the 13 patients who did not complete the core phase, nine experienced disease progression, three discontinued because of AEs, and one died.

The first patient enrolled in the 30-mg/week cohort developed grade 3 neutropenia, a DLT. Investigators agreed to decrease everolimus to 20 mg/week after taking into consideration that the target patient population would be heavily pretreated. However, the six patients treated with everolimus 20 mg/week did not experience any DLTs and tolerated the treatment well. Therefore, it was decided to re-escalate to 30 mg/week, and an additional 13 patients were enrolled. Three patients developed a DLT at the end of cycle 1 (grade 3/4 neutropenia). For the daily treatment arm, the starting dose level of everolimus 5 mg/day was consistently considered optimal based on the DLT model. Because daily everolimus may ensure better mTOR inhibition as shown in preliminary pharmacodynamic studies [12, 15, 27], additional patients were enrolled in

the 5-mg/day cohort (30 patients total) to ensure sufficient toxicity data. Fifteen patients experienced 16 DLTs at the end of cycle 1 in the 5-mg/day cohort: grade 3/4 neutropenia (*n* = 10), febrile neutropenia (n=1), grade 3 stomatitis with concomitant fatigue (n=1), grade 2 stomatitis (n=1), grade 3 anorexia (n=1), and grade 2 acneiform dermatitis (n=1).

By the end of the core phase, everolimus 5 mg/day and 30 mg/week were considered feasible and were chosen as the optimal dose levels according to the Bayesian model. Probabilities of the end-of-cycle-1 DLT falling within underdosing, targeted, excessive, or unacceptable toxicity intervals according to the Bayesian model are reported in Appendix C. The model estimated that in the daily arm, 5 mg/day maximized the probability of the end-of-cycle-1 DLT rate falling within the targeted toxicity interval (71.6%) and also controlled the rate within the excessive (24.8%) and unacceptable toxicity intervals (≈0%). In the weekly arm, the probability of the end-of-cycle-1 DLT rate being within excessive toxic interval is ≈0 for both the 30-mg/week and 20-mg/week cohorts, but 30 mg/week (14.1%) had a greater chance of being within the targeted toxicity interval than 20 mg/week (1%).

Dose reductions and interruptions of everolimus, vinorelbine, or trastuzumab as a result of AEs or abnormalities in laboratory test results occurred in all treatment groups. Of the 30 patients in the 5 mg/day cohort, 11 and 8 had everolimus dose reductions because of AEs and abnormal laboratory values, respectively, and 29 had dose interruptions as a result of AEs and/or abnormal laboratory values. Six patients in the 20-mg/week cohort had dose interruptions. Of the 14 patients in the 30-mg/week cohort, 11 completed the core phase, three had everolimus dose reductions because of AEs or

abnormal laboratory results, and 12 had dose interruptions. At the cutoff date, five patients in the 5-mg/day cohort and one patient in the 30-mg/week cohort remained on treatment.

The median cumulative RDI of everolimus was 0.62 (range, 0.38–1.0) with the 5-mg/day regimen, 0.82 (range, 0.72–0.84) with the 20-mg/week regimen, and 0.80 (range, 0.57–0.98) with the 30-mg/week regimen. Corresponding median RDI for vinorelbine was 0.76 (range, 0.51–0.99), 0.92 (range, 0.79–0.99), and 0.85 (range, 0.61–1.0) in the everolimus 5-mg/day, 20-mg/week, and 30-mg/week groups, respectively.

Safety

Neutropenia (92%) was the most common hematologic AE, and stomatitis (70%) was the most common nonhematologic AE suspected to be related to study treatment across all dose cohorts (Table 2). Neutropenia was the most common study-related grade 3/4 AE across all dose cohorts; however, it was manageable, with only three patients experiencing febrile neutropenia and four patients receiving granulocyte colony-stimulating factor. Grade 3/4 stomatitis occurred in five patients in the 5-mg/day cohort and one patient in the 30-mg/week cohort. Stomatitis was manageable with appropriate care, with only one patient in the 5-mg/day cohort having grade 3 anorexia associated with grade 3 stomatitis. Other AEs of interest were grade 1/2 thrombocytopenia (n = 2 in the 5-mg/day cohort) and grade 2 pneumonitis (n = 1 in the 5-mg/day cohort). One patient enrolled in the 30-mg/week cohort died due to pneumonia. This patient received the first administration of vinorelbine and trastuzumab on day 1 of cycle 1 but did not

receive the first dose of everolimus scheduled on day 2 of cycle 1 (by protocol) due to a severe worsening of clinical symptoms.

Based on the overall safety data (DLT and overall toxicities) and the Bayesian model, both daily and weekly doses were feasible for further study. The 5-mg/day dose was selected for further study based on previous pharmacodynamic studies and clinical studies in metastatic breast cancer that indicated outcomes were better with daily rather than weekly inhibition of mTOR by everolimus [12, 15, 27].

Antitumor activity and survival

Investigator-based efficacy data are presented in Table 3. Among the 47 patients evaluable for efficacy, ORR was 19% and disease control rate (CR, PR, stable disease [SD]) was 83%. Clinical benefit rate (CR + PR + [SD ≥ 24 weeks]) was 54%. Median progression-free survival was 30.7 weeks (95% confidence interval [CI], 28–44.9) in the daily arm, 27.1 weeks (95% CI, 25.6–not available) in the weekly arm, and 30.7 (95% CI, 25.9–43) for the overall population (Fig 2).

Pharmacokinetics

No meaningful changes in t_{max}, C_{max}, C_{min}, $AUC_{0\text{-}tlast}$ were observed when study drugs were given in combination, suggesting a lack of relevant pharmacokinetic interaction between everolimus and vinorelbine (Table 4). Trastuzumab trough concentrations showed no clinically important variation between treatment cycles or across everolimus dosing cohorts (data not shown).

Discussion

In this study, the rationale for adding everolimus to trastuzumab was related to the potential mechanism of trastuzumab resistance mediated by mTOR activation; however, there are various mechanisms by which everolimus may exert its therapeutic effect. These include inhibiting angiogenesis and decreasing activation of regulatory T-cells [28, 29]. Further, mTOR inhibition may result in disruption of the negative feedback loop between S6K and Akt, resulting in increased activation of PI3K/Akt [30]. As HER2 is able to activate the PI3/Akt pathway [31], the addition of trastuzumab, in theory, may overcome the increased activation of PI3K/Akt caused by mTOR inhibition, resulting in synergistic blockade of this pathway. Another explanation for resistance to HER2-directed therapy is the potential loss of HER2 amplification/overexpression in patients treated with conventional trastuzumab-based combinations [32].

The results of this phase I study of heavily pretreated patients (four median previous therapies) with HER2-overexpressing breast cancer that progressed on trastuzumab suggest that the administration of both 5 mg/day and 30 mg/week of everolimus combined with weekly administration of trastuzumab and vinorelbine are feasible and safe. However, a pharmacodynamic model [27] supported by a clinical tumor pharmacodynamic study [15] showed that the daily dosage achieved a more profound and sustained suppression of mTOR activity than weekly dosing. This was further supported in a study comparing daily and weekly everolimus administration in patients with advanced breast cancer [12]. In addition, the Bayesian model predicted that, among all evaluated dose levels, everolimus 5 mg/day maximized the probability of the end-of-cycle-1 DLT rate falling within the targeted toxicity interval by the end of the

core treatment phase. Therefore, the 5-mg/day schedule was selected as the recommended dose in combination with trastuzumab and vinorelbine for further development, despite the relatively low RDI for vinorelbine at this dose level.

Given the heavily pretreated patient population that was enrolled in this trial, the level of efficacy observed with everolimus combined with trastuzumab and vinorelbine is promising. Disease control was achieved in 83% of patients; 19% had CR or PR, and the overall clinical benefit rate was 54%. Responses and disease stabilization were durable; the median duration of response was 32.7 weeks for CR/PR and 38.6 weeks for SD.

The efficacy of everolimus/vinorelbine/trastuzumab combination therapy observed in this study compares favorably to published phase II trials of vinorelbine/trastuzumab combination in patients without prior trastuzumab [33, 34]. The efficacy also is consistent with another phase I study of daily or weekly everolimus combined with weekly paclitaxel and trastuzumab in a similar patient population with HER2-overexpressing metastatic breast cancer with prior resistance to trastuzumab [16]. In those heavily pretreated patients, everolimus combined with paclitaxel and trastuzumab was efficacious, with a 44% ORR and 74% clinical benefit rate, and generally was well tolerated. In addition, efficacy was observed in a single-agent study in which 33 patients with recurrent/metastatic breast cancer treated with everolimus 10 mg/day had a 12% ORR and a 21% clinical benefit rate [12]. Single-agent activity also was demonstrated in patients with renal cell carcinoma failing sunitinib or sorafenib treatment [35].

The toxicities observed in this study are consistent with the results of previous studies of everolimus among patients with breast cancer and the expected safety profiles of trastuzumab, vinorelbine, or combination trastuzumab and vinorelbine, namely characterized by grade 3/4 manageable neutropenia [15, 36-38]. Noninfectious pneumonitis has been identified as a key clinical event in patients with metastatic renal cell carcinoma treated with everolimus [35]. In the present study, one patient had grade 2 noninfectious pneumonitis. Following diagnosis, all study treatments were temporarily interrupted and the event was resolved with no change in lung function.

The results of this phase I dose-escalation study indicate that everolimus combined with weekly trastuzumab and vinorelbine is feasible and generally well tolerated for the treatment of patients with HER2-overexpressing metastatic breast cancer that progressed on trastuzumab. The promising antitumor activity and long-term disease control further suggest that mTOR inhibition with everolimus may provide an avenue for achieving long-lasting benefit from trastuzumab-based therapy in this patient population. A randomized, placebo-controlled, phase III study (BOLERO-3) is underway to determine the efficacy and safety of everolimus in combination with vinorelbine and trastuzumab in patients with HER2-overexpressing breast cancer whose disease progressed on previous trastuzumab therapies.

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Conflicts of interest

G. Jerusalem: Consultant/advisory role, honoraria, and research funding from Novartis.

A. Fasolo: No conflicts to disclose.

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J. Bergh: Consultant/advisory role for Affybodies, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, i3 Innovus, Onyx/Bayer, Pfizer, Roche, Sanofi-Aventis, and Tapestry Network on behalf of Asklepios Medicin Hb; honoraria from Amgen, AstraZeneca, Novartis, Pfizer, Roche, and Sanofi-Aventis on behalf of Asklepios Medicin Hb; research funding from Pfizer (grant to Karolinska University Hospital enabling substudy of SUN 1064 with biopsies, PET, and gene expression profiling); Karolinska has received grants or funding from Merck (array and SNP studies) for which Prof. Bergh served as principal investigator.

L. Vittori: Employee of Novartis (Clinical Trial Head); stock ownership in Novartis.

Y. Zhang: Employee of Novartis (Senior Biostatistician).

C. Massacesi: Employee of Novartis (Global Clinical Leader); stock ownership in Novartis.

T. Sahmoud: Employee of Novartis (Executive Medical Director); stock ownership in Novartis.

L. Gianni: Consultant/advisory role for Roche, Genentech, Wyeth, Novartis, Eisai, Pfizer, Millennium, Takeda, Sanofi-Aventis, Boehringer-Ingelheim, and Wellcare.

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Table 1 Baseline patient characteristics

	Everolimus cohorts						All	
	5 mg/day +HV		20 mg/week +HV		30 mg/week +HV			
	n = 30	%	*n* = 6	%	*n* = 14	%	*N* = 50	%
Age, years (median, range)	53 (30-72)		52 (44-63)		48 (38-68)		49 (30-72)	
WHO performance status (0:1)	22/8		5/1		6/8		33/17	
Visceral disease[a]	22	73	6	100	9	64	37	74
Lung involvement	7	23	2	33	4	29	13	26
Liver involvement	16	53	4	67	6	43	26	52
Histologic tumor grade[b]								
I/II	7		0		4		11	
III	18		4		6		28	
Unknown	5		2		4		11	
Previous lines of therapy for advanced disease (median number, range)[c]	4 (1-9)		5 (2-6)		4 (2-10)		4 (2-10)	
Previous hormonal therapy[c]	15	50	4	67	7	50	26	52
Pretreated with trastuzumab[c]	30	100	6	100	14	100	50	100
Resistant to trastuzumab[d]	28	93	6	100	14	100	48	96
Pretreated with taxanes[c]	29	97	6	100	14	100	48	96
Resistant to taxanes[d]	12	43	3	50	10	71	25	52
Pretreated with lapatinib[c]	7	23	0	0	5	83	12	24
Resistant to lapatinib[d]	6	56	0	0	5	100	11	22
Pretreated with anthracyclines[c]	27	90	5	83	12	86	44	88

Abbreviations: HV, trastuzumab and vinorelbine; qd, every day; qw, every week; WHO, World Health Organization.

[a]Liver, lung, pleura, peritoneum, brain.

[b]I, well differentiated; II moderately differentiated; III, poorly differentiated; IV undifferentiated; unk = unknown.

[c]Any setting (including adjuvant/neoadjuvant).

[d]Criteria for resistance: progression/relapse within 3 months of trastuzumab/lapatinib therapy for advanced disease, within 4 months of taxane therapy for advanced disease, within 12 months of (neo)adjuvant trastuzumab, lapatinib, and taxane therapies.

Table 2 Adverse events suspected to be related to study treatment occurring in ≥ 10% of patients in the daily cohort

	Everolimus 5 mg/day + HV (*n* = 30)		Everolimus 20 mg/week + HV (*n* = 6)		Everolimus 30 mg/week + HV (*n* = 14)	
Adverse events, n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematologic						
Neutropenia	3 (10.0)	25 (83.3)	0	6 (100.0)	0	12 (85.7)
Leukopenia	0	14 (46.7)	0	5 (83.3)	0	3 (21.4)
Lymphopenia	0	4 (13.3)	0	3 (50.0)	0	0
Anemia	5 (16.7)	2 (6.7)	1 (16.7)	0	3 (21.4)	0
Nonhematologic						
Stomatitis	21 (70.0)	5 (16.7)	5 (83.3)	0	8 (57.1)	1 (7.1)
Asthenia/fatigue	20 (66.7)	2 (6.7)	5 (83.3)	0	7 (50.0)	0
Anorexia	8 (26.7)	2 (6.7)	1 (16.7)	0	4 (28.6)	0
Pain	15 (50.0)	1 (3.3)	4 (66.7)	0	4 (28.6)	2 (14.3)
GI disorders	10 (33.3)	1 (3.3)	2 (33.3)	0	7 (50.0)	0
Other ororhinopharyngeal conditions	15 (50.0)	0	0	0	6 (42.9)	1 (7.1)
Nausea/vomiting	13 (43.3)	0	2 (33.3)	0	6 (42.9)	0
Skin toxicity	11 (36.7)	0	0	0	7 (50.0)	0
Pyrexia	10 (33.3)	0	4 (66.7)	0	2 (14.3)	0

Headache	9 (30.0)	0	2 (33.3)	0	9 (64.3)	0
Rash, erythema, and pruritis	7 (23.3)	0	3 (50.0)	0	4 (28.6)	0
Neurologic toxicity	4 (13.3)	0	1 (16.7)	0	4 (28.6)	0
Cystitis	5 (16.7)	0	1 (16.7)	0	1 (7.1)	0
Muscle spasms	4 (13.3)	0	0	0	3 (21.4)	0
Eye and ear disorders	4 (13.3)	0	0	0	1 (7.1)	0
Cardiac disorders	3 (10.0)	0	0	0	2 (14.3)	0
Edema	3 (10.0)	0	1 (16.7)	0	1 (7.1)	0
Dyspnea	3 (10.0)	0	0	0	2 (14.3)	0
Cough	3 (10.0)	0	1 (16.7)	0	0	0

Abbreviation: HV, trastuzumab and vinorelbine.

n is the number of subjects with any adverse event under each hematologic status.

Percentages are calculated based on the subgroup population *N*.

Hematologic or nonhematologic adverse events are sorted in descending frequency based on the number of grade 3/4 and then grade 1/2 events in the 5 mg/day cohort.

A subject with multiple occurrences of an adverse event is counted only once under each grade group.

Other gastrointestinal disorders not include in nausea and vomiting includes constipation, diarrhea, flatulence, and gastroesophageal reflux disease.

Table 3 Antitumor activity in evaluable patients with measurable disease

Best response, *n* (%)	Everolimus 5 mg/day +HV (*n* = 30)	Everolimus 20 mg/week + HV (*n* = 6)	Everolimus 30 mg/week + HV (*n* = 14)
Complete response (CR)	1 (3.3)	0 (0)	0 (0)
Partial response (PR)	5 (16.7)	1 (16.7)	2 (14.3)
Stable disease (SD)	18 (60.0)	3 (50.0)	9 (64.3)
Progressive disease	4 (13.3)	2 (33.3)	2 (14.3)
Not evaluable	2 (6.7)	0 (0)	1 (7.1)
Clinical benefit rate, CR + PR + (SD ≥ 24 weeks)	15 (50.0)	4 (66.7)	8 (57.1)

Abbreviation: HV, trastuzumab and vinorelbine.

Table 4 Everolimus and vinorelbine pharmacokinetic parameters

Parameter	5 mg/day Everolimus + HV		20 mg/week Everolimus + HV		30 mg/week Everolimus + HV	
Everolimus PK	Everolimus alone	With vinorelbine	Everolimus alone	With vinorelbine	Everolimus alone	With vinorelbine
C_{min} (ng/mL)	6.7 ± 3.8 (*n* = 9)	6.7 ± 3.4 (*n* = 23)	0.42 (*n* = 1)	0.5 ± 0.1 (*n* = 4)	0.72 (*n* = 1)	0.96 ± 0.8 (*n* = 7)
C_{max} (ng/mL)	42.1 ± 19.8 (*n* = 9)	41.3 ± 14.9 (*n* = 23)	89.5 ± 19.8 (*n* = 3)	79.3 ± 36.5 (*n* = 6)	120.8 ± 45.0 (*n* = 8)	107.4 ± 31.8 (*n* = 9)
t_{max} (h)	1.0 (0.5-4.0) (*n* = 9)	1.0 (0.4-1.3) (*n* = 23)	0.5 (0.5-1.0) (*n* = 3)	1.1 (0.5-23.5) (*n* = 6)	0.6 (0.5-2.0) (*n* = 8)	0.5 (0.5-1.0) (*n* = 9)
AUC(ng•h/mL)	358 ± 127 (*n* = 9)	314 ± 99 (*n* = 20)	1819 (*n* = 1)	1741 (*n* = 2)	2850 ± 1892 (*n* = 3)	2453 ± 737 (*n* = 3)
CL/F (L/h)	16.4 ± 8.8 (*n* = 9)	17.7 ± 6.1 (*n* = 20)	11.0 (*n* = 1)	11.5 (*n* = 2)	13.6 ± 7.2 (*n* = 3)	13.0 ± 3.67 (*n* = 3)
Vinorelbine PK	Vinorelbine alone	With everolimus	Vinorelbine alone	With everolimus	Vinorelbine alone	With everolimus
Number of patients with values	*n* = 23	*n* = 21	*n* = 6	*n* = 3	*n* = 9	*n* = 9
C_{max} (ng/mL)	116 ± 111	127 ± 113	227 ± 22.3	239 ± 50.4	62.6 ± 39.1	69.9 ± 39.1
t_{max} (h)	0.67 (0.5-1.70)	0.67 (0.5-1.40)	0.7 (0.1-0.8)	0.68 (0.70-0.80)	0.75 (0.70-1.4)	0.67 (0.70-24.4)
AUC(ng•h/mL)	509 ± 414	539 ± 434	1620 ± 596	1480 ± 415	326 ± 204	482 ± 368

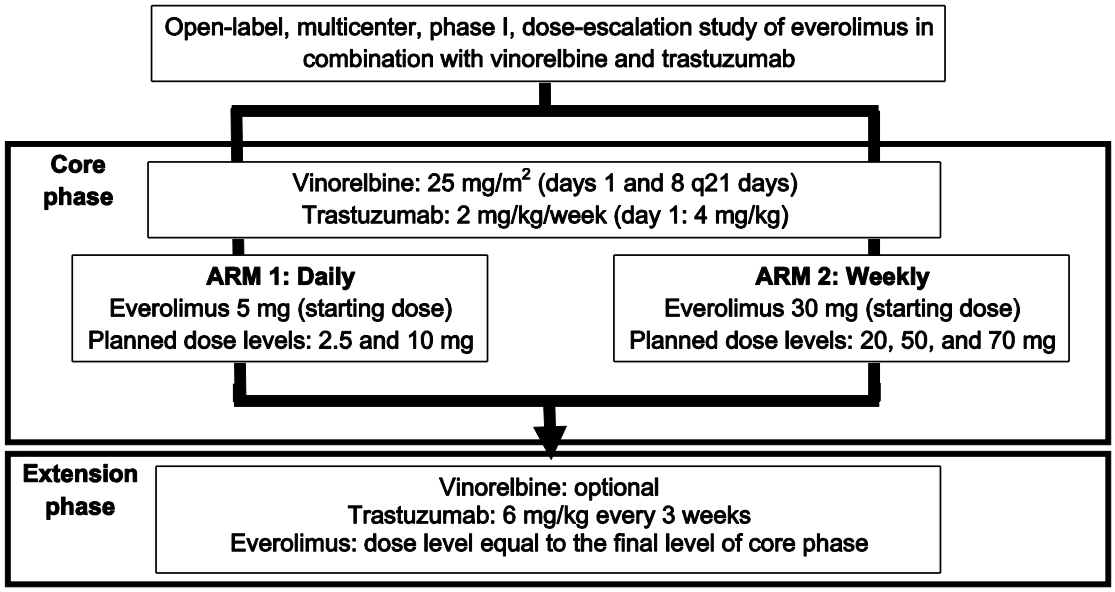
Abbreviations: AUC, area under the curve from time 0 to the last sample point; CL/F, oral clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; HV, trastuzumab and vinorelbine; PK, pharmacokinetics; t_{max}, time to C_{max}.

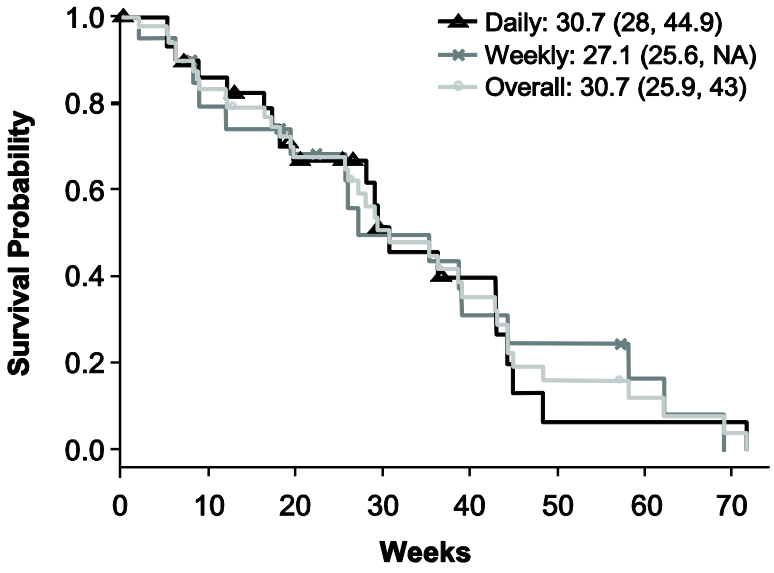
Values are listed as mean ± standard deviation except for t_{max}, which is listed as median (range).

FIGURE LEGENDS

Fig. 1 Study design

Fig. 2 Kaplan-Meier plot with median progression-free survival (95% confidence intervals)




Daily: 30.7 (28, 44.9)
Weekly: 27.1 (25.6, NA)
Overall: 30.7 (25.9, 43)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
Weeks