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ORIGINAL PAPER

Everolimus as treatment for breast cancer patients with bone metastases only: results of the phase II RADAR study

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Abstract
Purpose Everolimus has shown to stop formation and activity of osteoclasts. Breast cancer patients with bone metastases only are candidates for effective but low toxic treatment.
Patients and methods We evaluated everolimus in a double-blind, placebo-controlled, phase II, randomized discontinuation study in breast cancer patients with HER2 negative breast cancer patients with bone metastases only. After being stable on 8 weeks of everolimus 10 mg/day, patients were randomized to everolimus-continuation or placebo. Primary outcome was time (from randomization) to progression (TTP). Seventy-six patients would have had to be randomized to show a hazard ration (HR) of 0.5 for everolimus-continuation.
Results Eighty-nine patients were enrolled in 4 years. Thirty-nine patients with SD after 8 weeks on everolimus were randomized to everolimus-continuation or placebo. TTP in patients with everolimus-continuation was 37.0 (95 % CI 16.7–40.3) versus 12.6 weeks (95 % CI 7.1–17.9) with placebo [HR 0.554 (95 % CI 0.282–1.09) $p = 0.0818$], adjusted for endocrine therapy [HR 0.464 (95 % CI 0.226–0.954) $p = 0.037$]. TTP in everolimus responders ($n = 6$) was 86 weeks.
Conclusion The RADAR study is mainly hypothesis generating. It suggests that everolimus has single-agent activity, and patients with bone metastases only may retrieve long-term benefit from everolimus if they do not progress within 8 weeks of treatment.

Keywords Metastatic breast cancer · Everolimus · Bone metastases

The study has been previously presented as an oral presentation at the 8th European Breast Cancer Conference (EBCC-8), Vienna, March 21–24, 2012, and as a poster at the 34th Annual Meeting of the American Society of Clinical Oncology Chicago, June 1–5, 2012.

Nicolai Maass and Nadia Harbeck have contributed equally to this work.

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Introduction

Approximately half of all patients with solid tumors that metastasize to bone experience one or more skeletal events, including pathologic fractures, spinal cord compression, radiotherapy or surgery, and hypercalcaemia, during the course of their disease (Lipton et al. 2000). Malignant bone disease can result in chronic morbidity that often requires repeated interventions over several years (Theriault et al. 1999). The main aim of a palliative treatment is to stabilize the disease with low toxicity. Inhibiting the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin pathway with everolimus has been tested as monotherapy and in combination with endocrine therapy and chemotherapy in breast cancer (Meric-Bernstam and Gonzalez-Angulo 2009; Baselga et al. 2009; Ellard et al. 2009; Andre et al. 2010). In vitro and in vivo experiments have shown that RAD001 (everolimus) is a potent inhibitor of mouse and human osteoclast activity and formation (Kneissel et al. 2004). RAD001 could thus be a potent agent against breast cancer bone metastases caused by osteoclast stimulation. Therefore, in 2007, we started the RADAR study investigating the effect of everolimus in metastatic breast cancer patients with bone metastases only who had received an 8-week treatment with everolimus. Patients with stable disease were then randomized to everolimus-continuation or placebo.

Patients and methods

Patients

Pre- and postmenopausal women with only bone metastases in HER2-negative breast cancer were eligible independent of the hormone-receptor status of the tumor. Endocrine pretreatment for metastatic disease was allowed. A single prior line of chemotherapy for metastatic disease was allowed.

Patients had to have at least one target lesion according to WHO criteria; a Karnofsky index of at least 60 % and an adequate organ and hematological function.

Exclusion criteria included, other than bone metastases, the need of radiotherapy during study treatment and uncontrolled diabetes with a fasting blood glucose level above 120 mg/dl.

All patients gave written informed consent. The ethics committee and the competent authorities approved the study which was conducted in accordance with the principles of Good Clinical Practice and the provision of the Declaration of Helsinki. The GBG (German Breast Group) palliative sub-board supervised the study, and the standing independent data monitoring committee of GBG semiannually reviewed the safety data and the general conduct of the study. Novartis Germany provided financial support and drug supply but had no other role in conducting the trial. The trial is registered under clinicaltrials.gov (NCT00466102).

Therapy

This is a multi-center, double-blinded, placebo-controlled, prospectively, randomized discontinuation phase II study. All eligible patients received after registration everolimus 10 mg/day for 8 weeks. Thereafter, response was evaluated. Patients with complete or partial response continued with everolimus on the same dose until disease progression or unacceptable toxicity. Patients who progressed went off study. Patients who remained stable were randomized in a 1:1 ratio to receive placebo or to continue with everolimus 10 mg/day until disease progression or unacceptable toxicities. All patients received zoledronic acid according to the manufacturers' recommendation and 1000 mg vitamin D together with 800 I.U. calcium daily (Supplementary Fig. 1). Starting from amendment 2, patients with hormone-receptor-positive disease received concomitantly an endocrine agent at the investigator's discretion but in

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accordance with current guidelines (www.ago-online.de/en/guidelines-mamma/ assessed on 21.08.2013).

Objectives

Primary objective was to compare time to disease progression (TTP) defined as time from randomization until disease progression or disease-related death within the group of patients who were stable after 8-week run-in therapy on everolimus between patients who continued on everolimus compared to those on placebo. Secondary objectives included TTP in patients who responded to everolimus (counted from end of run-in phase), overall response rate, overall clinical benefit rate, bone metastases-related event rate (i.e., radiotherapy, surgery, pathological fractures due to bone metastases, spinal cord compression, and hypercalcaemia), pain intensity measured on a numeric pain scale, safety, and compliance. Objectives were assessed within the randomized and the total population.

Assessment

Response was assessed by imaging according to modified WHO criteria. The first assessment was performed at the end of the run-in-phase 8 weeks after start of everolimus and every 12 weeks thereafter. To rule out a progression, tumor marker CA 15-3 evaluation, performed every 4 weeks similar to the GCIG criteria for CA 125, was introduced as an ancillary method (Rustin et al. 2006). Progression was defined as a 25 % increase in CA 15-3 from baseline which was confirmed within 7 days or a 10 % increase in CA 15-3 level upper normal limit measured twice within 4 weeks and confirmed after 7 days. In addition, bone metastases-related events including pathologic fractures, spinal cord compression, radiotherapy, or surgery to bone, and hypercalcaemia were considered as progression. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria version 3.0 (NCI CTCAE v3.0) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf assessed on 21.08.2013).

Statistics

The primary efficacy analysis for TTP was a two-sided log-rank test in the intend-to-treat population (ITT). A total of 76 randomized patients were needed in order to detect a hazard ratio (HR) of 0.5 with 80 % power, assuming that the TTP would be 8 and 16 weeks in the placebo and the everolimus group, respectively, a recruitment period of 16 months, and an exponential dropout rate of 5 %. It was further assumed that 70 % of the patients would be stable after 8 weeks on everolimus. Overall, 109 patients would have needed to be recruited. All patients who started therapy were included in the safety analyses. All patients randomized were included in the ITT-population for the primary endpoint. In addition, a per-protocol analysis for the primary endpoint was conducted.

TTP was assessed using the Kaplan–Meier product-limit method, and median TTP and the corresponding 95 % CI are reported together with the log-rank p value. HR between the randomized arms and the corresponding 95 % CI was determined using univariable Cox proportional hazards model. Additionally, a stratified log-rank test (stratified by concomitant endocrine treatment) and an adjusted HR from the Cox model were reported to take into account the stratification according to endocrine therapy after amendment 2. Subgroup analysis was not pre-specified in protocol but in statistical analysis plan. Interaction of the treatment arm with the subgroup variable was tested using interaction term in Cox model.

Adverse events are categorized as maximal grade 1–4 and maximal grade 3–4, reported as number and percentage of patients. Incidence of each AE was compared between randomized treatment groups with the exact test of Fisher. HbA1c level was compared between treatment groups using Wilcoxon test. Valid percentages are reported.

Results

Patients

A total of 89 patients had been enrolled between February 2007 and December 2010 in 24 centers in Germany. Due to slow recruitment, the study was closed prematurely. Three patients never started therapy and 41 patients stopped during or after the run-in phase. Forty-five patients completed the run-in phase of whom 6 continued with everolimus as responder and 39 were randomized, 18 to everolimus and 21 to placebo (Fig. 1). Baseline characteristics were well balanced within the randomized treatment groups, with the exception of nodal status at primary diagnosis. More patients had nodal involvement in the everolimus group compared to the placebo group (15/18 (88.2 %, 1 missing) vs. 9/21 (42.9 %) $p = 0.004$). Overall, median age was 59.5 years. Overall, one-third of the patients received concomitant endocrine therapy following amendment 2 (Table 1).

Efficacy

Randomized cohort

At the cutoff date (December 20, 2011), three patients were still under therapy, one in the everolimus group and 2 in the placebo group receiving an AI. The median time of follow-up was 96 weeks.

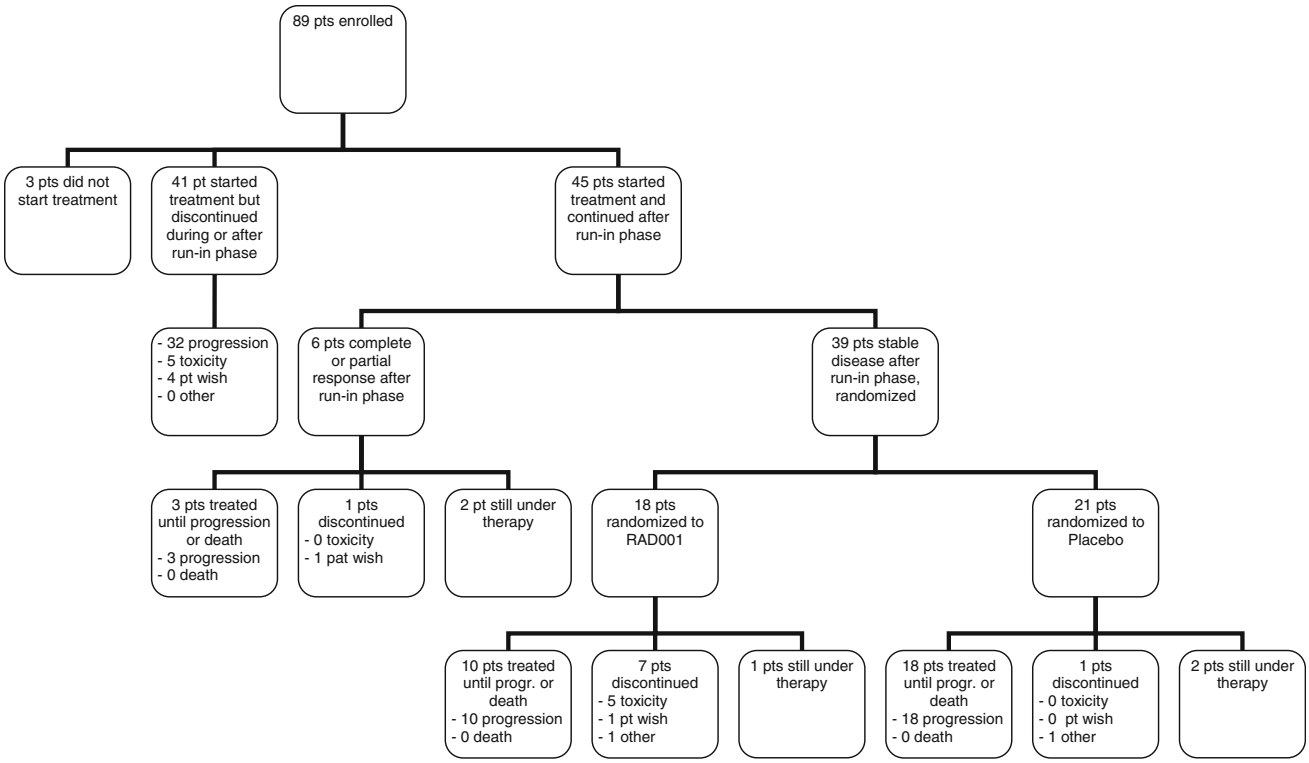

Fig. 1 Consort statement (disposition of patients)

The median TTP was 37 weeks (95 % CI 16.7–40.3) in the group which continued with everolimus after 8-week run-in treatment and 12.6 weeks (95 % CI 7.1–17.9) in the placebo group; [log-rank $p = 0.0818$; HR 0.554 (95 % CI 0.282–1.09), Wald $p = 0.087$] (Fig. 2). After adjusting the Cox model for endocrine therapy, the difference between everolimus and placebo was significant [HR 0.464 (95 % CI 0.226–0.954] Wald $p = 0.037$]; log-rank test was stratified by concomitant endocrine treatment $p = 0.0549$. Subgroup analyses revealed that everolimus was more effective than placebo in patients ≥65 years [HR 0.176 (95 % CI 0.035–0.896) $p = 0.036$], with a good performance status [HR 0.424 (95 % CI 0.186–0.970) $p = 0.042$), who did not receive concomitant endocrine therapy [HR 0.346 (95 % CI 0.136–0.879) $p = 0.026$], those with more than one involved skeletal region [HR 0.339 (95 % CI 0.151–0.761) $p = 0.009$] or who were treated in 2nd-line [HR 0.337 (95 % CI 0.120–0.941) $p = 0.038$], but tests for interaction did not reach significance (Fig. 3 and Supplementary Table 1). In the per-protocol cohort, 16 patients received everolimus and 20 patients placebo. Median TTP was 37.9 weeks (95 % CI 17.6–46.1) with everolimus and 12.3 weeks [(95 % CI 5.9–17.9); log-rank $p = 0.0042$; adjusted HR 0.293; 95 % CI (0.131–0.659); Wald $p = 0.003$] for placebo (Fig. 4).

In 14 (77.8 %) out of 18 patients who continued everolimus, a clinical benefit was observed compared to 10 (47.6 %) out of 21 patients on placebo ($p = 0.098$).

One bone metastases-related event was reported in each randomized group (pathological fracture in the everolimus group and hypercalcaemia in the placebo group). 21 (61.8 %) randomized patients had progressive bone metastases or new bone lesions, 9 (52.9 %) in the everolimus group, 12 (70.6 %) in the placebo group, and 13 (38.2 %) patients had new lesions outside the skeleton, in one patient the location of progression was unknown.

Non-randomized cohort

The median follow-up of all patients was 99 weeks. Six of the 86 patients (7.0 %) had a complete or partial remission after the 8-week run-in phase and continued with everolimus (four plus AI). The median TTP was 85.9 weeks (95 % CI 13.1 not reached), one patient was lost to follow-up. The response rate after the 8-week run-in phase was higher if endocrine treatment was given concomitantly (14.3 vs. 3.4 %).

Treatment adherence

Randomized cohort

Within the randomized cohort, the median time on everolimus was 17 weeks (0–115 weeks) and on placebo

Table 1 Baseline characteristics

Parameter	Parameter value	Overall	Stopped during or after run-in ($N = 41$)	CR of PR after run-in ($N = 6$)	Randomized ($N = 39$)	RAD001 ($N = 18$)	Placebo ($N = 21$)
Age, years	Median	59.5	66.0	61.0	55.0	57.0	55.0
	Range	27.0, 78.0	44.0, 78.0	55.0, 72.0	27.0, 77.0	36.0, 77.0	27.0, 75.0
Karnofsky index	<90 %	26 (30.3)	14 (34.2)	1 (16.7)	11 (28.2)	4 (22.2)	7 (33.3)
	90–100 %	60 (69.7)	27 (65.8)	5 (83.3)	28 (71.8)	14 (77.8)	14 (66.7)
ER/PgR	Both ER, PgR negative	6 (7.0)	1 (2.4)	0 (0.0)	5 (12.8)	3 (16.7)	2 (9.5)
	ER and/or PgR positive	80 (93.0)	40 (97.6)	6 (100)	34 (87.2)	15 (83.3)	19 (90.5)
Chemotherapy for metastatic disease	No	73 (84.9)	36 (87.8)	4 (66.7)	33 (84.6)	16 (88.9)	17 (81.0)
	Yes	13 (15.1)	5 (12.2)	2 (33.3)	6 (15.4)	2 (11.1)	4 (19.0)
Radiotherapy for metastatic disease	No	46 (53.5)	22 (53.7)	5 (83.3)	19 (48.7)	10 (55.6)	9 (42.9)
	Yes	40 (46.5)	19 (46.3)	1 (16.7)	20 (51.3)	8 (44.4)	12 (57.1)
ET for metastatic disease	No	36 (41.9)	13 (31.7)	3 (50.0)	20 (51.3)	10 (55.6)	10 (47.6)
	Yes	50 (58.1)	28 (68.3)	3 (50.0)	19 (48.7)	8 (44.4)	11 (52.4)
Concomitant endocrine therapy	SERM or fulvestrant	7 (8.1)	3 (7.3)	0 (0.0)	4 (10.3)	2 (11.1)	2 (9.5)
	AI	21 (24.4)	5 (12.2)	4 (66.7)	12 (30.8)	6 (33.3)	6 (28.6)
	No	58 (67.4)	33 (80.5)	2 (33.3)	23 (59.0)	10 (55.6)	13 (61.9)
Therapy line	1st line	33 (38.4)	12 (29.3)	3 (50.0)	18 (46.2)	9 (50.0)	9 (42.9)
	2nd line	53 (61.6)	29 (70.7)	3 (50.0)	21 (53.8)	9 (50.0)	12 (57.1)
Baseline CA 15–3	<28 U/ml	14 (16.5)	4 (9.8)	1 (16.7)	9 (23.7)	5 (29.4)	4 (19.0)
	≥28 U/ml	71 (83.5)	37 (90.2)	5 (83.3)	29 (76.3)	12 (70.6)	17 (81.0)
Number of skeletal parts	1	17 (19.8)	9 (22.0)	0 (0.0)	8 (20.5)	2 (11.1)	6 (28.6)
	>1	69 (80.2)	32 (78.0)	6 (100)	31 (79.5)	16 (88.9)	15 (71.4)

15 weeks (4–109 weeks). Of the 39 patients who were randomized, 55.6 % (10/18) on everolimus and 85.7 % (18/21) on placebo stopped treatment due to progression ($p = 0.037$). Within the randomized cohort, 11 (64.7 %) out of 18 interrupted everolimus compared to 4/21 (19 %) with placebo ($p = 0.007$). The interruptions were mainly related to toxicity (41.2 % with everolimus and 9.5 % with placebo). There was no difference in dose reductions in the randomized cohort between everolimus- and placebo-treated patients.

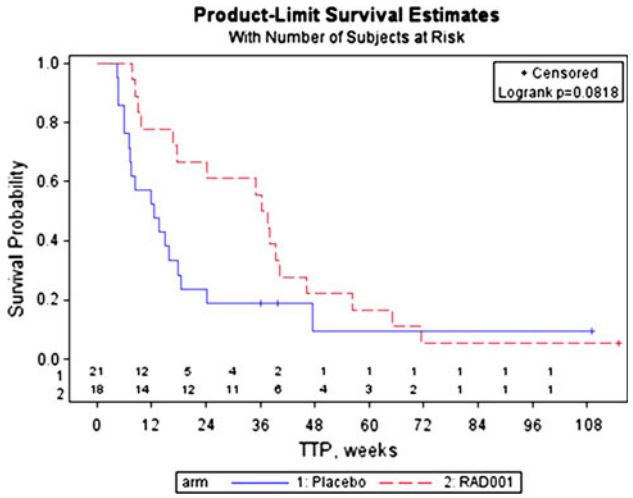

Fig. 2 Time to progression in patients who continued with everolimus compared to placebo after 8-week run-in. Intent to treat population

Non-randomized cohorts

Overall, 30 out of 86 patients (37.0 %, missing $n = 5$) interrupted everolimus, 21 (70 %) due to toxicity. There was no difference in interruptions due to concomitant endocrine therapy.

In total, 14 out of 86 patients (17.9 %, missing $n = 8$) reduced the dose of everolimus at any time, 11 of 58 patients (19 %) without endocrine treatment and 3 of 28 (11 %) with endocrine treatment. Twelve out of 86 (15.4 %, missing $n = 8$) patients reduced the dose of everolimus during the run-in phase all due to toxicity.

Toxicity

Randomized cohort

Within the randomized cohort, four serious adverse events (SAEs) were reported, one with everolimus and three with placebo. There were no unexpected adverse events reported. All patients who continued with everolimus developed anemia which was severe in one patient only. Leucopenia and anemia of any grade were more common in the group who continued with everolimus than in the placebo group (Table 2). Hyperglycemia of any grade was significantly more common in the group that continued with everolimus than in the group with placebo (50 vs. 14.3 %; $p = 0.035$) (Table 3). The median HbA1c level was significantly higher in the group that continued with everolimus than in the placebo group [6.3, range (5.2–8.1) vs. 5.7 range (5.0–6.0); $p = 0.014$]. Hypertriglyceridemia

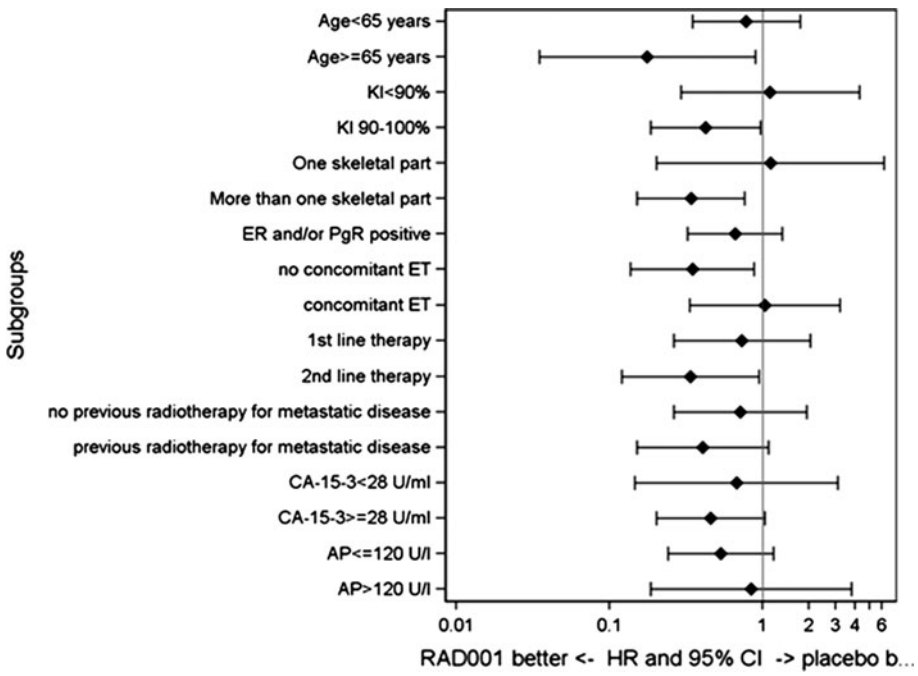

Fig. 3 Forest plot indicating the time to progression across various subgroups

any grade and increased liver enzymes were more common in the group that continued with everolimus than with placebo (Table 3). All other adverse events reported were not significantly different between the two randomized groups.

Non-randomized cohorts

SAEs were reported in 14 of 86 patients who started therapy. The majority of adverse events occurred during the run-in phase and improved in patients on placebo (Tables 2 and 3). Addition of endocrine therapy did not influence the adverse events.

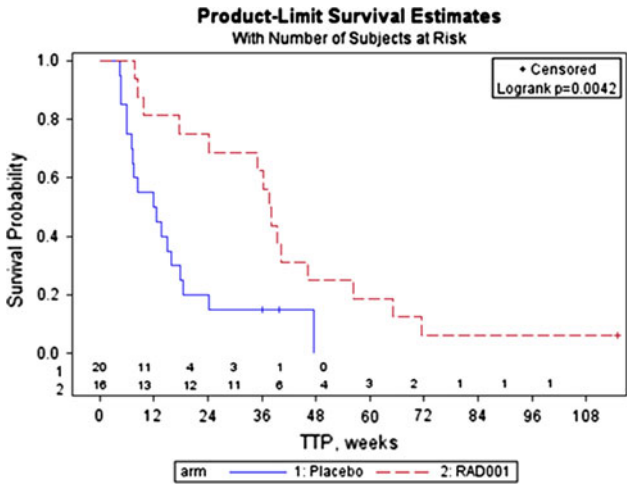

Fig. 4 Per protocol analysis. Time to progression in patients who continued with everolimus compared to placebo after 8-week run-in. For the per-protocol analysis, three of the 39 patients were excluded from the ITT-population, one patient with radiotherapy during the run-in phase, one patient with an extended run-in phase of 10 weeks, and one patient never started treatment after randomization

Discussion

RADAR evaluated everolimus as a single agent in breast cancer patients with bone metastases only irrespective of the hormone-receptor status of the tumor. The TTP was longer in the group of patients who continued with everolimus (37 weeks) compared to those who received placebo (11.6 weeks) after achieving stable disease on 8 weeks of everolimus. Subgroup analysis suggests that everolimus has single-agent activity and the activity is not confined to patients with hormone-receptor-positive disease. All patients responding to everolimus during the run-in phase had a hormone-sensitive primary tumor and four received concomitant AI. In the phase II TAM-RAD study, patients with secondary endocrine resistance benefitted most from receiving everolimus in addition to tamoxifen. The effect size observed in RADAR is in line with previous reports from the BOLERO-2 and the TAM-RAD study (Baselga et al. 2012; Campone et al. 2012; Bachelot et al. 2012).

Bone metastases due to breast cancer are usually considered low risk and patients have a chance of long-term survival without visceral metastases (Gnant et al. 2012). Although the majority of patients with bone metastases only have an endocrine responsive primary tumor and will therefore receive an endocrine treatment, everolimus could be an alternative to chemotherapy for patients with hormone-receptor-negative tumors.

There are some strengths and limitations of the RADAR study. First of all, we were not able to complete the study due to slow recruitment. Less patients than expected had stable disease to qualify for randomization. Patients with hormone-receptor-positive disease received concomitant endocrine therapy after an amendment. This led to a more heterogeneous patient population but supported the trial in general. The double-blind, placebo-controlled randomized

Table 2 Hematological adverse events irrespective of relationship to study drug

AE	All ($N = 86$)	W/o ET ($N = 58$)	With ET ($N = 28$)	All run-in phase ($N = 86$)	Everolimus ($N = 18$)	Placebo ($N = 21$)	*p* value comparison RAD001 versus placebo
Any AE, grade 1–4	85 (98.8)	58 (100)	27 (96.4)	85 (98.8)	18 (100)	21 (100)	n.a.
Any AE, grade 3–4	34 (39.5)	26 (44.8)	8 (28.6)	29 (33.7)	5 (27.8)	7 (33.3)	0.742
Anemia grade 1–4	57 (67.9)	40 (70.2)	17 (63.0)	49 (58.3)	18 (100)	13 (61.9)	0.004
Anemia grade 3–4	3 (3.6)	3 (5.3)	0 (0.0)	1 (1.2)	1 (5.6)	0 (0.0)	0.462
Thrombopenia grade 1–4	32 (38.1)	22 (38.6)	10 (37.0)	31 (36.9)	5 (27.8)	2 (9.5)	0.215
Thrombopenia grade 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Leucopenia grade 1–4	59 (70.2)	39 (68.4)	20 (74.1)	53 (63.1)	13 (72.2)	4 (19.0)	0.001
Leucopenia grade 3–4	4 (4.8)	4 (7.0)	0 (0.0)	3 (3.6)	1 (5.6)	0 (0.0)	0.462
Neutropenia grade 1–4	37 (44.0)	25 (43.9)	12 (44.4)	34 (40.5)	6 (33.3)	4 (19.0)	0.465
Neutropenia grade 3–4	6 (7.1)	6 (10.5)	0 (0.0)	5 (6.0)	1 (5.6)	0 (0.0)	0.462

Table 3 Non-hematological adverse events reported in >10 % per patients irrespective of relationship to study drug

AE	All	W/O ET ($N = 58$)	With ET ($N = 28$)	All run-in phase ($N = 86$)	Everolimus ($N = 18$)	Placebo ($N = 21$)	*p* value comparison RAD001 versus placebo
Bilirubin grade 1–4	2 (2.4)	1 (1.8)	1 (3.7)	1 (1.2)	0 (0.0)	1 (4.8)	1.00
Bulirubin grade 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
AP grade 1–4	42 (50.0)	31 (54.4)	11 (40.7)	37 (44.0)	11 (61.1)	8 (38.1)	0.205
AP grade 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
ASAT grade 1–4	69 (82.1)	49 (86.0)	20 (74.1)	65 (77.4)	16 (88.9)	13 (61.9)	0.074
ASAT grade 3–4	2 (2.4)	1 (1.8)	1 (3.7)	1 (1.2)	1 (5.6)	0 (0.0)	0.462
ALAT grade 1–4	52 (61.9)	36 (63.2)	16 (59.3)	48 (57.1)	13 (72.2)	8 (38.1)	0.054
ALAT grade 3–4	3 (3.6)	2 (3.5)	1 (3.7)	2 (2.4)	1 (5.6)	0 (0.0)	0.462
Creatinine grade 1–4	19 (22.6)	13 (22.8)	6 (22.2)	15 (17.9)	3 (16.7)	2 (9.5)	0.647
Creatinine grade 3–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Serum albumin grade 1–4	12 (14.6)	10 (18.2)	2 (7.4)	7 (8.6)	5 (27.8)	5 (23.8)	1.00
Serum albumin grade 3–4	1 (1.2)	0 (0.0)	1 (3.7)	0 (0.0)	1 (5.6)	0 (0.0)	0.0.462
Cholesterol grade 1–4	76 (92.7)	50 (90.9)	26 (96.3)	74 (90.2)	16 (88.9)	16 (76.2)	0.418
Cholesterol grade 3–4	2 (2.4)	2 (3.6)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	n.1.
Triglycerides grade 1–4	63 (76.8)	41 (74.5)	22 (81.5)	61 (74.4)	13 (72.2)	8 (38.1)	0.054
Triglycerides grade 3–4	2 (2.4)	2 (3.6)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	n.a.
Glucose grade 1–4	42 (52.5)	27 (50.0)	15 (57.7)	38 (47.5)	9 (50.0)	3 (14.3)	0.035
Glucose grade 3–4	3 (3.8)	2 (3.7)	1 (3.8)	3 (3.8)	0 (0.0)	0 (0.0)	n.a.
Infection grade 2–4	21 (24.4)	12 (20.7)	9 (32.1)	15 (17.4)	6 (33.3)	3 (14.3)	0.255
Loss of appetite/weight grade 1–4	11 (12.8)	5 (8.6)	6 (21.4)	8 (9.3)	4 (22.2)	1 (4.8)	0.162
Metabolic disorders grade 1–4	3 (3.5)	2 (3.4)	1 (3.6)	2 (2.3)	1 (5.6)	0 (0.0)	0.462
Psychiatric disorders grade 1–4	5 (5.8)	2 (3.4)	3 (10.7)	5 (5.8)	0 (0.0)	1 (4.8)	1.00
Sensory neuropathy, grade 1–4	3 (3.5)	1 (1.7)	2 (7.1)	0 (0.0)	2 (11.1)	0 (0.0)	0.206
Taste disorder grade 1–4	10 (11.6)	7 (12.1)	3 (10.7)	6 (7.0)	3 (16.7)	1 (4.8)	0.318
Vertigo grade 1–4	5 (5.8)	3 (5.2)	2 (7.1)	1 (1.2)	2 (11.1)	2 (9.5)	1.00
Headache grade 1–4	9 (10.5)	3 (5.2)	6 (21.4)	6 (7.0)	3 (16.7)	4 (19.0)	1.00
Other neurological disorder grade 1–4	4 (4.7)	3 (5.2)	1 (3.6)	2 (2.3)	1 (5.6)	1 (4.8)	1.00
Cardiac disorder 1–4	3 (3.5)	2 (3.4)	1 (3.6)	1 (1.2)	1 (5.6)	1 (4.8)	1.00
Dyspnea grade 1–4	8 (9.3)	5 (8.6)	3 (10.7)	4 (4.7)	2 (11.1)	0 (0.0)	0.206
Alveolitis/pneumonitis grade 1–4	2 (2.3)	0 (0.0)	2 (7.1)	0 (0.0)	2 (11.1)	1 (4.8)	0.586
Other respiratory disorders grade 1–4	19 (22.1)	11 (19.0)	8 (28.6)	15 (17.4)	3 (16.7)	5 (23.8)	0.702
Nausea grade 1–4	16 (18.6)	11 (19.0)	5 (17.9)	14 (16.3)	0 (0.0)	4 (19.0)	0.110
Vomiting grade 1–4	9 (10.5)	7 (12.1)	2 (7.1)	8 (9.3)	0 (0.0)	1 (4.8)	1.00
Diarrhea grade 1–4	17 (19.8)	12 (20.7)	5 (17.9)	14 (16.3)	1 (5.6)	2 (9.5)	1.00
Diarrhea grade 3–4	3 (3.5)	2 (3.4)	1 (3.6)	3 (3.5)	0 (0.0)	0 (0.0)	n.a.
Skin disorders grade 1–4	21 (24.4)	12 (20.7)	9 (32.1)	19 (22.1)	4 (22.2)	4 (19.0)	1.00
Musculoskeletal pain grade 1–4	32 (37.2)	21 (36.2)	11 (39.3)	29 (33.7)	6 (33.3)	8 (38.1)	1.00
Edema grade 1–4	11 (12.8)	6 (10.3)	5 (17.9)	6 (7.0)	4 (22.2)	5 (23.8)	1.00
Fatigue grade 1–4	18 (20.9)	11 (19.0)	7 (25.0)	16 (18.6)	6 (33.3)	6 (28.6)	1.00
Stomatitis (mucositis) grade 1–4	22 (25.6)	13 (22.4)	9 (32.1)	20 (23.3)	4 (22.2)	3 (14.3)	0.520
Stomatitis (mucositis) grade 3–4	2 (2.3)	0 (0.0)	2 (7.1)	2 (2.3)	0 (0.0)	1 (4.8)	0.348

discontinuation design was chosen to strengthen the results. The sample size in the randomized group is small but due to the large effect size, a clear trend could be demonstrated which was significant after adjusting for concomitant endocrine therapy. The 8-week run-in phase preselected the patients. Progression was assessed by local investigators. Although in the updated RECIST version from 2009, bone metastases are no longer considered non-measurable (Eisenhauer et al. 2009), this assessment could be highly subjective as even newer methods for measuring bone

metastases are not sensitive enough to detect early progressions (Costelloe et al. 2009; Hayashi et al. 2013). Determination of the tumor marker CA 15-3 (similar to the GCIG criteria for CA125) was therefore implemented as an ancillary method to detect early primary progressions, because patients were further randomized to a placebo. To further avoid under-treatment, all patients received zoledronic acid and later during the trial an endocrine treatment if indicated.

The safety profile of the study is comparable to that of other everolimus studies (Ellard et al. 2009; Baselga et al. 2012; Campone et al. 2012). All except one patient experienced an adverse event and 40 % of the patients had an adverse event grade 3–4, which seems high but may be due to the small sample size. Grade 3–4 adverse events were reported for anemia, neutropenia, hyperglycemia and increased triglycerides, stomatitis, and other respiratory disorders (not pneumonitis). The rate of hyperglycemia with 50 % of all patients was higher in the RADAR study compared to the BOLERO-2 and TAM-RAD study. After stopping everolimus, hyperglycemia disappeared and HBA1c decreased to normal (Busaidy et al. 2012).

In conclusion, our study is mainly hypothesis generating. It suggests that everolimus has single-agent activity, and patients with bone metastases only—irrespective of their hormone-receptor status—may retrieve long-term benefit from everolimus if they do not progress within 8 weeks of treatment.

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