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Original article

Sorafenib in combination with docetaxel as first-line therapy for HER2-negative metastatic breast cancer: Final results of the randomized, double-blind, placebo-controlled phase II MADONNA study☆

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ABSTRACT

Background: This multicenter, double-blind phase II study assessed the antitumor activity and toxicity profile of docetaxel with the antiangiogenic multikinase inhibitor sorafenib or matching placebo as a first-line treatment in patients with metastatic or locally advanced HER2-negative breast cancer.
Patients and methods: Patients were randomized 1:1 to receive docetaxel 100 mg/m^2 on day 1 every 3 weeks in combination with sorafenib 400 mg bid or placebo on days 2–18 of each cycle until tumor progression, or unacceptable toxicity. Sorafenib/placebo could be continued at the investigator's discretion if docetaxel was stopped due to toxicity. Primary endpoint was progression free survival (PFS).
Results: From October 2008 to December 2013, 102 patients were randomized; 98 patients were evaluable. The trial was prematurely terminated due to slow accrual. Due to increased toxicity the dose of docetaxel was reduced to 75 mg/m^2 and an increasing sorafenib dosing schedule was implemented as part of a protocol amendment. The addition of sorafenib to docetaxel did not improve PFS (8.2 vs. 7.3 months for docetaxel/placebo; HR 0.84, log rank $p = 0.43$), but led to higher rates of early treatment discontinuation. There were no statistically significant differences between sorafenib dosing schedules.
Conclusions: Addition of sorafenib to taxane-based first-line chemotherapy in patients with metastatic breast cancer failed to improve PFS and resulted in increased toxicity.

1. Introduction

Antiangiogenic therapies play an important role in the treatment of several cancers, such as colorectal, renal and hepatocellular carcinoma. However, their role in breast cancer treatment is still debated. Indeed, despite phase III trials demonstrated improved objective response rates (ORR) and PFS when the monoclonal *anti-*

☆ The study was registered at EudraCT (2008-001090-15).

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VEGF-A antibody bevacizumab was added to cytotoxic chemotherapy in the first- and second-line setting of metastatic breast cancer treatment, overall survival was not improved [1–6]. A prospective biomarker-driven phase III trial (MERiDIAN) failed to demonstrated a role for plasma VEGF-A as predictive of benefit from bevacizumab-containing regimens [7]. The presence/selection of compensatory pro-angiogenic mechanisms could in part explain the relatively poor efficacy of *anti*-VEGF-A targeted therapies, while potentially leading to enhanced angiogenesis and more aggressive disease behavior after bevacizumab discontinuation. Agents targeting a broader range of angiogenic kinases and additional tumor cell targets might offer an advantage in this respect [8].

Sorafenib (SOR) is an oral multikinase inhibitor, exerting anti-angiogenic and antiproliferative activities by blocking VEGFR-1, -2, -3, PDGFR, c-kit and Flt-3 [9]. It is currently approved in EU for treatment of metastatic renal cancer, unresectable hepatocellular carcinoma and radioactive iodine-refractory thyroid cancer. Its efficacy as a single agent in MBC is modest [10,11], similar to other antiangiogenic agents like bevacizumab (BEV), pazopanib or sunitinib [10–16]. However, three randomized phase IIb trials have reported efficacy of SOR in combination with chemotherapy in MBC, even after progression under BEV [17–21]. A major challenge from combining sorafenib with chemotherapy consists in overlapping toxicity between SOR and cytostatic/cytotoxic agents, such as a high incidence of high-grade palmoplantar erythrodysesthesia (PPE) when SOR is combined with capecitabine. The randomized, multicenter, double-bind phase II MADONNA trial evaluated the activity and safety of SOR or placebo (PLAC) in combination with docetaxel (DOC) as first-line therapy for MBC, whilst avoiding overlapping toxicities. Here we report the results of the primary (PFS) and secondary endpoints (safety and tolerability, ORR, duration of response (DOR), time to progression (TTP) and OS).

2. Patients and methods

2.1. Study design

Patients with $\geq$18 years having metastatic or unresectable locally advanced, histologically confirmed HER2-negative breast cancer and measurable disease according to RECIST 1.0 were eligible. Further main inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, life expectancy > 12 weeks, adequate bone marrow, liver and renal function. No prior chemotherapy for metastatic disease was allowed. Patients with prior (neo)adjuvant therapy had to have a taxane-free interval of $\geq$ 12 months. Prior endocrine treatment in adjuvant or metastatic setting was allowed. Exclusion criteria included CNS metastases, distinct previous or concurrent cancer (except for locally resected carcinoma in situ or curatively treated cancer > 3 years in any organ/tissue). Patients with medical conditions limiting ability to undertake study treatment (uncontrolled cardiovascular disease, seizures, HIV infection, chronic viral hepatitis, status post organ allograft, autologous bone marrow transplant < 4 months, drug abuse) were excluded.

Patients were randomized to receive DOC 100 mg/m^2 on day 1 of a 21 day-cycle in combination with SOR 400 mg bid on days 2–18 of each cycle or PLAC. Treatment allocation was stratified by hormone receptor (HR) status. Due to hematological side effects, the protocol was amended and DOC was reduced to 75 mg/m^2. Upon publication of phase IIb study data in December 2009 [22,23] showing high rates of grade 3 skin toxicity, an escalating SOR dosing schedule with 200 mg bid on cycle 1, 200 mg a.m. and 400 mg p.m. on cycle 2 and 400 mg bid from cycle 3 and on, was implemented as part of a further amendment. Treatment was administered until disease progression, patient death from any cause, unacceptable toxicity or consent withdrawal, whichever came first. SOR/PLAC could be continued at the investigator's discretion if DOC was stopped due to toxicity.

Local tumor assessments based on RECIST were performed every 6 weeks until disease progression. Primary endpoint was PFS, defined as the time from start of treatment to disease progression or death. Secondary endpoints included DOR, TTP, OS, patient reported outcomes, safety and tolerability. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

The study was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Signed informed consent was obtained from each participant. Study protocol and amendments were approved by independent ethics committees.

2.2. Statistical analysis

The sample size for this study was based on the assumption that the median PFS for patients receiving DOC as first-line treatment is 6 months. An improvement by 50% to a median of 9 months in the experimental arm was deemed clinically significant. A total of 208 events were needed to detect a difference in median PFS of 6 vs. 9 months with a 90% power and a one-sided $\alpha = 0.05$. Assuming a recruitment period of 12 months, follow-up of at least 12 months and accounting for 10% drop-outs, 288 patients were planned to be randomized.

Time-to-event related data were calculated for the intention-to-treat (ITT) population (all patients with at least one dose of study medication) and for subgroups defined by HR status; analyses were estimated by the Kaplan–Meier product limit method and compared using the log-rank test.

3. Results

3.1. Demographics and baseline characteristics

Between October 2008 and December 2013, 102 patients were randomized among 27 centers in Germany; 98 out of these were evaluable (CONSORT diagram). The trial was prematurely terminated due to slow accrual. Data cut-off for analysis was 12 May 2014 at a median follow up of 10.3 months, when 81 PFS events occurred (84.4%). Median age was 56 years. Patient baseline characteristics were similar in both groups, including HR status, which was positive in 78.6% of patients. 71.4% of patients were postmenopausal. 89.6% and 82% of patients had visceral metastases in experimental and control arms, respectively. 50% and 48% of patients had grade 3/4 and grade 2 tumors, respectively. A non-significantly lower proportion of patients in the experimental arm had received prior adjuvant chemotherapy, compared to the control arm (45.8% vs. 52%; $p = 0.54$). Prior exposure to taxanes was similar (Table 1). Common comorbidities included arterial hypertension (18.4%), allergies (17.2%) and heart disease (6.9%) (not shown).

3.2. Treatment exposure

25 patients in experimental arm received an upfront SOR dose of 800 mg, whereas the remaining 23 received SOR escalating dosing. 2% of patients did not start treatment. Median number of treatment cycles was 6 and 6.5 in experimental and control arms, respectively. Significantly more patients in the experimental arm discontinued treatment after Cycle 1 (17.4% vs. 4%; $p = 0.038$). Cycle 4 was completed by 65% and 76% of patients in experimental and control arms, respectively ($p = 0.22$), with a mean DOC dose ranging from

Table 1
Baseline characteristics.

Characteristics	Experimental arm N = 48		Control arm N = 50		p-value
Age (years)					
Mean	55.3		56.8		0.36 *
Range	33.0–81.0		32.0–76.0		
	N	**%**	**N**	**%**	
ECOG status					
0	35	72.9	31	62.0	0.25 **
1	13	27.1	19	38.0	
Hormone receptor (HR) status					
Positive	38	79.2	39	78.0	0.89 **
Negative	10	20.8	11	22.0	
Tumor grade					
1 (well differentiated)	1	2.1	0	0.0	0.92 ***
2 (moderately differentiated)	22	45.8	25	50.0	
3 (poorly differentiated)	23	47.9	24	48.0	
4 (anaplastic)	1	2.1	1	2.0	
Unknown	1	2.1	0	0.0	
Location of metastases					
Visceral (liver/lungs)	43	89.6	41	82.0	0.62 ***
Non-visceral	2	4.2	3	6.0	
No metastases	3	6.2	6	12.0	
Prior adjuvant chemotherapy					
Any chemotherapy	22	45.8	26	52.0	0.54 **
Anthracyclines	17	35.4	24	48.0	0.88 **
Taxanes	10	20.8	13	26.0	

*Wilcoxon-test; **χ^2-test; *** Fisher's exact test.

74.2 to 80 mg/m^2. Cycle 6 was completed by 50% and 64% of patients in both arms, respectively ($p = 0.16$), with a mean DOC dose ranging from 71.9 to 72.5 mg/m^2. Five patients in both arms completed a total of 30 DOC cycles.

In Cycle 1, SOR/PLAC was interrupted by 52.1% and 14% of patients ($p < 0.0001$), for a mean of 6.5 and 4.2 days, respectively. Cycle 2 was completed by 66.7% of patients under SOR, compared to 84% under PLAC ($p = 0.34$); herein, dose interruptions were reported at 35% for SOR and at 14.6% for PLAC ($p = 0.025$), for a mean of 7.8 and 0.9 days, respectively. In Cycle 6, treatment with SOR and PLAC was continued among 43.7% and 54% of patients, respectively ($p = 0.74$). 2 patients receiving SOR completed 33 cycles and 1 patient a total of 47 cycles.

Primary reasons for treatment discontinuation were tumor progression (49%), toxicity (20.8%) and patient's wish (11.5%), with a marked imbalance between both arms: 30.4% of patients under SOR discontinued therapy due to an adverse event (AE) compared to 12% under PLAC ($p = 0.03$). Inversely, 56% of patients under PLAC stopped treatment due to progression, opposed to 40.1% under SOR ($p = 0.15$).

3.3. Efficacy

96 out of 98 patients were evaluable for PFS and TTP. No significant differences between experimental and control arm were found for PFS (median PFS 8.2 vs. 7.3 months; HR = 0.84, $p = 0.43$) and ORR (52.1% vs. 54.0%; HR = 0.96, $p = 0.85$) (Fig. 1i and Table 2, respectively). There was a trend for a longer DOR in the experimental arm with a median of 11.5 vs. 7.9 months ($p = 0.06$), possibly indicating some efficacy of SOR maintenance. Median TTP was 11.2 months in experimental vs. 7.6 months in control arm (HR = 0.68, $p = 0.28$). OS did not significantly differ (25.6 vs. 21.2 months; HR = 0.94, $p = 0.72$), despite a numerical increase in favor of SOR (Fig. 1ii).

An exploratory comparative analysis of the two SOR dosing schedules showed no statistically significant differences in ORR and median DOR (Table 3). PFS was similar in SOR 800 mg upfront and escalating dosing, (10.0 months (95%CI 5.6–12.9) vs. 6.3 months (95%CI 4.0–11.8; HR = 0.781, $p = 0.45$)), but a significantly longer OS was observed in SOR 800 mg upfront dosing (Fig. 1iii and iv). A multivariate cox regression analysis revealed a tendency towards increased OS among HR positive patients both in experimental arm ($p = 0.0235$), as well as in the total patient population (p = 0.0444), but no significant differences according to prior anthracycline/taxane treatment (Fig. 2A and B).

3.4. Safety

During the treatment period anemia, neutropenia, lymphopenia, fatigue, nausea, vomiting, stomatitis, diarrhea, arthralgia, myalgia, polyneuropathy, PPE, rash and nail disorder were the most frequent AEs. Considering AEs of all grades, statistically significant higher rates of nail disorder (29.2% vs. 12%, $p = 0.035$) and PPE (58.3% vs. 6%, $p < 0.0001$) were observed in the experimental arm (Table 4). Regarding grade 3/4 toxicities, higher rates of nail disorder (10.4% vs. 0%, $p = 0.025$), PPE (41.7% vs. 0%, $p < 0.0001$) and diarrhea (18.8% vs. 4%, $p = 0.021$) were reported under SOR.

Regarding SOR dosing subgroups, despite small patient numbers, we found a trend towards increased hematological toxicities with upfront SOR 800 dosage (leukopenia 56% vs. 26.1%, $p = 0.036$; neutropenia 48% vs. 17.4%, $p = 0.025$) was noticed (Table 5). Inversely, significantly more nausea/vomiting (65.2% vs. 24%, $p = 0.004$) was reported under SOR escalating dosing. Rates of nail disorder, PPE and diarrhea did not differ between SOR dosing schedules. Concerning grade 3/4 AEs, there was a trend towards increased hematotoxicity under SOR 800 mg upfront dosing (leukopenia 48% vs. 17.4%, $p = 0.025$; neutropenia 44% vs. 13%, $p = 0.018$) (Table 5). Grade 3/4 febrile neutropenia was reported only among patients under SOR 800 mg upfront (24% vs. 0%, $p = 0.023$). However, a relevant proportion of these patients also received DOC 100 mg/m^2, as used prior to first amendment. In total, 94 serious adverse events (SAEs) were reported; significantly more

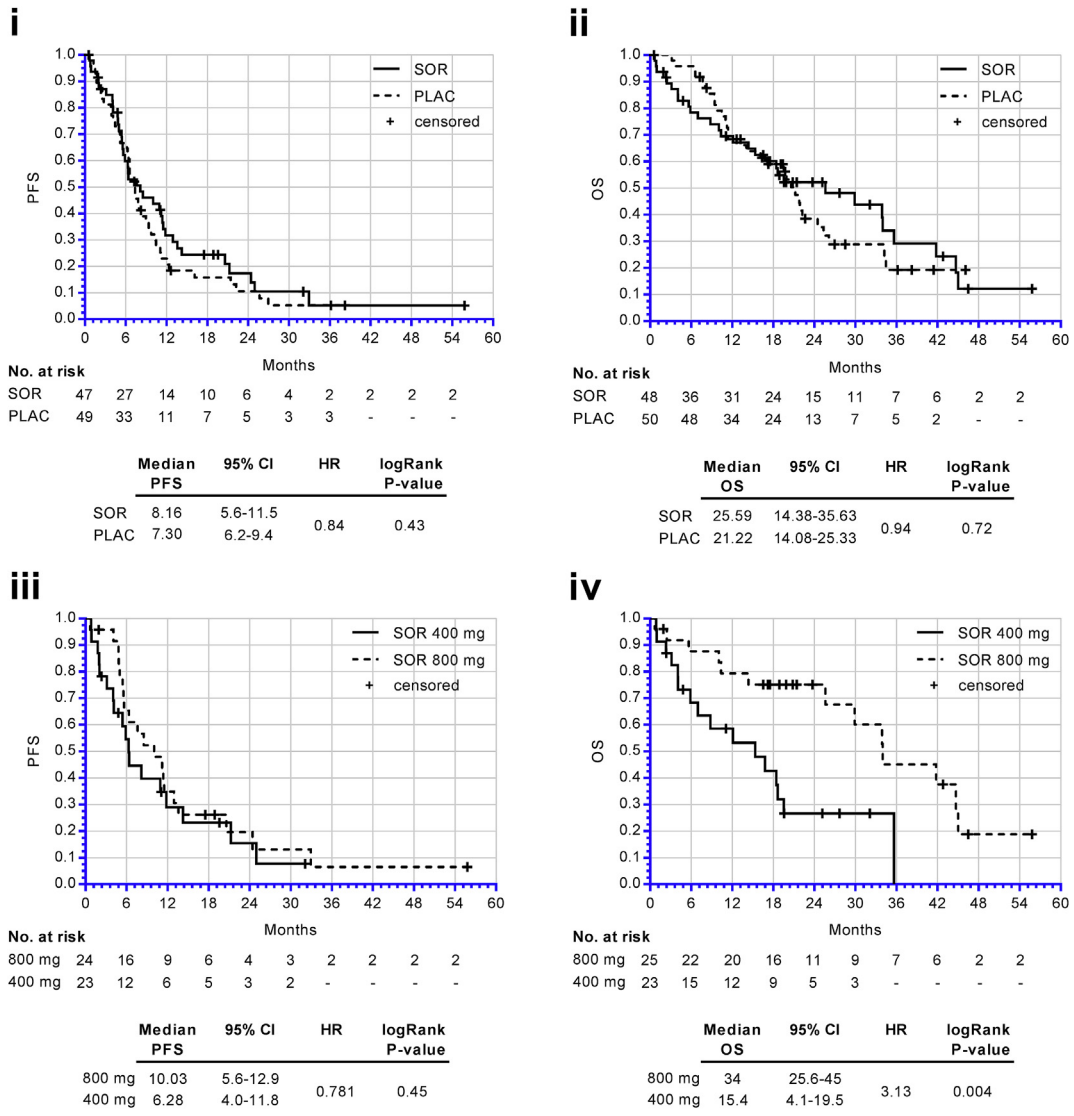

Fig. 1. Kaplan-Meyer estimates for (i) PFS and (ii) OS according to treatment arm; for (iii) PFS and (iv) OS according to SOR dosing schedule.

Table 2
Response rates according to treatment arm.

Response	Experimental arm N = 48			Control arm N = 50			HR	p-value
	N	%	95% CI	N	%	95% CI		
Overall response rate (ORR)	25	52.1	37.2–66.7	27	54.0	39.3–68.2	0.964	0.85*
Best response								
CR	3	6.3	1.3–17.2	1	2.0	0.1–10.7	3.125	0.54**
PR	22	45.8	31.3–60.8	26	52.0	37.4–66.3	0.881	
SD	15	31.3	18.7–46.3	17	34.0	21.2–48.8	0.919	
PD	4	8.3	2.3–20.0	5	10.0	3.3–21.8	0.833	
Non evaluable	4	8.3	n.e.	1	2.0	n.e.	n.e.	
Duration of response (DOR) [months]	11.5		8.2–20.6	7.9		6.3–11.3	0.06***	

*χ^2-test; ** Fisher's exact test; *** log-rank.

in patients under SOR (67% vs. 28%, $p = 0.0001$).

4. Discussion

The main objective of the phase II MADONNA study was to evaluate the antitumor activity and tolerability of SOR in combination with DOC as first-line treatment for HER2-negative MBC. The trial was terminated precociously due to slow accrual, likely attributable to the unfavorable toxicity profile of the combination therapy. The final results presented here did not show any improvement in PFS, OS, TTP, ORR or median DOR by addition of SOR. Regarding the SOR 800 mg upfront dose subgroup, a trend

Table 3
Response rates according to Sorafenib dosing schedules.

Response	Sorafenib 800 mg upfront dosing N = 25			Sorafenib 400 mg escalating dosing N = 23			HR	p-value
	N	%	95% CI	N	%	95% CI		
Overall response rate (ORR)	14	56.0	34.9–75.6	11	47.8	26.8–69.4	1.171	0.57*
Best response								
CR	3	12.0	2.6–31.2	0	0.0	-	-	0.49**
PR	11	44.0	24.4–65.1	11	47.8	26.8–69.4	0.921	
SD	8	32.0	15.0–53.5	7	30.4	13.2–52.9	1.052	
PD	1	4.0	0.1–20.4	3	13.0	2.8–33.6	0.307	
Non evaluable	2	8.0	n.e.	2	8.8	n.e.	n.e.	
Duration of response (DOR) [months]	11.5		5.6–20.6	11.8		5.4–24.9	0.97***	

*χ^2-test; ** Fisher's exact test; *** log-rank.

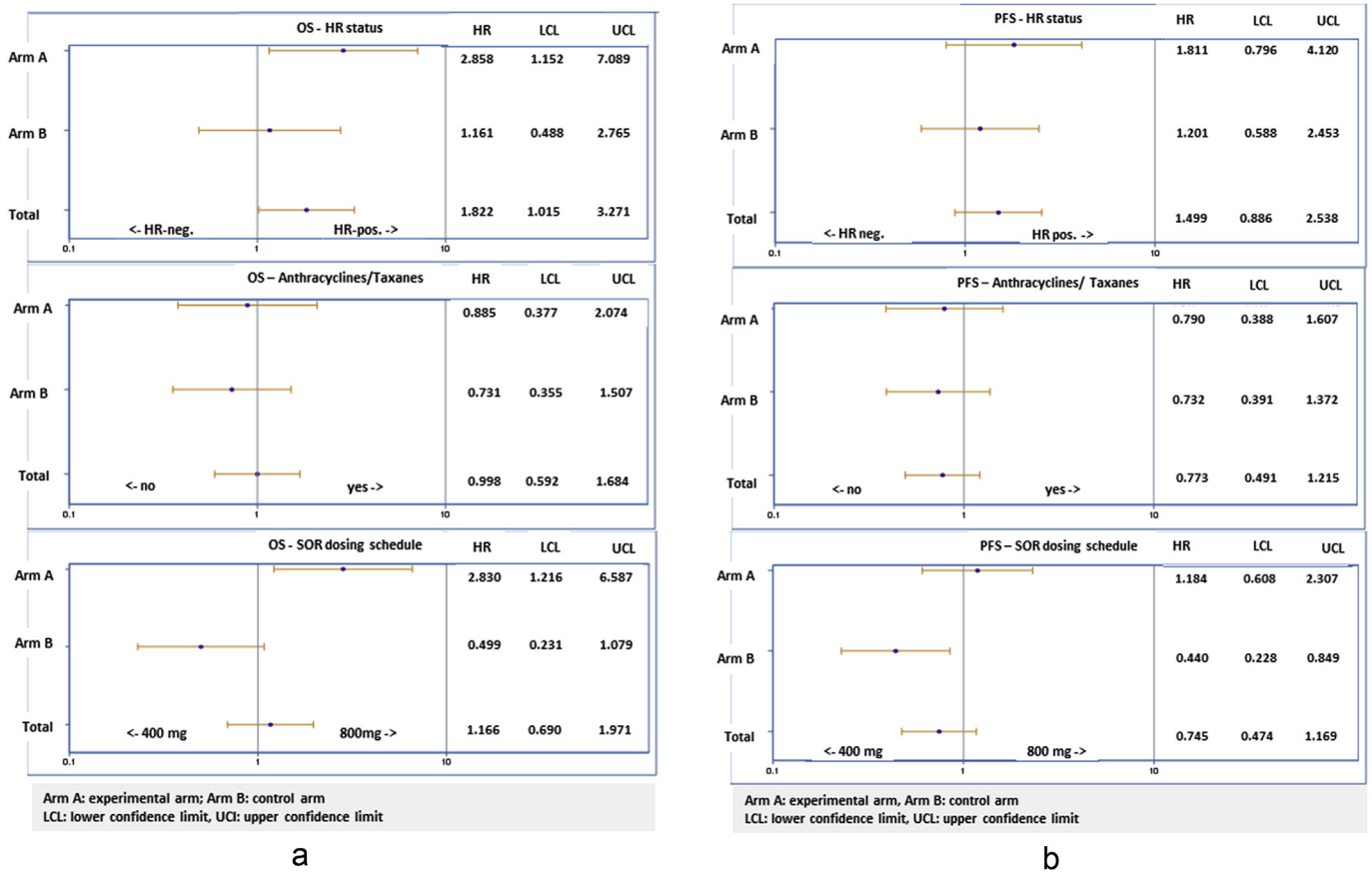

Fig. 2. A Forest plot of multivariate Cox regression for OS. B Forest plot of multivariate Cox regression for PFS.

towards longer OS was found; however this was limited by small patient numbers.

Addition of SOR resulted in higher toxicity with significantly more SAEs, reflected in higher rates of early treatment discontinuation. Overall, more patients under SOR stopped treatment because of AEs. The addition of SOR did not result in increased taxane-associated hepato- or neurotoxicity, but in significantly increased nail disorder and PPE. SOR 800 mg upfront dosing combined with DOC 100 mg/m^2 resulted in increased hematotoxicity. Upon recommendation of the trial steering committee, dose reduction of DOC and consequent implementation of SOR escalating dosing improved hematotoxicity, without ameliorating skin/nail toxicity. However, this can only be regarded as an exploratory observation, since the comparison was not preplanned, not based on randomized groups and impeded by the limited patient numbers in each SOR subgroup. In addition, all observations are confounded by the frequent SOR interruptions ranging from 1 to 21 days in up to 52.1% of patients within the first treatment cycles.

Similar experiences have been reported in the trial NU07B1 combining upfront SOR 800 mg or placebo with paclitaxel 90 mg/m^2 weekly. Here, grade 3/4 PPE rates led to dose interruptions or reductions of SOR in 55.5% and 49.6% of patients, respectively. Although comparisons with results from other trials (SOLTI-0701, AC01807 and FM-B07-01) may be flawed by different patient populations, treatment settings, or combinations, a similar frequency of dose reductions and discontinuations of SOR and/or the combined cytostatic/cytotoxic was reported, and attributed to unacceptably high treatment-related skin toxicity. Recently, the randomized, placebo-controlled phase III RESILIENCE trial, comparing SOR 600 mg per day or matching placebo in combination with

Table 4
All-grade adverse events occurring in >10% of patients and most common grade 3/4 adverse events, stratified by treatment arm.

Toxicities	Experimental arm N = 48				Control arm N = 50				p-value	
	All grades		Grade 3/4		All grades		Grade 3/4		All grades	Grade 3/4
	N	%	N	%	N	%	N	%		
Anemia	14	29.2	-	-	14	28.0	1	2.0	0.898	1 *
Leukopenia	20	41.7	16	33.3	16	32.0	11	22.0	0.321	0.209
Lymphopenia	26	54.2	13	27.1	24	48.0	13	26.0	0.541	0.903
Neutropenia	16	33.3	14	29.2	23	46.0	18	36.0	0.200	0.471
Febrile Neutropenia	7	14.6	6	12.5	3	6.0	3	6.0	0.161	0.265
Diarrhea	23	47.9	9	18.8	16	32.0	2	4.0	0.108	0.021
Nausea/Vomiting	21	43.8	3	6.3	21	42.0	2	4.0	0.861	0.613
Stomatitis	13	27.1	1	2.1	11	22.0	-	-	0.559	0.49*
Fatigue	22	45.8	5	10.4	22	44.0	2	4.0	0.855	0.218
Arthralgia	8	16.7	-	-	12	24.0	1	2.0	0.368	1*
Myalgia	5	10.4	1	2.1	11	22.0	-	-	0.121	0.49*
Nail disorder	14	29.2	5	10.4	6	12.0	-	-	0.035	0.025*
Hand foot syndrome (PPE)	28	58.3	20	41.7	3	6.0	-	-	< 0.0001	0.00002*
Rash	8	16.7	6	12.5	4	8.0	1	2.0	0.191	0.057
Polyneuropathy	12	25.0	3	6.3	8	16.0	1	2.0	0.269	0.288

* Fisher's exact test.

Table 5
All-grade adverse events occurring in >10% of patients and most common grade 3/4 adverse events, stratified by SOR dosing schedule.

Toxicities	Sorafenib 800 mg upfront dosing N = 25				Sorafenib 400 mg escalating dosing N = 23				p-value	
	All grades		Grade 3/4		All grades		Grade 3/4		All grades	Grade 3/4
	N	%	N	%	N	%	N	%		
Anemia	7	28.0	-	-	7	30.4	-	-	0.853	n.a.
Leukopenia	14	56.0	12	48.0	6	26.1	4	17.4	0.036	0.025
Lymphopenia	13	52.0	9	36.0	13	56.5	4	17.4	0.753	0.147
Neutropenia	12	48.0	11	44.0	4	17.4	3	13.0	0.025	0.018
Febrile Neutropenia	6	24.0	6	24.0	1	4.3	-	-	0.054	0.023*
Diarrhea	12	48.0	5	20.0	11	47.8	4	17.4	0.990	0.817
Nausea/Vomiting	6	24.0	1	4.0	15	65.2	2	8.7	0.004	0.502
Stomatitis	8	32.0	1	4.0	5	27.1	-	-	0.424	1*
Fatigue	12	48.0	3	12.0	10	43.5	2	8.7	0.753	0.708
Arthralgia	3	12.0	-	-	5	21.7	-	-	0.366	n.a.
Myalgia	4	16.0	-	-	1	4.3	1	4.3	0.187	0.479*
Nail disorder	7	28.0	4	16.0	7	30.4	1	4.3	0.853	0.187
Hand foot syndrome (PPE)	16	64.0	11	44.0	12	52.2	9	39.1	0.406	0.732
Rash	6	24.0	4	16.0	2	8.7	2	8.7	0.155	0.445
Polyneuropathy	5	20.0	1	4.0	7	30.4	2	8.7	0.404	0.502

* Fisher's exact test.

capecitabine (CAP) as first- or second-line treatment in MBC, was presented [24]. Despite the lower SOR dose, resulting in lower skin toxicity (grade 3 PPE 15.8% in SOR vs. 7.5% in PLAC), treatment-emergent AEs necessitated dose interruptions/reductions of both combination agents among two thirds of patients. The lower dose intensity and shorter treatment exposure of CAP under SOR combination could in part explain the lack of efficacy (SOR arm: PFS 5.5 months, OS 18.9 months; PLAC arm: PFS 5.4 months, OS 20.3 months).

Further phase I/II trials investigating SOR at the MTD of 400 mg daily combined with vinorelbine [21], or at the MTD of 800 mg daily combined with ixabepilone [25] in MBC, showed similarly discouraging results regarding tolerability and anti-tumor activity. Recent trials in solid tumors investigate intermittent dosing schedules. This apparently results in lower toxicity with sustained anti-tumor activity in MBC [26]. Alternative dosing regimens of SOR in MBC are currently evaluated in a phase II trial in combination with Pemetrexed (NCT02624700), as well as in a phase I trial in combination with whole brain radiotherapy (NCT01724606). Similar approaches are currently under evaluation also for other multi-receptor tyrosine kinase inhibitors (multi-TKIs), like sunitinib.

The results from the MADONNA trial showed that addition of SOR to DOC as a first-line palliative treatment in patients with MBC led to a significant increase of dose-limiting toxicity, translating into a disappointing treatment efficacy. The unfavorable toxicity profile appeared to be the main reason for the slow accrual and early termination of the trial. Clinical development of anti-angiogenic RTKIs in MBC is impaired by an increased systemic toxicity when combined to standard cytostatic regimens. Further clinical trial designs implementing antiangiogenic RTKIs in alternative dosing regimens aiming at improved clinical outcomes and greater therapeutic benefits for MBC patients may be warranted. However, since other novel targeted therapeutic strategies, like immunotherapies and PARP-inhibitors, have gained more interest, development of antiangiogenic RTKIs in combination with standard chemotherapies is unlike to regain momentum.

5. Conclusion

Herein we report the final results of the multicenter, randomized, double-blind, placebo-controlled phase II MADONNA study, assessing the antitumor activity and toxicity profile of DOC with the antiangiogenic RTKI SOR or matching PLAC as first-line treatment in patients with HER2-negative MBC. Despite dose modifications upon consecutive protocol amendments, this combinational regime resulted in significantly increased dose-limiting toxicities, with no improvement in PFS, OS, TTP, ORR or median DOR.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2019.02.002.

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