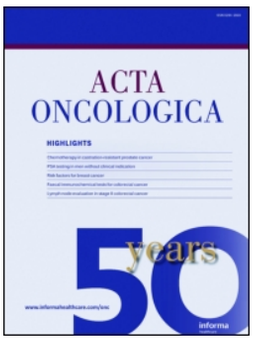

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ORIGINAL ARTICLE

Secondary analyses of the randomized phase III Stop&Go study: efficacy of second-line intermittent versus continuous chemotherapy in HER2-negative advanced breast cancer

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ABSTRACT

Background: Previously, we showed that reintroduction of the same (first-line) chemotherapy at progression could only partially make up for the loss in efficacy as compared to continuously delivered first-line chemotherapy. Here, we report the probability of starting second-line study chemotherapy in the Stop&Go trial, and the progression-free survival (PFS) and overall survival (OS) of patients who received both the first- and second-line treatment in an intermittent versus continuous schedule.

Methods: First-line chemotherapy comprised paclitaxel plus bevacizumab, second-line capecitabine or non-pegylated liposomal doxorubicin, given per treatment line as two times four cycles (intermittent) or as eight consecutive cycles (continuous).

Results: Of the 420 patients who started first-line treatment within the Stop&Go trial (210:210), a total of 270 patients continued on second-line study treatment (64% of all), which consisted of capecitabine in 201 patients and of non-pegylated liposomal doxorubicin in 69 patients, evenly distributed between the treatment arms. Median PFS was 3.7 versus 5.0 months (HR 1.07; 95% CI: 0.82–1.38) and median OS 10.9 versus 12.4 months (HR 1.27; 95% CI: 0.98–1.66) for intermittent versus continuous second-line chemotherapy. Second-line PFS was positively influenced by prior hormonal therapy for metastatic disease and longer first-line PFS duration, while triple-negative tumor status had a negative influence. Patients with a shorter time to progression (TTP) in first-line ($\leq$10 months) had a higher probability of starting second-line treatment if they received intermittent compared to continuous chemotherapy (OR 1.97; 95% CI: 1.02–3.80).

Conclusion: We recommend continuous scheduling of both the first- and second-line chemotherapy for advanced breast cancer.

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Background

Although several improvements have been made in the treatment of early breast cancer, advanced breast cancer remains largely incurable with a median survival of ~2–3 years [1,2]. Treatment of patients with advanced breast cancer focuses both on improving length and quality of life, but the optimal duration of a particular line of chemotherapy is still not clarified [3]. This results in a high variety of treatment strategies in daily clinical practice, with some using a predefined number of cycles and others continuing treatment till progression of disease (PD) or unacceptable toxicity. Considering the fact that the likelihood of response to each subsequent line of treatment decreases, optimization of especially the initial treatment lines may be important.

A previous meta-analysis of 11 randomized trials on shorter (4–6 cycles) versus longer (8–12 cycles) chemotherapy durations reported inferior PFS results with shorter durations of treatment [4]. However, most of the trials included in this pooled analysis comprised outdated treatment agents, with only three trials investigating taxane-containing treatments, showing inconclusive results [5–7]. As taxanes are suggested for first-line chemotherapy by current guidelines [3], the question remained if these recommendations were also applicable for these modern agents, with expected higher efficacy in the initial treatment cycles. Therefore, the Stop&Go study intended to make a comparison of an interrupted versus a continued chemotherapy schedule with agents that were frequently used in current clinical practice.

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*Individual names of collaborators associated with the research group are given in Online Table 1.

Supplemental data for this article can be accessed here.

The results presented in this paper were partly presented at ESMO-Breast Cancer 2019, Poster 158P and were mentioned in an official ESMO press-release.

The Stop&Go trial is a phase III trial, investigating the efficacy and tolerability of intermittent versus continuous scheduling of the first two chemotherapy lines [8]. For first-line chemotherapy [8], we found that reintroduction of the same therapy at progression (intermittent schedule) could only partially make up for the loss in efficacy as compared to continuously delivered chemotherapy. In the current exploratory analysis, we focus on the results of second-line treatment scheduling. We hypothesized that the most efficient treatment approach in first-line (intermittent or continuous) would lead to a differential patient selection in second-line and to an increased effectiveness in second-line and overall, when using the same approach in second-line.

Methods

Study design and participants

The randomized, open-label phase III Stop&Go trial was conducted at hospitals affiliated to the Dutch Breast Cancer Research Group (BOOG). Patients with HER2-negative incurable locally advanced or metastatic breast cancer who were candidates for first-line chemotherapy and who fulfilled the eligibility criteria were randomized to intermittent or continuous chemotherapy [8]. Participants were allocated in a 1:1 ratio by minimization, using the computer program ALEA (https://www.tenalea.com/nkiavl/alea/Default.aspx).
Stratification factors included institute, hormone receptor status and site of disease (visceral versus non-visceral). No placebo treatments were used. After allocation, participants were to receive the same treatment strategy (intermittent or continuous) both in first- and in second-line (no cross-over and no repeated randomization).

The study was conducted in agreement with the Declaration of Helsinki (version 1 May 1996) and local regulations (ethics committee Eindhoven, the Netherlands). All participants provided written informed consent. The study protocol is registered at the EU Clinical Trials Register, number 2010-021519-18 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021519-18).

In the intermittent treatment arm, four cycles of chemotherapy were given followed by another four cycles of the same treatment, if a PD-event occurred $\geq$3 months after the initial cycles. If PD occurred $<$3 months or after a second PD after re-introduction, second-line treatment had to be started if the patient was still fit enough. In the continuous treatment arm, a maximum of eight cycles of chemotherapy were given successively in both first- and second-line (Figure 1), without re-introduction at PD. In the current analysis, we determined the effect of chemotherapy scheduling in the patients who were able to receive both first- and second-line study treatment.

Treatment and assessments

First-line treatment consisted of paclitaxel 90 mg/m^2 intravenously on days 1, 8 and 15, combined with bevacizumab 10 mg/kg intravenously on days 1 and 15, repeated every 28 days. Bevacizumab maintenance was continued at 15 mg/kg once every 21 days until the occurrence of PD or unacceptable toxicity. For extensive information, see previous publication [8]. Second-line treatment consisted of either capecitabine at 1000 mg/m^2 orally BID for 2 weeks, followed by 1 week off, or of non-pegylated liposomal doxorubicin intravenously at 60 mg/m^2 once every 3 weeks, chosen at the discretion of the physician and depending on prior use of anthracyclines in the adjuvant setting. Receiving endocrine- or other systemic anti-tumor treatments – during the study period was considered a major protocol violation, leading to censoring within the PFS analyses.

Toxicity-related dose adjustment or treatment delays were to be performed according to dose-modification guidelines described in the study protocol (see Online Supplement).

Disease response assessment was based on local clinical evaluation according to the RECIST criteria version 1.1 [9]. During the follow-up period, date of progression after the end of study treatment, and start date of new anti-tumor treatment was registered every three months until death or study withdrawal.

Outcomes

Here, we report on secondary endpoints from the Stop&Go study, with the main endpoint being PFS of second-line treatment, calculated from the start of second-line study treatment until the date of final progression as defined by the investigator, or death, whichever occurred first. Additionally, the combined PFS of both first- and second-line treatment was assessed, from randomization date to date of progression after two study-line treatments, or date of progression on first-line treatment if not started with second-line, or death, whichever occurred first. Within the PFS analyses, patients who started non-protocol anti-tumor treatment before PD were censored at the date the non-protocol anti-tumor therapy was started or at the date of last follow-up if non-progressive. OS was calculated from the start of second-line study treatment as well as from randomization. Other endpoints included predictive factors for PFS in second-line and the probability of starting second-line treatment. For the probability of starting second-line treatment, patients who died during first-line treatment were excluded. Predictive parameters included the time to progression (TTP) in first-line treatment, defined as the time from randomization until date of final progression defined by the investigator. Toxicity of second-line treatment was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. All AE's grade $\geq$3 were recorded.

Statistical analyses

Sample size calculations were done based on the primary endpoint of the Stop&Go study, first-line PFS. In order to demonstrate non-inferiority of the intermittent arm compared to the continuous arm for this endpoint with 80% power at a 0.025 significance level, a total number of 420 patients were required for randomization to first-line treatment [8]. All efficacy analyses, comparing the intermittent with the continuous treatment arm, were performed

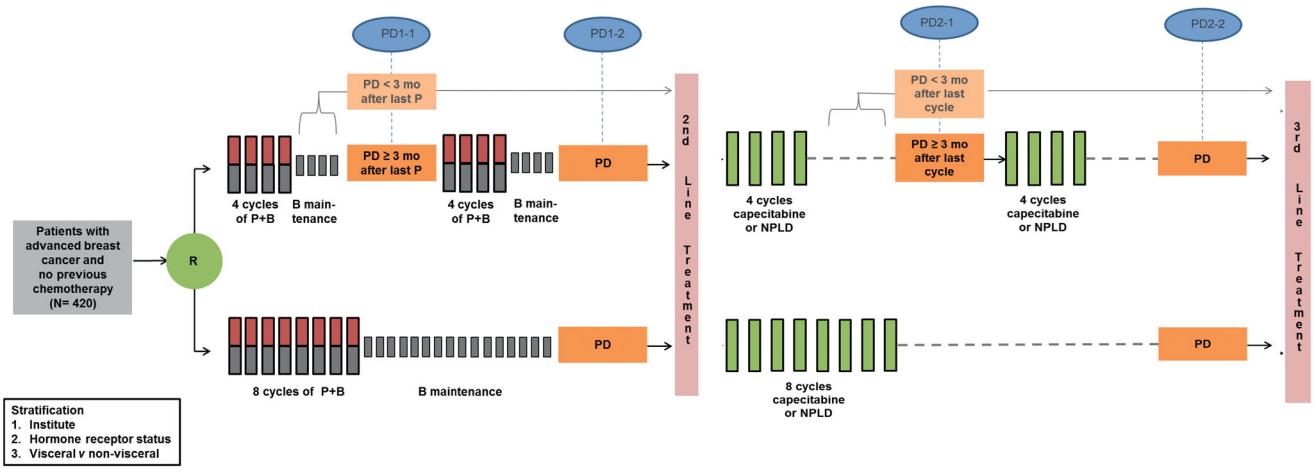

Figure 1. Flowchart of study design. R: randomization; P: paclitaxel; B: bevacizumab; NPLD: non-pegylated liposomal doxorubicin; PD: progressive disease; PD1-1: first disease progression during first-line intermittent treatment; PD1-2: final disease progression during first-line intermittent treatment; PD2-1: first disease progression during second-line intermittent treatment; PD2-2: final disease progression during second-line intermittent treatment.

according to the intention-to-treat principle. The safety analysis included all patients who received at least one dosage of second-line study medication. PFS and OS endpoints measured from randomization were performed on all patients, and separately for those who started second-line treatment. In this paper, we only report results for the patients who received both the first- and second-line study treatment. Results for all randomized patients are displayed in the online supplement, and include PFS and OS endpoints of the combined first- and second-line treatment (Online Figure 2).

The Kaplan–Meier (KM) method was used to assess PFS and OS, calculated from start of second-line study treatment and from the date of randomization. Survival curves were compared between study arms by log-rank tests. To account for possible unbalanced compliance in the study arms with respect to second-line treatment, a propensity score (PS) model was estimated, and stabilized inverse probability weights (SIPW) were calculated. Curves weighted by SIPWs were also displayed and differences between treatment groups were assessed. The (weighted) Cox proportional-hazards model was used to estimate hazard ratios (HRs) of the intermittent arm versus the continuous arm and their corresponding 95% confidence intervals (CIs). The Cox model was stratified by hormonal receptor status and site of disease, and adjusted for other patient and clinical characteristics in the case of multivariable analyses. The proportional hazards assumption was assessed by including time-by-covariate interaction terms in the model and scaled Schoenfeld residuals plots over time. In case the hazard ratio changed over time, Cox models were fitted for different time periods where the assumption of proportionality might hold. No multiple imputation of missing values in clinical characteristics was performed for multivariable analyses, as the percentage missing was 5% or less. Relevant multivariable analyses are displayed in the full paper. The remaining results, including weighted analyses, are displayed in the Online Supplement (Online Figures 2 and 3).

To model the probability of starting second-line study treatment, a mixed-effects logistic regression was performed among eligible patients (i.e., those alive after the end of first-line treatment), adjusting for several patient and clinical characteristics.

All analyses were performed using SAS (Cary, NC, USA, version V9.4) and R (Auckland, New Zealand, version 3.5).

Results

A total of 420 participants were randomized to first-line chemotherapy between December 2011 and March 2016 from 43 hospitals. At the time of database lock for the current analyses (1 November 2018), median duration of follow-up was 51.2 months (95% CI: 48–61.3). Updated OS analyses had an additional follow-up of 20.7 months compared to previously published results (previous data cutoff 3 April 2017).

Patient characteristics and received treatments

Of the 420 patients who started first-line treatment within the Stop&Go trial (210:210), a total of 270 patients continued on second-line study treatment (64% of all), which consisted of capecitabine in 201 patients and of non-pegylated liposomal doxorubicin in 69 patients, evenly distributed between the treatment arms (Online Figure 1). The key characteristics at randomization were well-balanced between treatment arms for the patients who started second-line study treatment, and these were in line with the baseline characteristics of the total study population (Table 1).

Main reasons for final second-line treatment discontinuation in the safety population were disease progression (55% in both arms), major protocol violations (e.g., receiving more than the prescribed amount of cycles; 24% versus 0%) and toxicity (11% versus 10%), for the intermittent and the continuous arms, respectively (Online Table 2).

Table 1. Baseline characteristics measured at randomization for subgroups based on actually received treatment in intermittent and continuous arm (ITT population, $N = 420$).

	Intermittent arm		Continuous arm	
Characteristics measured at randomization	All randomized ($N = 210$)	Started 2nd-line study treatment ($N = 131$)	All randomized ($N = 210$)	Started 2nd-line study treatment ($N = 139$)
Median age in years (range)	60 (36–76)	59 (38–76)	61 (28–77)	61 (28–77)
Median BMI (IQR)	25 (23–28)	25 (24–28)	26 (23–29)	26 (23–29)
ECOG PS[a]				
0–1	197 (94%)	126 (96%)	195 (93%)	134 (96%)
2	12 (6%)	5 (4%)	15 (7%)	5 (4%)
Stage at initial diagnosis[b]				
Stage I–III	185 (88%)	118 (90%)	187 (89%)	120 (86%)
Stage IV	16 (8%)	9 (7%)	18 (9%)	15 (11%)
Hormonal receptor status[c]				
ER + and/or PgR+	166 (79%)	104 (79%)	171 (81%)	116 (83%)
ER − PgR−	36 (17%)	21 (16%)	34 (16%)	19 (14%)
Median DFI (months) between initial diagnosis and metastatic diagnose (IQR)	56 (25–89)	59 (30–90)	44 (21–87)	47 (23–87)
Site of metastatic disease				
Visceral	20 (10%)	12 (9%)	19 (9%)	14 (10%)
Non-visceral	31 (15%)	22 (17%)	26 (12%)	21 (15%)
Combination visceral and non-visceral	159 (76%)	97 (74%)	165 (79%)	104 (75%)
Prior (neo)adjuvant therapy				
(Neo)adjuvant chemotherapy	131 (62%)	87 (66%)	122 (58%)	82 (59%)
Adjuvant hormonal therapy	118 (56%)	83 (63%)	110 (52%)	78 (56%)
Hormonal therapy for M1 disease				
1 line	100 (48%)	70 (53%)	93 (44%)	60 (43%)
2 lines	56 (27%)	37 (28%)	65 (31%)	41 (29%)
≥3 lines	31 (15%)	21 (16%)	38 (18%)	29 (21%)

There were no significant differences between treatment arms in any of the variables listed in the table above as tested by Chi-square, Ranksum and Fisher's exact tests.

Abbreviations: ITT: intention-to-treat; BMI: body mass index; IQR: interquartile range; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: estrogen receptor; PgR: progesteron receptor; DFI: disease free interval; M1: metastatic.

[a]Missing ECOG PS: $n = 1$ versus $n = 0$ for patients intermittent versus continuous arm.

[b]Missing stage at initial diagnosis: $n = 9$ versus $n = 5$ for intermittent versus continuous arm.

[c]Missing hormonal receptor status: $n = 8$ versus $n = 5$ for intermittent versus continuous arm.

PFS in second-line and combined PFS of first- and second-line

Median PFS on second-line study treatment ($n = 270$) was 3.7 months (95% CI: 2.8–4.7) for the intermittent treatment arm versus 5.0 months (95% CI: 4.4–5.9) for the continuous treatment arm, with a HR of 1.07 (95% CI: 0.82–1.38) in a Cox model stratified by hormonal receptor status and site of disease (Figure 2(A)). However, the assumption of proportionality of hazards was not met, so a time-by-arm interaction term was introduced. The HR was found to decrease with time. Period-specific HRs indicated that until 7 months after the start of second-line treatment, the risk of progression was higher in the intermittent arm (HR 1.39; 95% CI: 1.01–1.92, adjusted for hormonal receptor status, site of disease and other patient and clinical characteristics available in 255 patients). Considering the small population of patients left at risk at 7 months, caution is required in comparing the treatment arms beyond this point.

For the 270 patients starting second line of treatment, the combined median PFS of first- and second-line treatment was 14.6 months versus 16.4 months for intermittent versus continuous chemotherapy scheduling, with a HR of 1.12 (95% CI: 0.86–1.45) (Figure 2(C)). However, the same phenomenon was seen as for the PFS of second-line alone: non-proportional hazards were found for study treatment. At 12 months after randomization, the PFS curve reached a small plateau for the intermittent arm. Up until this time, hazards for combined PFS were significantly higher with intermittent treatment (HR 1.85; 95% CI: 1.14–3.00 adjusted for hormonal receptor status, site of disease and other patient and clinical characteristics available in 255 patients).

Survival in second-line and combined first- and second-line

Median OS calculated from the start of second-line study treatment was 10.9 months (95% CI: 8.2–13.4) versus 12.4 months (95% CI: 10.4–15.1) for intermittent and continuous treatment, respectively with a HR of 1.27 (95% CI: 0.98–1.66), in a Cox model stratified by hormonal receptor status and site of metastasis (Figure 2(B)).

Median OS calculated from randomization was 21.0 for intermittent versus 23.2 months for continuous treatment with a HR of 1.27 (95% CI: 0.98–1.66) for the patients who started second-line study treatment ($n = 270$) (Figure 2(D)).

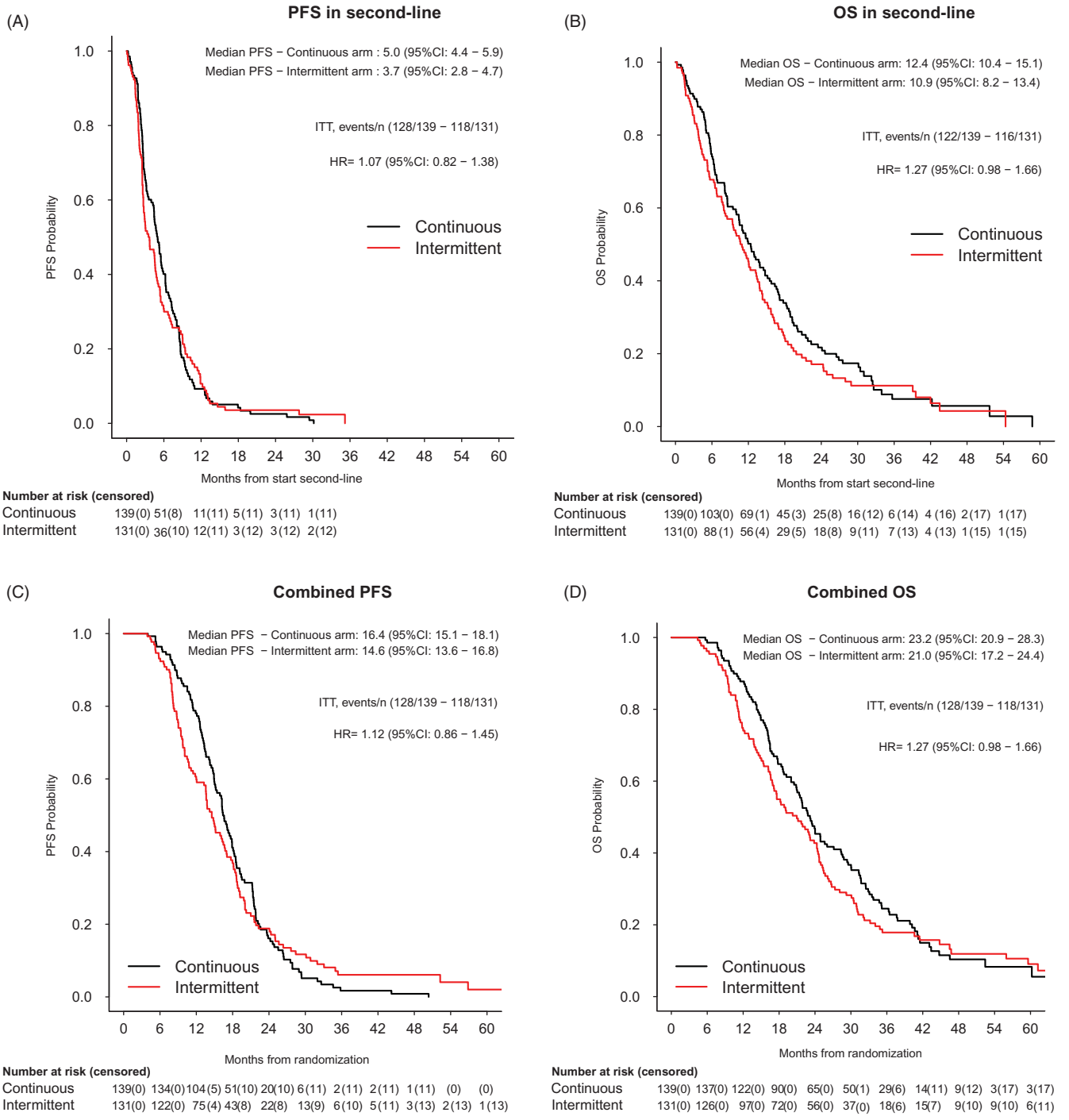

Figure 2. Kaplan–Meier estimates for the subgroup of patients in the intermittent and continuous arms that started second-line study treatment in the ITT population ($n = 270$) of: (A) progression-free survival (PFS) calculated from the start of second-line study treatment, (B) overall survival (OS) calculated from the start of second-line study treatment, (C) combined PFS of first- and second-line study treatment, (D) OS measured from randomization. Hazard ratios (HRs) of the intermittent arm versus the continuous arm and their corresponding 95% confidence intervals (CIs) were estimated using Cox proportional-hazards models, stratified by hormone receptor status and site of disease (visceral versus non-visceral).

Factors associated with second-line PFS duration

In the exploratory multivariable Cox-regression model, receiving prior hormonal therapy for metastatic disease (HR 0.68 [95% CI: 0.50–0.91]), first-line PFS duration of >10 months versus ≤10 months (HR 0.73 [95% CI: 0.55–0.97]), and increasing age (HR 0.99 [95% CI: 0.97–1.00]), were linked to a better second-line PFS. Conversely, patients with triple-negative tumors had a higher risk of progression in second-line as compared to those with hormone receptor positive/HER2- tumors (HR 1.6; 95% CI: 1.05–2.44) (Table 2).

Factors associated with the probability of starting second-line study treatment

The crude odds ratio (OR) for the intermittent compared to the continuous arm with respect to starting second-line

Table 2. Associations[a] with second-line progression-free survival.

	HR	95% CI	*p* Value
Baseline characteristics			
Treatment arm: intermittent versus continuous	1.15	0.87 − 1.53	.31
Age at randomization (years) (per additional year)	*0.99*	*0.97–1.00*	*.05*
ECOG PS 2 versus 0–1	0.87	0.39–1.92	.72
TN versus ER + and/or PgR + tumor	*1.60*	*1.05–2.44*	*.03*
DFI ≤12 months between initial diagnosis and M1 disease versus DFI >12 months	1.35	0.88–2.07	.17
Stage IV at initial diagnosis versus stage I–III	0.85	0.49–1.47	.56
Prior HT for M1 disease versus no prior HT	*0.68*	*0.50–0.91*	*.01*
Only non-visceral metastasis versus visceral localizations	0.87	0.58–1.30	.50
First-line treatment characteristics			
First-line TTP of > 10 months versus ≤ 10 months	*0.73*	*0.55–0.97*	*0.03*

Abbreviations: ITT: intention-to-treat; HR: hazard ratio; 95%CI: 95% confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HT: hormonal therapy; M1: metastatic disease; TN: triple negative: ER: estrogen receptor; PgR: progesteron receptor; DFI: disease free interval; TTP: time to progression.
Italic values considered statistically significant. For $n = 15$ patients one or more baseline characteristics were missing.
[a]Multivariable Cox-regression model.

study treatment was 0.90 (95% CI: 0.59–1.37). The odds of starting second-line treatment were lower for patients with baseline ECOG performance status 2 compared to 0–1 (OR 0.24; 95% CI: 0.09–0.63) (Table 3).

The probability of starting second-line treatment in the different treatment arms was linked to the TTP in first-line. Within the continuous arm, the probabilities of starting second-line study treatment were 0.80 and 0.61 for patients with a first-line TTP of >10 months and ≤10 months, respectively. For the intermittent treatment, these probabilities were 0.68 and 0.75. To further evaluate this association, we first looked at the treatment arms separately. For the continuous arm, the odds of starting second-line chemotherapy in patients with TTP >10 months were significantly higher compared to the odds for patients with a TTP of ≤10 months (adjusted OR 2.73; 95% CI: 1.36–5.46). In contrast, no evidence for such interaction was found for the intermittent treatment arm (OR 0.70; 95% CI: 0.34–1.43). Secondly, we compared the odds of starting second-line study treatment between treatment arms for patients with a specific TTP duration in first-line. Patients with a TTP of ≤10 months had a higher probability of starting second-line treatment if they received intermittent treatment compared to continuous treatment (OR 1.97; 95% CI: 1.02–3.80). For a TTP of >10 months, there was an indication of the opposite (OR 0.50; 95% CI: 0.24–1.06). See Table 3 for all parameters.

Toxicity of second-line treatment

Generally, the number AEs of grade ≥3 was lower in the intermittent arm compared to the continuous arms. Key AEs of grade ≥3 were neutropenia (5% versus 9%), palmar–plantar erythro-dysesthesia syndrome (5% versus 8%), fatigue (5% versus 8%), pain (5% versus 7%), diarrhea (2% versus 6%), dyspnea (5% versus 1%) and hypertension (13% versus 14%) for intermittent versus continuous treatment, respectively (Table 4). There were two treatment-related deaths during second-line treatment, one due to left ventricular dysfunction and one due to hepatic failure, both in the continuous treatment-arm.

Discussion

The Stop&Go study was designed to assess the impact of chemotherapy scheduling in first- and second-line chemotherapy in patients with HER2-negative advanced breast cancer. Previously, we reported that continuous chemotherapy during first-line treatment might be the preferred strategy, because of the observed trend in improved PFS and OS as compared to intermittently delivered first-line chemotherapy [8]. Now, we addressed the question whether maintaining the same scheduling during second-line would further improve outcome. Indeed, we found that continuous scheduling of both first- and second-line treatment showed an improved OS by approximately two months (21.0 versus 23.2 months, at a HR of 1.27 [95% CI: 0.98–1.66]). Although there was an absence of statistical significance, results showed a clear favorable trend for continuous treatment.

Although the observed efficacy of second-line study treatment (median PFS 3.7 versus 5.0 months, median OS 10.9 versus 12.4 months) seemed relatively poor, results were comparable to other studies. A review on phase II and III studies on single-agent second-line chemotherapy for advanced breast cancer noted median OS of 8–13 months for the majority of trials [10]. In comparison, trials reporting second-line PFS within this review were scarce, and medians varied from 2.5 to 9.8 months depending on the investigated single-agent [10]. Observational studies on multiple lines of chemotherapy for advanced breast cancer reported median second-line PFS or TTP between 2.5 and 11.7 months [11–21]. However, comparison of these outcomes between trials is limited due to the large variety in (amount of) previous treatments, selection of patients, type of chemotherapy and whether or not concurrent treatments were given.

To our knowledge, this is the first randomized controlled trial that evaluated the efficacy of intermittently delivered chemotherapy over several treatment lines. Although other studies comparing different durations of first-line chemotherapy found significant benefits in PFS with prolonged chemotherapy, effects on OS were less consistent [5,6,22–32]. From this current study, we learned that the same phenomenon occurred in first- and second-line study treatment; a relatively rapid progression of disease in the period after cessation of

Table 3. Probabilities[a] of starting second-line study treatment (ITT population excluding deaths during first-line treatment, $N = 376$).

Baseline characteristics	OR	95% CI	*p* Value
Age at randomization: >65 years versus ≤65 years	0.81	0.49–1.36	.43
BMI: >25 versus ≤25	1.08	0.67–1.76	.75
ECOG PS 2 versus 0-1	*0.24*	0.09–0.63	*.00*
TN versus ER + and/or PgR + tumor	0.73	0.36–1.48	.38
DFI ≤ 12 months between initial diagnosis and M1 disease versus DFI > 12 months	0.56	0.28–1.10	.09
Stage IV at initial diagnosis versus stage I-III	1.35	0.49–3.69	.56
Prior HT for M1 disease versus no prior HT	1.21	0.72–2.05	.47
Only non-visceral metastasis versus visceral localizations	2.16	0.94–4.97	.07

Abbreviations: ITT: intention to treat; OR: odds ratio; 95% CI: 95% confidence interval; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: estrogen receptor; PgR: progesterone receptor; DFI: disease free interval; M1: metastatic.
Italic values are considered statistically significant.
[a]Mixed-effects logistic regression model adjusted for time to final progression (grouped ≤ versus >10 months) in first-line treatment, and for baseline characteristics.

Table 4. Adverse events Grade 3 or higher with an incidence of at least 2% in any study arm occurring during second-line, irrespective of relation to study treatment (maximum grade) (safety population, $n = 270$)[c].

	Capecitabine or non-pegylated liposomal doxorubicin							
	Intermittent ($N = 131$)				Continuous ($N = 139$)			
Adverse event	All (%)	Gr. 3 (%)	Gr. 4 (%)	Gr. 5 (%)	All (%)	Gr. 3 (%)	Gr. 4 (%)	Gr. 5 (%)
Blood and lymphatic system disorder								
Anemia	4 (3)	4 (3)	–	–	6 (4)	5 (4)	1 (1)	–
Leucopenia	4 (3)	4 (3)	–	–	2 (1)	1 (1)	1 (1)	–
Neutropenia	7 (5)	5 (4)	2 (2)	–	12 (9)	10 (7)	2 (1)	–
Febrile neutropenia	3 (2)	3 (2)	–	–	1 (1)	–	1 (1)	–
Gastrointestinal disorders								
Diarrhea	3 (2)	3 (2)	–	–	9 (6)	9 (6)	–	–
Mucositis oral	3 (2)	3 (2)	–	–	3 (2)	3 (2)	–	–
Nausea	4 (3)	4 (3)	–	–	5 (4)	5 (4)	–	–
Vomiting	4 (3)	4 (3)	–	–	4 (3)	4 (3)	–	–
General disorders and administration site conditions								
Edema	–	–	–	–	3 (2)	3 (2)	–	–
Fatigue[a]	6 (5)	6 (5)	–	–	11 (8)	10 (7)	1 (1)	–
Pain[b]	7 (5)	7 (5)	–	–	10 (7)	10 (7)	–	–
Infections and infestations								
Urinary tract or bladder infection	–	–	–	–	4 (3)	4 (3)	–	–
Lung infection	2 (2)	2 (2)	–	–	3 (2)	3 (2)	–	–
Nervous system disorders								
Peripheral sensory neuropathy	4 (3)	4 (3)	–	–	2 (1)	2 (1)	–	–
Respiratory, thoracic and mediastinal disorders								
Dyspnea	7 (5)	5 (4)	2 (2)	–	2 (1)	2 (1)	–	–
Skin and subcutaneous tissue disorders								
Palmar-plantar erythro-dysesthesia syndrome	7 (5)	7 (5)	–	–	11 (8)	11 (8)	–	–
Vascular disorders								
Hypertension	17 (13)	17 (13)	–	–	20 (14)	20 (14)	–	–
Thromboembolic event	1 (1)	1 (1)	–	–	5 (4)	4 (3)	1 (1)	–

Reported adverse events (AE's) were graded using the National Cancer Institute Common Terminology Criteria for Adverse events version 4.0. The maximum grade per patient was reported here. There were two cases of grade 5 toxicity both in the continuous treatment arm ($n = 1$ left ventricular dysfunction, $n = 1$ hepatic failure).
[a]Fatigue also included AEs labeled malaise or performance status declined.
[b]Pain included AEs labeled pain, back pain, abdominal pain, pelvic pain, thoracic pain, Bone pain, pain in extremity, headache, non-cardiac chest pain, pleuritic pain and hepatic pain. Cardiac chest pain was not included.
[c]Additional AEs of grade 3 or higher of special interest occurred in the following incidences, taking into account the maximum grade per patient: heart failure/left ventricular systolic dysfunction/decreased ejection fraction $n = 1$ versus $n = 3$, myocardial infarction $n = 0$ versus $n = 1$, small intestinal perforation $n = 1$ versus $n = 0$, DPD-deficiency $n = 1$ versus $n = 0$, for the intermittent versus the continuous arm, respectively.

chemotherapy within the intermittent arm compared to a more stable course of disease within the continuous treatment arm. Additionally, the exploratory multivariable Cox-regression analysis indicated that the duration of PFS in first-line was of significant influence on second-line PFS (Table 2).

To implement a continuous chemotherapy schedule in clinical practice, the challenge is to use agents that provide disease control, are well tolerated and can be continued for a prolonged period without interruptions. Several studies have investigated the use of low-dose metronomic chemotherapy schedules, indicating the ideal agents should preferable be oral, have limited cumulative toxicity and low costs [33]. Possible candidates for the treatment of advanced breast cancer from phase I and II trials include oral cyclophosphamide and methotrexate, capecitabine and oral vinorelbine.[33] Additionally, the effects of metronomic chemotherapy include immune-mediated as well as endocrine, anti-angiogenic and stroma-targeted mechanisms, with several studies in advanced breast cancer suggesting a possible synergistic effect of combining metronomic chemotherapy with endocrine, immune- and/or targeted therapies [34–41]. Future research should thus focus on continuous administration of well-tolerated chemotherapy agents, as a background for other therapies. Additionally, the

implementation of continuous chemotherapy requires us to rethink the optimal sequence of available agents. Possibly, the more tolerable agents should be exploited first before moving onto the more toxic agents that can only be given for a limited amount of time.

Our current study indicated that when evaluating the treatment lines separately, efficacy decreased (PFS in first-line 7.4 versus 9.7 months; PFS in second-line 3.7 versus 5.0 months for intermittent versus continuous treatment, respectively). However, prospectively selecting the right population of patients that could benefit from additional treatment lines remains challenging in clinical practice. Literature on multiple lines of chemotherapy for advanced breast cancer proposes that the profile for suitable patients is determined by the benefits from previous lines and the performance status during the disease course [42]. Real-world studies indicate that response rates [11,13,43–50] and TTP or treatment failure [11,17–21,43–48,50,51] decline with subsequent chemotherapy lines. Additionally, response to and/or longer TTP or PFS of previous chemotherapy significantly influenced time to progression or PFS on next-line chemotherapy within multivariate analyses [12,17,18,45,47,49–52]. In our current study, a TTP of >10 months in first-line was associated with better PFS in second-line study treatment (Table 2). Furthermore, observational studies found similar results for OS with medians decreasing with each supplementary chemotherapy line [46–48,51]. Within the multivariate analyses of these studies, response to previous treatments [18,47,48,52–54], performance status [13,19,20,54,55] and time to progression or PFS [13,17,55] were of significant influence on OS.

A note of caution is due, since the lack of significant differences in second-line PFS might be caused by the fact that 24% of patients in the intermittent treatment arm received more than the allocated number of subsequent chemotherapy cycles (major protocol violation). If these patients would have been excluded from current analysis (a per protocol instead of intent-to-treat analysis), differences between the treatment arms could have been greater in disadvantage of intermittent scheduling. Additionally, more patients were censored due to start of non-protocol treatment (e.g., hormonal therapy) in the intermittent arm ($n = 24$ versus $n = 16$). Hypothetically these protocol violations might be due to uncertainty about the outcome caused by the chemotherapy-holiday, a relevant factor to take into account as endocrine consolidation treatment is a common practice. Another limitation includes the inability to soundly compare the subgroups of patients that received capecitabine as second-line study treatment ($n = 201$) with those who receives non-pegylated liposomal doxorubicin ($n = 69$), and the populations of patients in second-line with hormone-receptor positive ($n = 220$) disease with those who had triple-negative disease ($n = 40$) due to the imbalanced numbers. In the Stop&Go study protocol, the prolonged treatment arm consisted of eight treatment cycles. As the toxicity of especially capecitabine is generally mild, we now would recommend to continue therapy until progression of disease if well-tolerated. But, based on the results of our study we cannot make that recommendation as we did not formally test the benefit of more than eight treatment cycles.

In conclusion, the Stop&Go study found no efficacy benefits from an intermittent chemotherapy schedule across two treatment lines. The superior period-specific progression-free survival and the advantageous overall survival results of the continuous schedule prompt our advice to schedule both the first- and second-line chemotherapy for patients with HER2-negative advanced breast cancer without interruptions.

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Disclosure statement

FE has received honoraria from Roche and Novartis and has a consulting/advisory role for these companies. VTH has received honoraria from Pfizer, E. Lilly, Novartis and Roche, has a consulting or advisory role for Pfizer, E. Lilly, Novartis and Roche, has received research funding for her institution from Roche, Eisai, Pfizer, E. Lilly and Novartis, and has received travel, accommodations and/or expenses from Pfizer, Novartis and Roche. MB has received travel, accommodations and/or expenses from Roche, Novartis and Pfizer. All remaining authors have declared no conflicts of interest.

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Data availability

Additional data on the trial protocol can be found at the EU Clinical Trials Register, using number 2010-021519-18 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-021519-18).

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