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ORIGINAL RESEARCH

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Curcumin's effect in advanced and metastatic breast cancer patients treated with first or second-line docetaxel: A randomized trial

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Abstract

Background: In this study, we investigated whether the association of curcumin and docetaxel among advanced and metastatic breast cancer patients in first or second-line treatment potentiated the objective response rate.

Patients/Methods: A multicentre, randomized, open label, phase-II study was conducted and included 42 patients from July 2009 to January 2017. The primary endpoint was the objective response rate of the docetaxel-curcumin combination in comparison with docetaxel alone. The secondary endpoints were the assessment of clinical benefit, overall survival, time-to-progression, progression-free survival, compliance, and safety. An interim analysis was planned to evaluate safety and efficacy.

Results: In this interim analysis conducted on 37 patients (19 in the control group vs. 18 in the experimental group), no difference was observed for the objective response rate ($p = 0.25$, control 73.7% vs. experimental 55.6%). Concerning clinical benefit, overall survival and time-to-progression, we also failed to show any difference between the two arms. A slight tendency towards longer progression-free survival at 12 months after randomization was observed in the curcumin group (65.5% vs. 41.4%) but this difference did not reach significance ($p = 0.14$).

Conclusion: In this study, we showed for the first time that adding oral curcumin for advanced and metastatic breast cancer patients treated with first or second-line docetaxel was not efficacious, although safe. Consequently, this study was stopped for reasons of futility. Further studies with a larger number of patients, a different curcumin preparation, a longer treatment period and a pharmacokinetic evaluation of curcumin are needed to explore the real efficacy of this compound.

KEYWORDS

advanced and metastatic breast cancer, chemotherapy, curcumin, docetaxel, phytotherapy

1 | INTRODUCTION

Breast cancer is the most common malignancy among women and also the leading cause of cancer-related death among women in many countries worldwide.[1] However, the prognosis for breast cancer patients is not among the poorest, except for the triple-negative subtype and metastatic disease. Indeed, patients with metastatic breast cancer (MBC) have a poor prognosis with a median survival time of 2–3 years.[2] In fact, the primary goals of MBC treatments are not to cure the cancer but to prevent and/or alleviate symptoms, maximize quality-of-life (QoL) and prolong survival. The medical management of MBC or more generally stage-IV breast cancer (advanced and MBC) is varied and depends on tumor characteristics and the metastatic evolution. Systemic therapies are the most widely used options; they include endocrine therapy, chemotherapy, targeted drugs, immunotherapy or combinations of these. In some cases, local therapy such as surgery or radiotherapy, is required.[3,4]

Chemotherapy is generally used as first or second-line treatment for advanced and MBC patients. After failure with anthracycline, taxanes, and more specifically docetaxel, have been widely used, as a single drug or in combination, among patients with advanced and MBC. The efficacy of docetaxel (100 mg/m² every 21 days), has been demonstrated to obtain longer time to progression (TTP) and better overall survival (OS). Despite the improved outcome, docetaxel combinations also induce more toxicities. The combination of chemotherapy with a non-cytotoxic agent could help to obtain better outcomes and response to chemotherapy with reduced toxicity.[5–8]

Curcumin (diferuloylmethane) is a polyphenolic derivative extracted from *Curcuma longa L.* roots, commonly called turmeric. Apart from its use as a food coloring agent, turmeric has been used for centuries in traditional medicine (Ayurveda) in Asian countries as an antiseptic and an anti-inflammatory agent.[9,10] It is suggested that the use of curcumin could explain the reduced incidence of breast cancer among Asian women. Many in vitro and in vivo studies on curcumin have been conducted, and have demonstrated that curcumin, in addition to its anti-inflammatory properties, also has antiangiogenic, anti-invasive, antioxidant and antiproliferative effects. These properties have highlight the anticancer potential of curcumin.[11–18] The safety and tolerance of curcumin have also been demonstrated in animal models and in phase-I studies. Furthermore, some studies have focused on the chemo-preventive and chemo-potent roles of curcumin, making it a promising addition in the treatment of cancer despite its limited bioavailability.[19–22]

Moreover docetaxel and other chemotherapeutic agents are known for their side effects and toxicities: febril neutropenia, alopecia, fluid retention, nail toxicity, neuropathy.[23,24] Even if there are treatments to prevent or manage these sides effects, the need for an alternative natural drug with lower toxicity and side effects is of interest. On the other side, studies on curcumin are showing encouraging results as well-tolerated and a potential safe drug against cancer.[25–27]

Based on these facts, a phase-I study among advanced and MBC patients was conducted at the Jean Perrin Comprehensive Cancer Centre, and it concluded that the recommended dose of curcumin was 6000 mg/day for 7 consecutive days every 3 weeks in combination with a standard dose of docetaxel.[28] A phase-II trial was performed and demonstrated a high response rate, good tolerance and patient acceptability of curcumin.[29]

These encouraging results led us to conduct a randomized phase-II trial to compare docetaxel plus curcumin versus docetaxel alone. This study aims to evaluate the efficacy of docetaxel combined with oral curcumin in first or second-line treatment among patients with advanced, relapsed or metastatic Her2-negative breast cancer. An interim analysis was conducted to see the efficacy and the safety of this trial.

2 | PATIENTS AND METHODS

2.1 | Patients

Eligible patients were men or women (≥18 years old) with histologically confirmed HER2-negative metastatic or loco-regionally recurrent or inoperable breast cancer, with at least one measurable and/or evaluable lesion according to the RECIST 1.1 criteria. Treatment with docetaxel was normally indicated first-line or second-line (after anthracycline-based chemotherapy). At baseline, patients were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with a life expectancy of at least 3 months and adequate functioning of the main organs: bilirubin ≤ upper normal limit (UNL), AST and ALT ≤ 1.5 x UNL, alkaline phosphatase ≤2.5 x UNL, serum creatinine <140 µmol/l, neutrophils ≥2 $\times 10^9$/l, platelets >100 $\times 10^9$/l and hemoglobin ≥10 g/dl.

The exclusion criteria were pregnancy or lactation, history of another neoplasm (except for cured basal cell skin cancer or cervical carcinoma in situ), other serious illnesses or noncontrolled disease, known brain metastasis or primary brain tumors, experimental drugs, and pre-existing neurotoxicity ≥2 grade.

2.2 | Study design

This was a multicentre, randomized, open-label, phase-II clinical trial involving four French Comprehensive Cancer Centres. The study was approved by the CPP Sud Est VI Ethics Committee (10/09/2008) and the national review board (Agence National de Sécurité des Médicaments et des produits de santé) (28/11/2008). The study was registered at ClinicalTrials.gov (NCT 00852332). A total of 100 patients were expected to participate and an interim analysis was scheduled after the inclusion of 50 patients with outcomes at 6 months post-enrollment. Unfortunately, the pace of inclusion was too slow and curcumin reached expiry date before the 50 expected patients had been recruited for the interim analysis. Before proceeding with a new

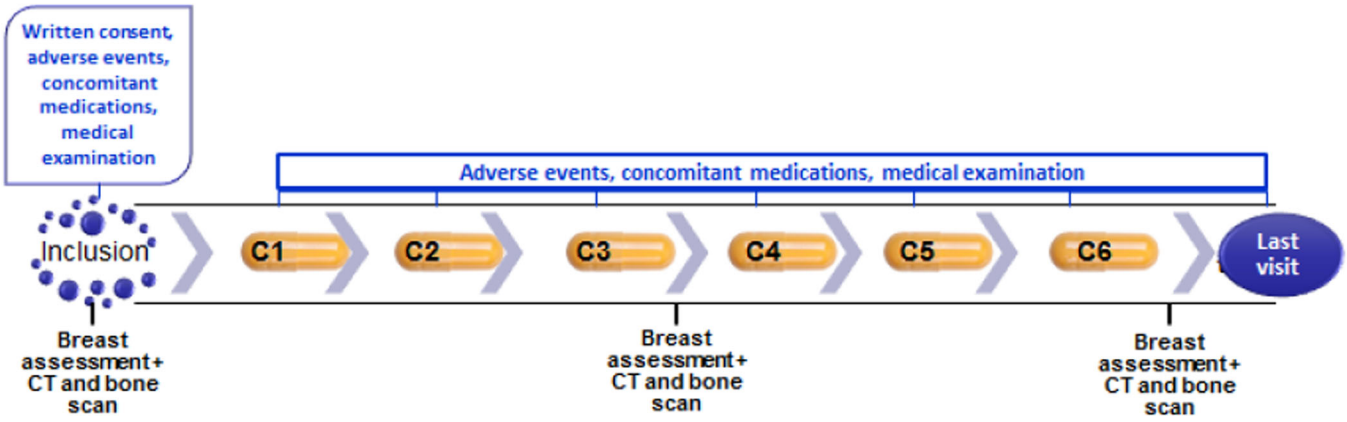

FIGURE 1 Study design. At enrollment and after patients' written informed consent pretreatment data were collected, including medical history, previous treatments, physical examination (weight, height, body mass index, and ECOG performance status), breast examination and scans (CT scan and bone scan), and a complete biological exploration. Breast examination, CT scan and bone scan were repeated after cycle 3 and cycle 6. C, chemotherapy cycle; CT scan, computerized tomography.

curcumin supply, we decided to analyze the data collected for the 42 patients to see whether it was reasonable to continue the study.

A total of 42 patients were thus included from July 2009 to January 2017 and all patients provided written informed consent before study enrollment. At baseline, pretreatment data was collected including medical history, previous treatments, and a physical examination with details on weight, height, body mass index, and performance status. A complete biology report was assessed at baseline and before each chemotherapy cycle. At each visit, patient compliance was also checked with the help of a notebook in which patients reported whether they had taken the capsules or not. At the same time, details of adverse events and concomitant medications were recorded (Figure 1).

2.3 | Treatment

A docetaxel-based chemotherapy at 100 mg/m^2 every 3 weeks during six cycles with methylprednisolone at 50 mg (six times in 3 days) was the standard treatment. Six grams of curcumin per day during 7 days (1 capsule contains 500 mg of curcumin, i.e., four capsules three times a day [4-4-4]) was given to patient in the experimental arm.

2.4 | Study endpoints

The primary endpoint of the study was an evaluation of the objective response rate (ORR) (complete response (CR) + partial response (PR)) of the docetaxel plus curcumin combination in comparison with docetaxel alone at the end of the treatment.

The secondary endpoints were the assessment of clinical benefit, OS, TTP, progression-free survival (PFS), compliance and safety.

The purpose of the interim analysis was to evaluate safety and the efficacy of the association of docetaxel plus curcumin.

2.5 | Response evaluation

Response evaluation was assessed twice in the course of the study (once every three cycles), using standard radiography, computed tomography, magnetic resonance imaging, scintigraphy and/or clinical examination. Complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) were characterized according to the RECIST 1.1 criteria. All patients with PD after the first three cycles were considered to have disease progression by the end of the study, that is, after the six cycles of treatment with docetaxel +/- curcumin.

2.6 | Statistical analysis

The analysis was primarily descriptive. Categorical parameters were described using the number of patients per class and the corresponding proportion. Quantitative values were presented with medians and range unless stated otherwise (means ± standard deviation). Student's *t*-test was used to compare quantitative parameters between treatment groups if distributions were Gaussian and homoscedastic. Otherwise, a Kruskal-Wallis H-test was preferred. For categorical parameters, the Chi^2-test was used and if class sizes were too small, Fisher's exact test was calculated. Survival curves were drawn using Kaplan-Meier's method and Log-Rank tests were computed to evaluate the difference between two curves. Differences concerning the main objective were considered statistically significant at $p < 0.03$ for this interim analysis. However, a standard p-value was used for other secondary objectives. Among the 42 patients included, five patients were excluded and no data concerning the response was available for them. The possibility of assigning the poorest response level to them was not retained because it would have been in favor of the experimental arm (3 excluded in the control group *vs.* 2 in the experimental group). Consequently, the efficacy and safety analyses were conducted on the modified Intent-to-treat population for this interim analysis. At

the end of the interim analysis, study discontinuation was planned if toxicity was 20% higher than control (determined by +20% grade III and IV toxicity), if less than 10% response rate compared with control, if the difference in response rate is in favor of the curcumin arm with a $p < 1\%$. Database management and statistical calculations were performed using SEM software.[30]

3 | RESULTS

3.1 | Patient characteristics

A total of 42 patients were randomized from July 2009 to January 2018 in this study. Among them, five patients were excluded from the analysis: three patients withdrew their consent, one patient was wrongly included and one patient stopped the study on the investigator's decision (Figure 2). Patient baseline characteristics are summarized per treatment arm in Table 1; 37 patients were analyzed: 19 in arm A (docetaxel alone) and 18 in arm B (docetaxel + curcumin). The median age was 55 and 58 years respectively for patients in arm A and arm B. In both arms, the majority of patients had an ECOG performance status of 0 or 1. More than half of the patients had two or more sites of metastatic disease. Bone metastasis (73% of the patients) was the most dominant site of metastasis, followed by liver (49%), lymph nodes (40%), lung (30%) and other metastases including skin (19%). For the majority of the patients, chemotherapy with docetaxel was the first-line treatment (72%). Baseline characteristics were well balanced between the two arms with an effective randomization process ensuring comparability.

3.2 | Compliance

Overall compliance rate was 97.5% ± 7.9% for patients receiving curcumin.

3.3 | Objective response rate (ORR)

Assessment of ORR was done after the six cycles of treatment. Among the 37 evaluable patients, each patient had available data after the first three cycles. However, no data were available for five patients for the last evaluation, after the six cycles of treatment.

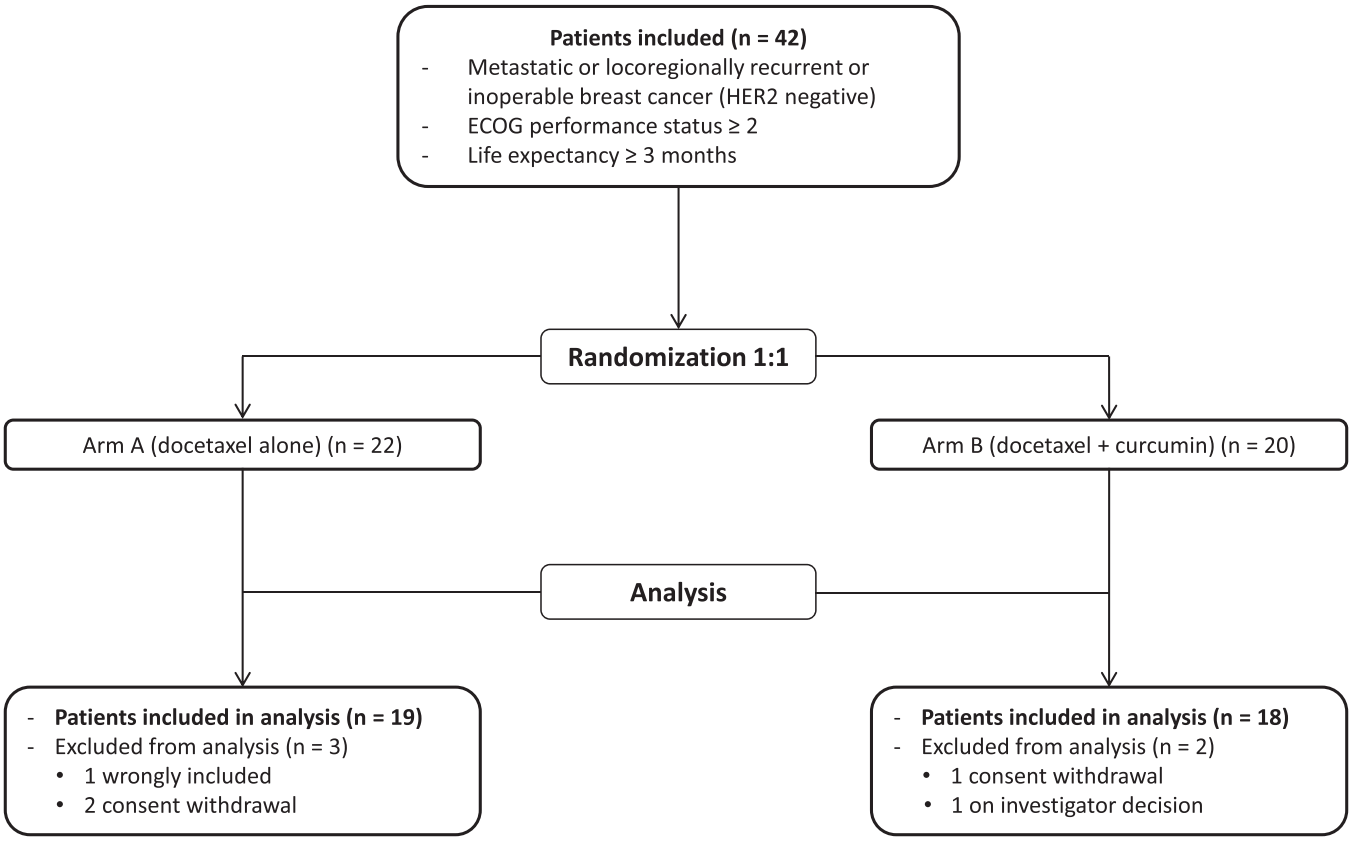

FIGURE 2 Participant flowchart. A total of 42 patients were enrolled according to the inclusion criteria. A 1:1 randomization was conducted with stratification on the centre and the number of chemotherapy lines; 22 patients were assigned to arm A (docetaxel alone) and 20 patients to arm B (docetaxel + curcumin). The interim analysis was conducted on the modified ITT population, that is, patients who were given at least one dose of docetaxel + curcumin. Among them, five patients (three in arm A and two in arm B) were excluded from the analysis: one patient was wrongly included and did not meet the inclusion criteria, three other patients withdrew their consent and one patient stopped the study on the investigator's decision. ECOG, Eastern Cooperative Oncology Group; ITT, Intention-to-treat.

TABLE 1 Patient characteristics.

	A	B	*P value*
Characteristics	N	N	
No. Patients	19	18	-
Median age at enrollment (years) [range]	55 [37–76]	58 [47–73]	0.69
ECOG Performance status	-	-	0.28
0	14	10	-
1	3	7	-
2	2	1	-
Breast cancer stage at enrollment	-	-	0.77
IIIc	1	-	-
V	18	18	-
Number of metastatic site involved		-	0.33
0	1	-	-
1	5	3	-
2	8	6	-
≥3	5	8	-
Unknown	1	-	-
Site of metastasis	-	-	0.57
Bone	15	12	-
Liver	8	10	-
Lymph node	7	8	-
Lung	3	8	-
Skin	1	-	-
Other	3	3	-
Prior chemotherapy	-	-	-
Chemotherapy	13	12	1
Endocrine therapy	14	12	0.72
Radiotherapy	17	13	0.40
Surgery	18	16	1
Treatment line for this study	-	-	0.47
First-line	14	12	
Second-line	3	5	
NA (local relapse)	1	-	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, Not applicable.

Among them, three patients with PD at the first evaluation were considered to be experiencing progression at the end of the study, and two patients with PR at the first evaluation had changed to another treatment because of toxicity with docetaxel, and they were noted as PR for the second evaluation.

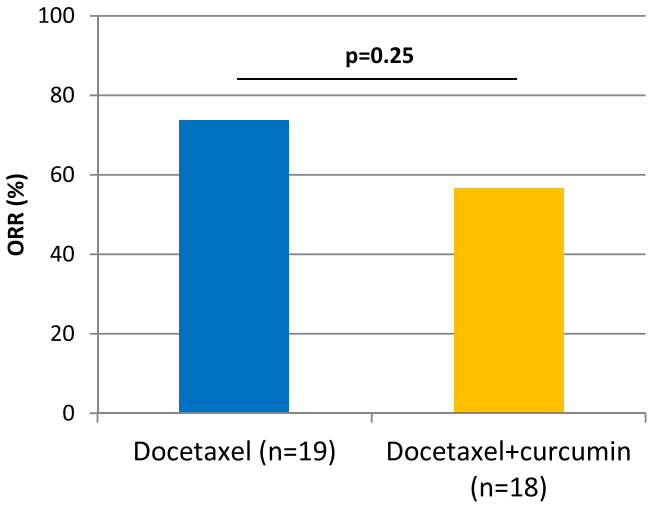

FIGURE 3 Objective response rate (ORR) in the mITT population.

When comparing the two arms, 73.7% of the patients had an ORR in the control arm versus 55.6% of the patients in the experimental arm; the difference was not significant ($p = 0.25$) (Figure 3). No CR was reported for any of the patients. This study initially hypothesized a superiority of at least 25% in the experimental arm, but there was a difference of 18% in favor of the control group. To determine whether the study should be continued despite this unfavorable balance, the chances of having a 25% difference in favor of the experimental group if accrual was continued till the end of the study were analyzed. The chances of ending up with a positive outcome were almost nil. A projection of these interim results was carried out for 100 patients and it showed that 39 other patients with ORR would be required in the experimental arm, while the maximum number of new patients in arm B could only be 30. According to this calculation, it was impossible to reach a difference of 25% in favor of the curcumin group so we decided to stop the study for futility.

3.4 | Secondary endpoints

3.4.1 | Clinical benefit

The clinical benefit for a patient, according to the RECIST criteria 1.1, was defined by CR, PR or SD and was evaluated after the six cycles of treatment. The comparison showed that 17 patients (89.5%) in the control group versus 16 patients (88.9%) in the curcumin group had a clinical benefit ($p = 0.79$).

3.4.2 | Overall survival (OS)

Overall, the median OS was 30.9 months. For control and curcumin groups, the median OS was 29.6 months versus 31.4 months respectively ($p = 0.20$) (Figure 4). The survival rate was 100% in both arms at 6 months, 83.9% versus 94.1% at 12 months ($p = 0.32$) and 59.3% versus

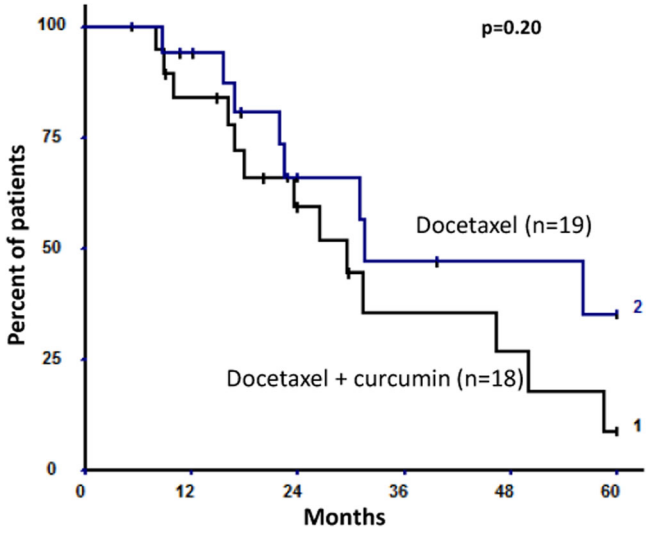

FIGURE 4 Overall survival in the mITT population.

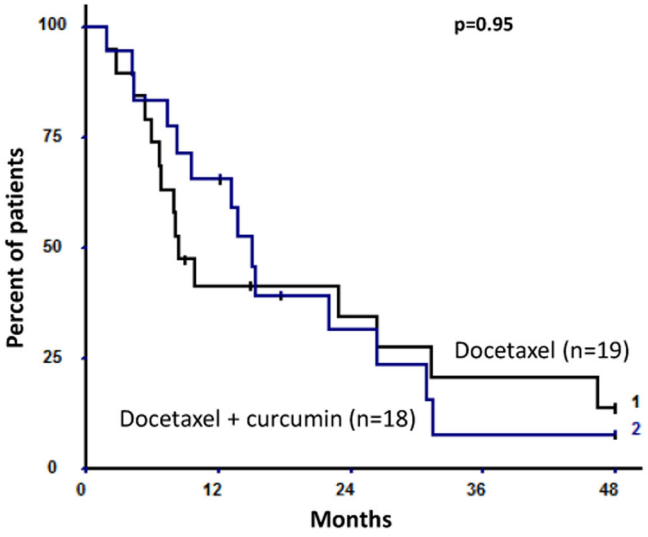

FIGURE 5 Time-to-progression in the mITT population.

66% at 24 months ($p = 0.70$), respectively for the control and curcumin groups.

3.4.3 | Time to progression (TTP) and progression-free survival (PFS)

The median TTP was 13.1 months for all 37 patients. For patients in the control group, the median TTP was 8.5 months versus 15 months for patients in the curcumin group. This difference did not reach significance ($p = 0.95$) (Figure 5).

At 12 months, that is, 6 months after the treatment with docetaxel +/- curcumin, the PFS rate was higher in the curcumin group (65.5%) than in the control group (41.4%); this difference was close to significance but failed to reach the usual level of significance ($p = 0.14$).

3.4.4 | Safety

Toxicity was evaluated among patients who had received at least one dose of treatment. No dose reduction of docetaxel or curcumin was reported in either arm but two patients in arm A (control) had to discontinue chemotherapy because of docetaxel toxicity. Apart from these two patients, the therapy was well tolerated. Among the 37 patients, the most common toxicities were asthenia (20%), neutropenia (20%), alopecia (18%), anemia (15%), myalgia (14%), diarrhea (13%), and nail toxicities (13%); they are also reported in Table 2. No difference was noted between the two groups of patients. Concerning the incidence of grade 3–4 toxicities, they are reported in Table 3 and no difference was highlighted between the treatment groups.

During the study, a total of 11 serious adverse events (SAEs) were notified, concerning six patients. Among the 11 SAEs, eight were attributed to chemotherapy with docetaxel, and were expected. However, none of them was related to curcumin.

TABLE 2 Grade 3 or 4 treatment related toxicity by arm.

Adverse event	Arm A: docetaxel alone	Arm B: docetaxel + curcumin
Anemia	1	0
Anorexia	1	0
Asthenia	1	1
Bronchospasm	1	1
Chest pain	1	0
Diarrhea	1	1
Dysepsia	1	0
Febril aplasia	3	3
Febril neutropenia	2	1
Flu	1	0
Hot flashes	1	0
Lymphedema	1	0
Lymphopenia	1	1
Mucositis	1	2
Nail toxicity	2	0
Neutropenia	11	8

4 | DISCUSSION

A large number of studies have explored the benefits of curcumin and its antineoplastic effects, making it a good candidate for cancer treatment strategies. Our team previously conducted a phase-I trial followed by a non-randomized phase-II study with positive outcomes, leading us to continue with this first randomized, open-label, phase-II

TABLE 3 Treatment related toxicity.

	Total population (n = 37)		Arm A: docetaxel alone (n = 19)		Arm B: docetaxel + curcumin (n = 18)		
Toxicity	No.	%	No.	%	No.	%	p
Asthenia	20	54	11	57,9	9	50,0	0,49
Neutropenia	20	54	12	63,2	8	44,4	0,57
Alopecia	18	48,2	10	52,6	8	44,4	0,6
Anemia	15	40,5	8	42,1	7	38,9	0,71
Myalgia	14	37,8	10	52,6	4	22,2	0,13
Diarrhea	13	35,1	4	21,1	9	50,0	0,25
Nail toxicity	13	35,1	7	36,8	6	33,3	0,51
Dysgeusia	9	24,3	4	21,1	5	27,8	0,45
Nausea	8	21,6	4	21,1	4	22,2	0,77
Neuropathy	8	21,6	4	21,1	4	22,2	0,77

study on advanced and MBC patients. This study aims to evaluate the benefit of docetaxel and oral curcumin association for advanced and MBC patients, in particular on ORR. A benefit of at least 25% for the ORR was expected in favor of the curcumin group.

The results of this interim analysis showed, for the first time, that the association of oral curcumin and docetaxel in advanced and MBC patients was no more effective than docetaxel alone.

The randomization process gave us comparable groups and compliance among the patients taking curcumin was also good. Despite this, the ORR tended to be better in the control group, but without reaching significance. The addition of curcumin to docetaxel treatment for advanced and MBC patients did not prove effective, and the study was discontinued for reasons of futility. This being so, if the study had been continued until the end (inclusion of 100 patients) the chances of concluding in favor of curcumin would have been almost nil. However, we investigated OS, which was similar in the two groups. The TTP and the PFS however seemed to be better in the experimental arm, but failed to reach significance, which leads us to confirm that adding curcumin to docetaxel did not potentiate the response. At the same time, the safety analysis showed that curcumin was well tolerated without any major toxicity, confirming that curcumin was safe to use even at a high dose of 6 g per day as in this study.[19,22]

The curcumin-docetaxel association among advanced and MBC patients did not seem to potentiate the effects of chemotherapy on cancer cells, even if no harmful effects of curcumin were noted. The fact that this result could be attributed to the small sample size and to the curcumins' reduce bioavailability cannot be overlooked. We observed a better PFS in the curcumin arm but without reaching significance, which once again tend to show that increasing the sample size may have improved the effect. To date, no clear evidence has been made available in the literature concerning the effects of curcumin in breast cancer patients despite what might be expected from in vitro studies. However, the actual bioavailability of curcumin is questionable and was not explored here, which was one of the main limitations of this study. As no difference was noted between the two groups (positively or negatively), we can conclude that adding curcumin seems not to reduce the side effects of docetaxel and does not seem to have any synergistic effects in our study.

Saghateylan et al. conducted approximately the same study on breast cancer patients using intravenous curcumin and evidenced a better ORR among patients with curcumin after 1 month (50.7% vs. 33.3%, $p < 0.05$) and 3 months following treatment termination (44.9% vs. 27.8%, $p = 0.0337$) but this difference was no longer significant for PFS at the end of the study (4 months after treatment termination).[31] This seems to confirm that the main problem of our study could be the curcumin formulation with its low bioavailability. It can be noted that another study using oral curcumin found negative outcomes in terms of Crohn's disease recurrence, and questioned the actual bioavailability of curcumin.[32] We also conducted the same study on metastatic prostate cancer patient treated by docetaxel + curcumin/placebo and failed to show any efficacy of curcumin.[33] Choi et al. also observed no significant difference in terms of off-treatment duration between placebo and curcumin among prostate cancer patients.[34] Our results could be attributed to the curcumin pharmacokinetics, with the short half-life and low bioavailability.[35,36] With this in mind, we could surmise that a better formulation or association of curcumin could enhance its bioavailability, and as a consequence, provide a better outcome on cancer treatment.[37]

Apart from the bioavailability problem, it seems that curcumin does not have long-term efficacy after treatment termination. Even intravenous curcumin, which seemed to be more efficacious because of improved bioavailability, no longer proved efficacious in the long term after treatment termination. In our study, we also observed a tendency towards improved PFS, among curcumin patients from 6 months to 12 months after the start of treatment, but this effect disappeared in the long-term follow up. At this stage, it could be hypothesized that curcumin seems effective when used continuously.

Choi et al.[34] used oral curcumin among prostate cancer patients and failed to show off-treatment efficacy in the longer term. Among the reasons for this failure, they mentioned the short curcumin administration period. Even if curcumin is available in the market in different form, its efficacy is yet to be proven. As a main reason, curcumin pharmacokinetics and pharmacodynamics play an important role, studies support the fact that curcuminoids undergo a rapid and efficient metabolism which eliminates a large quantity by feces or in bile.[16] As a result, we still have to enhance curcumins absorption from the gastrointestinal tract; to improve its solubility in the body fluids and its bioavailability to make curcumin a validated therapeutic agent against cancer.[38] More recently, nano-formulation of curcumin are being investigated with promising results but still have to be proven in larger cohort.[38–42]

The main limitation of our study was the design (open label) even if a randomization process was conducted. The other limitations were the small sample size due to the early discontinuation and the lack of pharmacokinetic information for curcumin and docetaxel. However, the pharmacokinetic of curcumin was done in the study conducted on metastatic prostate cancer patients and revealed that curcumin was absorbed and bio-available but the optimal dose of curcumin is yet to be defined to be efficacious.[33] Maybe, should curcumin be given continuously during the treatment and not only 7 days every 3 weeks.

5 | CONCLUSION

In this randomized, open-label, phase-II study, the association of oral curcumin and docetaxel was not efficacious for the treatment of advanced and metastatic breast cancer patients. Consequently, this study was stopped after this interim analysis for reasons of futility. As a conclusion, even if curcumin may be a good candidate for anticancer treatment, our results do not enable us to recommend its use in association with docetaxel among advanced and MBC patients. At the same time, the fact that this result could be an effect of the small sample size should not be overlooked. Further studies are required with a larger number of patients, a better curcumin formulation or association of curcumin, a long curcumin treatment period, and an evaluation of curcumin pharmacokinetics to explore the actual efficacy of curcumin.

AUTHOR CONTRIBUTIONS

Passildas Jahanmohan Judith: Project administration; resources; writing—original draft; validation; visualization. **Bernadach Maureen**: Investigation; writing—review and editing; data curation. **Pouget Mélanie**: Funding acquisition; writing—review and editing; project administration; resources; visualization. **Kwiatkowski Fabrice**: Methodology; formal analysis; software; data curation; writing—review and editing. **Vanpraagh-Doreau Isabelle**: Investigation; writing—review and editing. **Dubray-Longeras Pascale**: Investigation; writing—review and editing. **Abrial Catherine**: Supervision; writing—review and editing; resources; funding acquisition. **Nabholtz Jean-Marc**: Investigation; writing—review and editing. **Curé Hervé**: Investigation; writing—review and editing. **Delecroix Valérie**: Investigation; writing—review and editing. **Chollet Philippe**: Conceptualization; supervision; validation; funding acquisition; writing—review and editing. **Mouret-Reynier Marie-Ange**: Investigation; visualization; supervision; conceptualization; funding acquisition; writing—review and editing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TRANSPARENCY STATEMENT

The lead author Passildas Jahanmohan Judith affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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