The Breast 60 (2021) 147–154

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Fixed dose combination of capecitabine and cyclophosphamide in metastatic breast cancer: Results from THE ENCLOSE phase 2/3 randomized multicenter study

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ARTICLE INFO

Article history:
Received 16 May 2021
Received in revised form
28 September 2021
Accepted 30 September 2021
Available online 1 October 2021

Keywords:
Capecitabine
Cyclophosphamide
FDC
Fixed-dose combination
MBC

ABSTRACT

Aim: To evaluate pharmacokinetics, efficacy and safety of fixed-dose combination (FDC) of oral capecitabine + cyclophosphamide in metastatic breast cancer (MBC) patients progressing after anthracycline and/or taxane chemotherapy.

Methods: In this prospective, adaptive, phase-2/3, open-label study (CTRI/2014/12/005234), patients were randomized (1:1:1) to three FDC doses (doses/day: D1, capecitabine + cyclophosphamide 1400 mg + 60 mg; D2, 1800 mg + 80 mg; D3, 2200 mg + 100 mg) for 14 days, in 21-day cycles. In Part-I, multiple-dose pharmacokinetics and optimal dose(s) were evaluated with futility analysis. Group(s) with <3 responders based on best overall response rate (BOR, complete response [CR]+partial response [PR]), were discontinued. Efficacy (BOR, disease control rates [DCR; CR + PR + stable disease]) and safety of optimal dose(s) were evaluated in Part-II.

Results: Of 66 patients (n = 22/group) in Part-I, pharmacokinetics (D1 = 7/22, D2 = 9/22, D3 = 8/22) showed dose-proportionality for cyclophosphamide and greater than dose-proportionality for capecitabine. Modified intent-to-treat (mITT) analysis showed BOR of 7.14% (1/14) in D1 (discontinued), and 22.22% (4/18) each in D2 and D3, respectively. In Part-II, 50 additional patients were randomized in D2 and D3 (n = 144; total 72 [22 + 50] patients/group). mITT analysis in D2 (n = 54) and D3 (n = 58) showed BOR of 29.63% (16/54, 95%CI: 17.45–41.81%) and 22.41% (13/58, 95%CI: 11.68–33.15%), respectively. DCR in D2 and D3 were 87.04% (47/54, 95%CI: 78.08–96.00%) and 82.76% (48/58; 95%CI: 73.04–92.48%) after 3 and 57.41% (31/54; 95%CI: 52.41–79.50%) and 50.00% (29/58; 95%CI: 40.40–67.00%), after 6-cycles, respectively. Hand-foot syndrome (16.67%), vomiting (9.72%) in D2, and hand-foot syndrome (18.06%), asthenia (15.28%) in D3 were most-common adverse events.

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https://doi.org/10.1016/j.breast.2021.09.012
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Conclusion: FDC of capecitabine + cyclophosphamide (1800 + 80 mg/day) showed high disease control rates and good safety profile in MBC patients.
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1. Introduction

Management of metastatic breast cancer (MBC) aims at symptom palliation and prolongation of overall survival (OS). Chemotherapeutic agents, including anthracyclines and/or taxanes are important components of the therapeutic armamentarium [1,2]. Approximately one-third patients fail to these agents or have disease progression [2,3].

Capecitabine and cyclophosphamide are oral agents with potential synergy. Capecitabine exerts anti-angiogenesis activity [4] and cyclophosphamide upregulates thymidine phosphorylase (TP) [5], which catalyzes capecitabine to active 5-fluorouracil (5-FU) conversion. Hence, combining these two agents can be synergistic [5–7]. Full oral strength doses of capecitabine and cyclophosphamide can be administered together with favorable efficacy and tolerability [5,6,8]. An oral fixed-dose combination (FDC) tablet of capecitabine and cyclophosphamide developed to improve patient compliance is approved in India [9]. To our knowledge, no other FDC of capecitabine and cyclophosphamide is approved anywhere else in the world. We report a prospective study of FDC of capecitabine and cyclophosphamide in MBC patients after failure on anthracycline and/or taxane chemotherapy.

2. Methods

2.1. Study design and treatments

THE ENCLOSE (capEcitabiNe CycLophOsphamide Synergism brEast cancer) was a prospective, adaptive, randomized, multicenter, open-label study conducted in two parts (Part-I and Part-II) between February 2015 and November 2018 at 15 centers across India. In Part-I, multiple-dose pharmacokinetics and optimal dose(s) of FDC, and in Part-II, efficacy and safety of optimal dose(s), were evaluated.

The FDC tablet was developed in two stock keeping units (SKUs) of capecitabine 700 mg plus cyclophosphamide 30 mg, and capecitabine 400 mg plus cyclophosphamide 20 mg. The three tested doses were D1 (1400 mg capecitabine+60 mg cyclophosphamide per day [one tablet of 700 mg capecitabine+30 mg cyclophosphamide in morning and one tablet in evening]), D2 (1800 mg capecitabine+80 mg cyclophosphamide per day [one tablet of 700 mg capecitabine+30 mg cyclophosphamide plus one tablet of 400 mg capecitabine+20 mg cyclophosphamide in morning, and one tablet of 700 mg capecitabine+30 mg cyclophosphamide in evening]) and D3 (2200 mg capecitabine+100 mg cyclophosphamide per day [one tablet of 700 mg capecitabine+30 mg cyclophosphamide plus one tablet of 400 mg capecitabine+20 mg cyclophosphamide in morning and evening]). As per available literature on free dose combination of capecitabine and cyclophosphamide, the reported average doses per day have been 1650 mg/m^2 and 65 mg/m^2, respectively [7,8]. With an estimated average body surface area of Indian women of approximately 1.4–1.5 m^2, the highest dose level was estimated. Further, some studies have reported the use of fixed daily dose of capecitabine of 1500 mg/day [10,11], either as a single agent or in combination with other drugs. This data was used for the lowest dose level in this study. The FDC tablets were administered orally within 30 min after a meal for 14-days in 3-weekly cycles for up to 6 cycles. Central project designee sequentially randomized patients to either of the three dose-groups (1:1:1) using SAS® Version 9.3.

2.2. Study population

Female patients aged 18–65 years with histopathologically and/or cytologically confirmed breast cancer, who had metastatic disease and had received or experienced disease progression after prior anthracyclines and/or taxanes, were included. Patients were required to have ≥1 measurable lesion as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, left ventricular ejection fraction ≥50%, and completed previous chemotherapy/radiotherapy more than 4 weeks prior to inclusion. Patients who had received capecitabine within preceding 12 months, had taken >1 prior metastatic chemotherapy, had significant comorbidity or unwilling/unable to follow protocol, were excluded.

2.2.1. Sample size

In Part-I, multiple-dose pharmacokinetics was planned to be assessed in 24 patients (8/dose-group), and 66 patients (22/dose-group) were planned to be dosed. Based on efficacy in Part-I, patients were planned to be accrued into Part-II. The dose-group with ≤2 responders was planned to be discontinued, and dose-groups with ≥3 responders were to be continued in Part-II. If ≥3 responders in all three dose-groups, patients could be increased to 40/group and dose-group with ≥8 responders (of 40 patients) would be continued to Part-II. For a comparison of two independent binomial proportions using Fisher's exact test with a lower one-sided significance of 0.05, a sample size of 57 per group achieves a power of ≥0.8 to detect a difference of −0.2 when the reference proportion is 0.3. Considering a 20% drop-out/withdrawal, 72 patients per dose-group were planned to be enrolled to achieve ≥57 completers per dose-group in Part-II.

2.3. Pharmacokinetic evaluation

Pharmacokinetic (PK) evaluations were performed in Cycle 1. Multiple blood samples were collected at prespecified timepoints. Pre-dose plasma concentrations (C_{pd}) were evaluated on Days 2–5, and post-dose pharmacokinetics were evaluated on Day 5 using non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.). Samples were collected for PK evaluation at the following timepoints: 1 pre-dose sample of 06 mL on day 2 (before morning dose), 5 pre-dose samples of 04 mL on day 3 and 4 (before morning and evening dose) and day 5 (before morning dose), and 15 post-dose samples of 04 mL each on day 5 (0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.500, 4.000, 6.000, 8.000, 10.000 and 12.000 h, post-dose). Dose proportionality was also evaluated.

2.4. Analysis sets

The intent-to-treat (ITT) population included all randomized patients. The efficacy evaluations were based on the modified ITT (mITT, patients receiving ≥1 dose with response evaluation after

≥3 cycles) and per-protocol (PP, all patients in mITT population who did not withdraw consent, were not lost-to-follow-up, did not experience disease progression prior to the first efficacy evaluation and did not have major protocol violations or deviations) populations. We also performed a post-hoc additional efficacy analysis in a patient set which included the mITT population plus those who experienced disease progression or death prior to the first planned efficacy evaluation, wherein PD or death due to any cause was considered lack of response. This analysis was performed in order to include those patients in the analysis in whom the study treatment failed even prior to first efficacy evaluation, and convey a realistic estimate of the efficacy. Safety population included all randomized patients who received ≥1 dose. Efficacy and safety analyses were performed using SAS® Version 9.3 (SAS Institute Inc., USA).

2.5. Study evaluations

The primary endpoint was best overall response (BOR) rate, defined as proportion of patients with complete response (CR) or partial response (PR), and secondary endpoint was disease control rate (DCR), defined as proportion of patients with CR, PR and stable disease (SD). The efficacy response was evaluated after 3rd and 6th cycles of chemotherapy if there was no PD prior to these timepoints. Because the study participants were followed-up for 6 cycles as part of the study, further radiological evaluations after this point were not performed. The efficacy evaluations were performed by CT scan or MRI scan or bone scan, as per RECIST 1.1 [1]. The AEs were coded using MedDRA 17.1 and summarized by grades using Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

2.6. Statistical methods

Repeated Measure ANOVA was performed on log-transformed C_{pd} using three morning pre-dose concentrations on Days 3–5. Pharmacokinetic parameters up to 12 h were considered for dose proportionality assessment on $C_{max.ss}$ and $AUC_{0\text{-}\tau.ss}$ using Power Model [12] over the dose range above at steady state based on point estimates and 90% confidence interval (CI). The 95% CI was computed for BOR and DCR. *P*-values were calculated using χ^2 test. All statistical tests for data analysis were two-sided at $\alpha = 0.05$.

3. Ethics statement

The study was approved from the institutional ethics committees and conducted as per the regulatory requirements and Declaration of Helsinki. All patients provided written informed consent.

4. Results

Of 235 screened patients, 166 fulfilled the eligibility criteria; 66 patients were dosed in Part-I (n = 22/dose-group) (Fig. 1). The baseline characteristics for Part-I and –II were comparable across the groups (Table 1). All patients had received anthracycline and/or taxane chemotherapy with 53.5% having received one line of previous chemotherapy.

5. Part-I

5.1. Pharmacokinetics

Pharmacokinetic analysis was planned only in few study sites which had required trained personnel and infrastructure and was performed in patients who provided consent for PK sampling, which was optional. The pharmacokinetics was evaluated in 24 of 66 patients (D1 = 7/22; D2 = 9/22; D3 = 8/22). No abnormal pharmacokinetics were observed (Table 2), except in 3 patients: a sudden drop in post-dose concentration in one patient each for capecitabine at 2.00 h in D2 and cyclophosphamide at 4.00 h in D3 groups versus previous/subsequent concentrations; and abnormal pharmacokinetics for capecitabine and cyclophosphamide in one patient in D1 group. In the absence of sampling or analytical errors, the aberrant PK values could possibly be due to patient related factors. The $C_{max.ss}$ and $AUC_{0\text{-}\tau.ss}$ of cyclophosphamide were dose proportional at 60–100 mg daily dose whereas they were greater than dose proportional for capecitabine at 1400–2200 mg daily dose.

5.2. Optimal dose evaluation

In Part-I, 50 patients qualified for mITT and PP populations (D1 = 14, D2 = 18, and D3 = 18). The futility analysis demonstrated a BOR of 7.14% (n = 1/14; 95%CI: 0.00–20.63%) for D1, and was not considered optimal (≤3 responders) and discontinued. The BOR was 22.22% (n = 4/18; 95%CI: 3.02–41.43%) for both D2 and D3, and these dose groups were continued in Part-II. For both D2 and D3 groups, 50 patients were enrolled in addition to the 22 patients from Part-I leading to a total of 144 patients (D2: n = 72; D3: n = 72).

5.3. Part-II: efficacy

Data of Part-I and Part-II for D2 and D3 was pooled for final efficacy analysis. Of 144 patients, 112 qualified for mITT (D2: 54; D3: 58) and 95 for per protocol (D2: 47; D3: 48) analysis (Fig. 1). In mITT population, the BOR in D2 and D3 were 29.63% (16/54; 95%CI: 17.45–41.81%) and 22.41% (13/58; 95%CI: 11.68–33.15%), respectively. The DCR after 3 cycles in D2 and D3 were 87.04% (47/54; 95% CI: 78.08–96.00%) and 82.76% (48/58; 95%CI: 73.04–92.48%), respectively (Fig. 2). The DCR after 6 cycles in D2 and D3 were 57.41% (31/54; 95%CI: 52.41–79.50%) and 50% (29/58; 95%CI: 40.40–67.00%), respectively. In PP population, the BOR in D2 (n = 47) and D3 (n = 48) were 31.91% (15/47; 95%CI: 18.59–45.24%) and 25% (12/48; 95%CI: 12.75–37.25%), respectively while DCR after 3 cycles were 89.36% (42/47; 95%CI: 80.55–98.18%) and 85.42% (41/48; 95%CI: 75.43–95.40%), and after 6 cycles were 63.83% (30/47; 95%CI: 61.58–88.42%) and 56.25% (27/48; 95%CI: 46.98–75.75%), respectively.

5.4. Additional efficacy analyses

In additional analysis, 16 patients were included in D1 in Part-I, with 1 (6.25%, 95%CI: 0.00–18.11%) patient showing a PR. The additional analysis population in combined Part-I and Part-II of the study included 64 patients in D2 and 64 patients in D3. In this analysis, the BOR in D2 and D3 were 25.00% (16/64; 95%CI: 14.91–36.70%) and 20.31% (13/64; 95%CI: 10.83–31.10%), respectively. The DCR in D2 and D3 after 3 cycles were 75.00% (48/64; 95% CI: 67.01–87.83%) and 76.56% (49/64; 95%CI: 68.90–89.17%), respectively, and after 6 cycles were 48.44% (31/64; 95%CI: 43.26–69.47%) and 45.31% (29/64; 95%CI: 37.13–62.87%), respectively.

5.5. Part-I and II: safety

In Part-I, D1 group had 49 AEs in 63.64% (n = 14/22) patients. Asthenia (18.18%), leucopenia, increased aspartate aminotransferase and alanine aminotransferase, dizziness and alopecia (9.09%

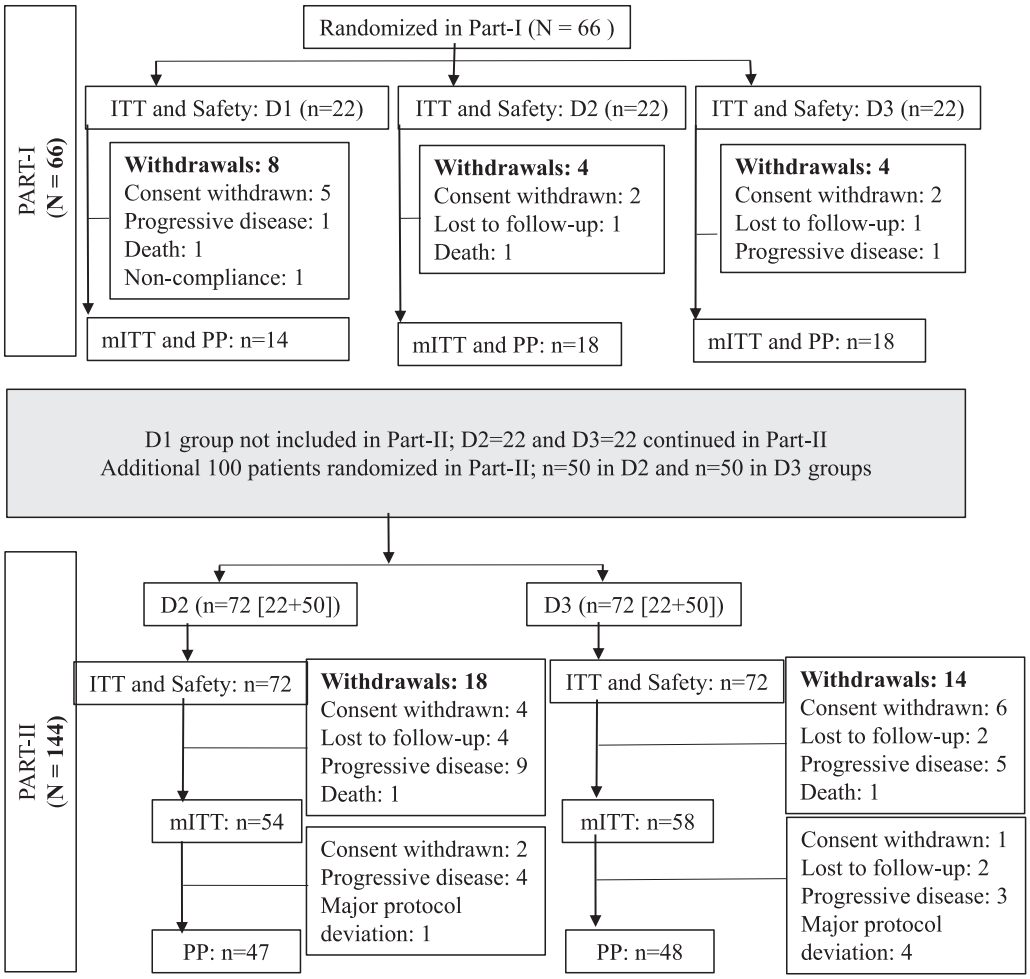

Fig. 1. CONSORT diagram. ITT population included all randomized patients. mITT population included all randomized patients who received at least one dose of study medication and evaluated for a response (CT/MRI scan) after receiving at least 3 cycles of treatment. PP population included all patients in the mITT population who did not withdraw consent, were not lost-to-follow-up, did not experience disease progression prior to 1st efficacy evaluation and did not have major protocol violations or deviations. The major protocol deviations were as follows: eligibility violation in 1 patient in the D2 group, scheduled assessment not as per protocol in 2 patients in D3 group and scheduled visits not as per protocol in 2 patients in D3 group. Safety population included all randomized patients who received at least one dose of study medication. ITT, intent-to-treat; mITT, modified intent-to-treat; PP, per-protocol.

each) were the most common AEs occurring in >5% patients. Grade 3 AEs of diarrhea, vomiting, increased γ-glutamyltransferase, convulsion, urinary incontinence and dyspnea were observed in one patient each. There were 2 deaths, which were not study drug related.

Safety analyses were pooled from Part-I and Part-II for D2 (n = 72) and D3 (n = 72) groups. Of 139 AEs (n = 32/72, 44.44%) in D2 (Table 3) group, the most common AEs were hand-foot syndrome (16.67%), vomiting (9.72%), pyrexia (8.33%) and nausea (8.33%). A total of 85 AEs were grade 1, 43 were grade 2 and 11 were grade 3. Grade 3 AEs included increased bilirubin and pain in extremity reported in 2 patients each; anemia, neutropenia, peripheral swelling, breast abscess, hypoglycemia, muscle weakness and proteinuria in one patient each. No grade 4 or 5 AEs were reported. In D2 group, one serious AE (SAE) of hypoglycemia, which was not related to the study drug, resulted in death and four SAEs of breast abscess, acute gastroenteritis, dyspnea and muscular weakness were reported in one patient each, of which all recovered without sequelae except the last, which worsened.

Of 167 AEs in D3 group (Table 3) (n = 40/72, 55.56%), the most common AEs were hand-foot syndrome (18.06%), asthenia (15.28%) and neutropenia (12.5%). A total of 107 AEs were grade 1, 47 were grade 2, 11 were grade 3 and 2 were grade 5 (2 deaths, not study drug related); no grade 4 AEs were reported. Grade 3 AEs were neutropenia in 4 patients, anemia in 3 patients, constipation, asthenia, infection, and dyspnea in one patient each. In D3 group, there were three SAEs of dyspnea (n = 2) and asthenia (n = 1), which recovered without sequelae, and there were two deaths, which were not related to the study drug. Filgrastim was administered in 2 patients in the D2 group versus 5 patients in the D3 group for correction of neutropenia or leucopenia.

6. Discussion

THE ENCLOSE study suggest that fixed dose combination of capecitabine plus cyclophosphamide had predictable pharmacokinetic properties, were well-tolerated and showed clinically meaningful response rates in MBC patients who had received prior treatment with anthracyclines and/or taxanes.

The dose combination in our study is similar to previous reports. A phase-1 study used capecitabine 628–829 mg/m^2 two times/day and cyclophosphamide 33–50 mg/m^2 two times/day on days 1–14, in 3-week cycles [10] and a phase-2 study used capecitabine 1657 mg/m^2/day with cyclophosphamide 65 mg/m^2/day for 14 days

Table 1
Baseline characteristics.

Parameter	Part-I				Part-II		
	D1 (1400 + 60 mg/day) (N = 22)	D2 (1800 + 80 mg/day) (N = 22)	D3 (2200 + 100 mg/day) (N = 22)	Total (N = 66)	D2 (1800 + 80 mg/day) (N = 72)	D3 (2200 + 100 mg/day) (N = 72)	Total (N = 144)
Age, years, mean (SD)	45.8 (8.23)	50.5 (9.13)	46.5 (9.92)	47.6 (9.22)	49.4 (9.41)	47.4 (9.13)	48.4 (9.29)
BSA (m^2), mean (SD)	1.5 (0.16)	1.5 (0.13)	1.5 (0.17)	1.5 (0.15)	1.50 (0.15)	1.51 (0.15)	1.51 (0.15)
BMI (kg/m^2), mean (SD)	25.0 (5.52)	24.7 (4.73)	24.2 (5.22)	24.7 (5.10)	24.39 (4.89)	24.30 (4.22)	24.35 (4.55)
ECOG performance score, n (%)							
0	1 (4.55)	4 (18.18)	7 (31.82)	12 (18.18)	11 (15.28)	12 (16.67)	23 (15.97)
1	15 (68.18)	17 (77.27)	12 (54.55)	44 (66.67)	60 (83.33)	56 (77.78)	116 (80.56)
2	6 (27.27)	1 (4.55)	3 (13.64)	10 (15.15)	1 (1.39)	4 (5.56)	5 (3.47)
Receptor status, n (%)							
ER/PR positive, HER 2 negative	Data not available				7 (9.72)	9 (12.50)	16 (11.11)
ER/PR (any status) positive, HER 2 positive (IHC 3+/FISH amplification)	Data not available				7 (9.72)	7 (9.72)	14 (9.72)
ER/PR (any status) positive, HER 2 negative	Data not available				3 (4.17)	4 (5.56)	7 (4.86)
TNBC	Data not available				5 (6.94)	5 (6.94)	10 (6.94)
Receptor status not available/test not done	22 (100)	22 (100)	22 (100)	66 (100)	50 (69.44)	47 (65.28)	97 (67.36)
Previous chemotherapy, n (%)							
Anthracycline based regimen (excluding anthracycline plus taxane based therapy)	16 (72.73)	19 (86.36)	16 (72.73)	51 (77.27)	59 (81.94)	58 (80.56)	117 (81.25)
Taxane based therapy (excluding anthracycline plus taxane based therapy)	16 (72.73)	12 (54.55)	11 (50.00)	39 (59.09)	47 (65.28)	38 (52.78)	85 (59.03)
Anthracycline plus taxane based therapy	3 (13.64)	0 (0.00)	3 (13.64)	6 (9.09)	0 (0.00)	5 (6.94)	5 (3.47)
Other regimens (excluding all above)[a]	1 (4.55)	1 (4.55)	1 (4.55)	3 (4.55)	3 (4.17)	1 (1.39)	4 (2.78)
Lines of chemotherapy, n (%)[b]							
One line of previous chemotherapy	9 (40.91)	13 (59.09)	13 (59.09)	35 (53.03)	36 (50.00)	41 (56.94)	77 (53.47)
Two lines of previous chemotherapy	12 (54.55)	6 (27.27)	9 (40.91)	27 (40.91)	24 (33.33)	30 (41.67)	54 (37.50)
>Two lines of previous chemotherapy	1 (4.55)	3 (13.64)	0 (0.00)	4 (6.06)	12 (16.67)	1 (1.39)	13 (9.03)

BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; PR, progesterone receptor; SD, standard deviation; TNBC, triple negative breast cancer.
Based on the efficacy results in Part-I of the study, D1 was not considered optimal as per prespecified criteria (<3 responders) and 22 patients of D1 were not continued in Part-II. As 22 patients each in D2 and D3 were already enrolled in Part-I, 50 additional patients in D2 and D3 each were enrolled in Part-II for a total of 72 patients in each group.
[a] Other regimens may have been administered in previous cycles but all patients were pre-treated/failure with anthracycline and/or taxane chemotherapy.
[b] Previous neoadjuvant or adjuvant chemotherapy were counted as one line of chemotherapy.

Table 2
Pharmacokinetic parameters of capecitabine and cyclophosphamide in Part-I.

Parameter	Capecitabine			Cyclophosphamide		
	D1 (1400 + 60 mg/day) (N = 7)	D2 (1800 + 80 mg/day) (N = 9)	D3 (2200 + 100 mg/day) (N = 8)	D1 (1400 + 60 mg/day) (N = 7)	D2 (1800 + 80 mg/day) (N = 9)	D 3 (2200 + 100 mg/day) (N = 8)
$T_{max.ss}$ (h), median (min-max)	1.667 (0.667–10.000)	2.000 (0.667–4.000)	1.333 (1.000–3.000)	1.667 (1.000–10.000)	2.333 (0.667–6.000)	2.333 (1.000–3.500)
$C_{max.ss}$ (ng/mL), mean ± SD	2754.695 ± 1802.3699	4087.251 ± 1755.4358	7282.884 ± 6140.8817	1258.521 ± 438.4275	1885.397 ± 326.4798	2072.076 ± 473.4895
$C_{min.ss}$ (ng/mL), mean ± SD	96.845 ± 141.9193	99.774 ± 121.3088	53.703 ± 42.9269	450.742 ± 157.1446	771.678 ± 155.0084	684.169 ± 201.9660
$AUC_{0-\tau.ss}$ (ng.h/mL), mean ± SD	2763.919 ± 1293.4526	4883.297 ± 2826.0045	6143.725 ± 3141.1694	8880.785 ± 3328.3720	14270.809 ± 2029.7824	14582.688 ± 3548.1686
$C_{avg.ss}$ (ng/mL), mean ± SD	230.327 ± 107.7877	406.941 ± 235.5004	511.977 ± 261.7641	740.065 ± 277.3643	1189.234 ± 169.1485	1215.224 ± 295.6807
Fluctuation (%), mean ± SD	1021.695 ± 548.1659	1057.800 ± 352.3183	1397.015 ± 678.2740	106.083 ± 36.2982	93.420 ± 19.1499	115.916 ± 27.0751
Swing (%), mean ± SD	12847.201 ± 17477.2980	10607.073 ± 8014.5502	25866.357 ± 34300.2075	183.462 ± 91.9971	148.844 ± 45.3996	217.438 ± 85.4750

$AUC_{0-\tau.ss}$, area under plasma concentration versus time curve from 0 to dosing interval (τ) at steady state; $C_{avg.ss}$, average plasma concentration at steady state; $C_{max.ss}$, maximum plasma concentration at steady state; $C_{min.ss}$, plasma concentration at the end of dosing interval at steady state; C_{pd}, Pre-dose plasma concentration; $T_{max.ss}$, time to reach $C_{max.ss}$.

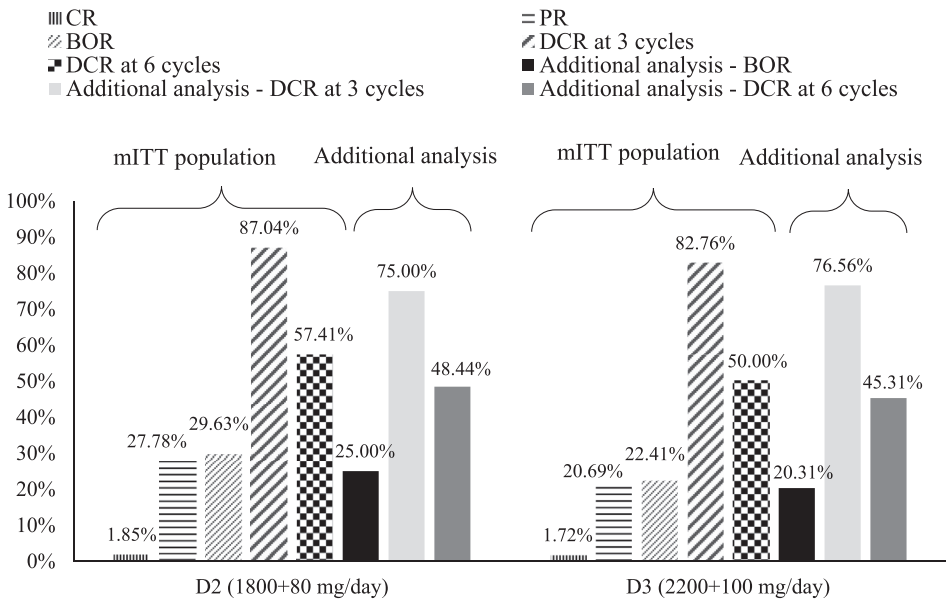

Fig. 2. Response rates from Part-II for mITT (D2: 54; D3: 58) and additional analysis (D2: 64; D3: 64) populations. BOR, best overall response; CR, complete response, DCR, disease control rate; mITT, modified intent-to-treat PR, partial response.

Table 3
Most common (>5%) occurring adverse events.

AE	D2 (1800 + 80 mg/day) (N = 72), n (%) e					D3 (2200 + 100 mg/day) (N = 72) n (%) e				
	All grade	Grade 1	Grade 2	Grade 3	Grade 4	All grade	Grade 1	Grade 2	Grade 3	Grade 4
Hematological AEs										
Anemia	2 (2.78) 4	–	2 (2.78) 3	1 (1.39) 1	–	4 (5.56) 7	1 (1.39) 1	3 (4.17) 3	3 (4.17) 3	–
Leucopenia	2 (2.78) 3	–	2 (2.78) 3	–	–	6 (8.33) 6	5 (6.94) 5	1 (1.39) 1	–	–
Neutropenia[a]	4 (5.56) 10	1 (1.39) 1	4 (5.56) 8	1 (1.39) 1	–	9 (12.5) 14	2 (2.78) 2	5 (6.94) 8	4 (5.56) 4	–
Non-hematological AEs										
Hand-foot syndrome	12 (16.67) 12	11 (15.28) 11	1 (1.39) 1	–	–	13 (18.06) 14	11 (15.28) 11	2 (2.78) 3	–	–
Asthenia	5 (6.94) 6	3 (4.17) 3	3 (4.17) 3	–	–	11 (15.28) 14	8 (11.11) 10	3 (4.17) 3	1 (1.39) 1	–
Decreased appetite	5 (6.94) 6	4 (5.56) 5	1 (1.39) 1	–	–	2 (2.78) 2	2 (2.78) 2	–	–	–
Vomiting	7 (9.72) 11	7 (9.72) 10	1 (1.39) 1	–	–	8 (11.11) 9	8 (11.11) 8	1 (1.39) 1	–	–
Pyrexia	6 (8.33) 6	6 (8.33) 6	–	–	–	5 (6.94) 5	4 (5.56) 4	1 (1.39) 1	–	–
Nausea	6 (8.33) 7	5 (6.94) 6	1 (1.39) 1	–	–	4 (5.56) 10	4 (5.56) 9	1 (1.39) 1	–	–
Cough[b]	1 (1.39) 1	1 (1.39) 1	–		–	7 (9.72) 7	6 (8.33) 6	1 (1.39) 1	–	–
Pain in extremity	5 (6.94) 7	3 (4.17) 3	2 (2.78) 2	2 (2.78) 2	–	3 (4.17) 3	2 (2.78) 2	1 (1.39) 1	–	–
Pain	4 (5.56) 4	2 (2.78) 2	2 (2.78) 2	–	–	3 (4.17) 4	3 (4.17) 4	–	–	–
Diarrhea	2 (2.78) 3	1 (1.39) 1	1 (1.39) 2	–	–	4 (5.56) 4	2 (2.78) 2	2 (2.78) 2	–	–
Constipation	1 (1.39) 1	1 (1.39) 1	–	–	–	4 (5.56) 5	2 (2.78) 2	2 (2.78) 2	1 (1.39) 1	–

AE, adverse event. 'n' indicates number of patients. 'e' indicates number of events.
[a] Neutropenia and neutrophil count decreased were reported separately according to MedDRA but clubbed together in the manuscript.
[b] Cough and productive cough were reported separately according to MedDRA but clubbed together in this manuscript.

in 3-week cycles [7]. On the basis of pharmacokinetic characteristics of capecitabine and cyclophosphamide wherein their clearance is not dependent on body surface area [12–14], a study by Schott et al., also evaluated a flat dose of cyclophosphamide 100 mg daily on days 1–14 along with capecitabine 3000 mg daily on days 8–21 in 3-weekly cycles in pretreated MBC patients [12].

Capecitabine and cyclophosphamide in combined formulation tablets is an attractive all-oral regimen which may be preferred by patients [10]. Further, cyclophosphamide has shown synergistic antitumor activity with capecitabine [10,15]. The intratumoral TP activates (~2.3-fold) capecitabine to the active moiety 5-FU, hence, there is a strong rationale to combine agents that up-regulate TP such as cyclophosphamide with capecitabine (Fig. 3) [16,17]. Several studies have established the efficacy and safety of capecitabine and cyclophosphamide combination in patients with pretreated MBC [7,10]. However, none of these studies have evaluated a

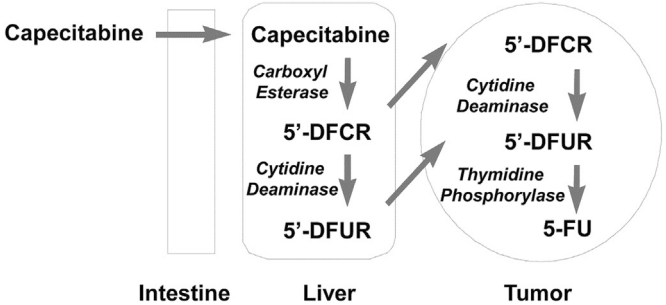

Fig. 3. Rationale for combining capecitabine and cyclophosphamide. 5-DFCR, 5'deoxy-5-fluorocytidine; 5-DFUR, 5'deoxy-5-fluorouridine; 5-FU, 5-fluorouracil.

formulation that combines the two drugs in one tablet. Response rates of ~30–45% have been reported with the combination of capecitabine and cyclophosphamide in MBC patients [5,7,8,12,18]. In our study, the DCR in mITT populations of D2 and D3 after 6 cycles were 57.41% and 50%, respectively, and after inclusion of additional patients with disease progression or death prior to first efficacy evaluation, were 48.44% and 45.31%, respectively. These results compare favorably with previous reports of DCR ranging from ~53% to 68% (Table 4) [5,7,8,12,18].

The response rates in our study are clinically relevant as these are pretreated MBC patients that have failed to respond or have experienced disease progression following anthracycline and/or taxane chemotherapy regimens. It is worth mentioning that disease control rate, which includes stable disease in addition to complete response and partial response may be the more appropriate measure of clinical benefit in patients with metastatic breast cancer, especially if achieved with a well-tolerated treatment like this combination.

Several studies have reported the efficacy and safety of the low dose chemotherapy against MBC patients [19–21]. The recommended doses of capecitabine (2500 mg/m^2/day) [22] and cyclophosphamide (1–5 mg/kg/day) [23] are higher than the corresponding doses in our study (1400 or 2200 mg/day of capecitabine and 60 or 100 mg/day of cyclophosphamide). The response rate in anthracycline- and taxane-pretreated MBC patients of 30.3% in one of these reports [5] is similar to 29.63% (25.00% with inclusion of additional patients with PD or death prior to first efficacy evaluation) observed with our dose level D2.

Our study suggests that $C_{max.ss}$ and $AUC_{0\text{-}\tau.ss}$ of cyclophosphamide were dose proportional at 60–100 mg daily dose and were greater than dose proportional for capecitabine at 1400–2200 mg daily dose, suggesting additional advantage on capecitabine pharmacokinetics, which merits further exploration.

Overall, D2 group had a better tolerability profile with any grade AE observed in 44.44% patients vs. 55.56% in D3 group. The lower doses used in our study is the likely reason for the lower incidence of clinically relevant adverse effects like hand-foot syndrome, neutropenia, diarrhea and nausea compared to those previously reported. Although it was not planned in the study, an exploratory analysis found no correlation between body mass index and PK parameters ($C_{max.ss}$, AUC_{τ} and $C_{min.ss}$) for either capecitabine or cyclophosphamide (data not shown).

In chronic diseases such as cancer, patients face issues with treatment adherence due to treatment fatigue resulting from long-term treatment [24,25]. Further, requirements of multiple pills for treatment of MBC and comorbidities can cause inconvenience and lower the compliance [26]. Hence, FDC of oral anti-cancer drugs may be convenient options in MBC patients. This two-tablet FDC formulation was developed using Intas Pharmaceuticals Limited's patented 'core tablet-in-tablet formulation' (US patent granted for particle size [US10016447B2] [27] and in process for 'tablet-in-tablet' [US20190142755A1] [28]), in which the first layer comprises capecitabine and the second layer comprises cyclophosphamide with a film coating separating these two layers to offer differential release of the drugs.

The study limitations include unavailability of receptor status

Table 4
Comparative efficacy and safety data with other published studies.

Parameter	Our study (FDC)		Yoshimoto et al. (1656 + 66 mg/m^2, 1–14 days) (%)	Harvey et al. (1332 mg/m^2 [1–28 days] + 100 mg/m^2 [1–14 days]) (%)	Schott et al. (3000 mg − 8–21 days + 100 mg 1–14 days) (%)	Tanaka et al. (1657 + 65 mg/m^2/day, 1–14 days) (%)	Wang et al. (2000 + 65 mg/m^2/day, 1–14 days) (%)
	D2 (1800 + 80 mg/day) (%)	D3 (2200 + 100 mg/day) (%)					
Efficacy, n	54	58	45	39	80	45	66
BOR (CR + PR)[a]	29.63	22.41	44.4	33	36	35.6	30.3
DCR (CR + PR + SD) after 3 cycles	87.04	82.76	Not available	Not available	Not available	Not available	Not available
DCR (CR + PR + SD) after 6 cycles[b]	57.41	50	57.8	56.4	67.5	62.2	53
Safety, n	**72**	**72**	**51**	**39**[c]	**95**	**45**	**68**
Alanine aminotransferase increased	1.39	0	25.5	Not available	6.31	40	8.9
Alopecia	1.39	4.17	2	Not available	Not available	8.88	Not available
Anemia	2.78	5.56	72.5[d]	0	40	35.55	19.1
Fatigue/asthenia	6.94	15.28	19.6	13	60	35.55	23.5
Decreased appetite/anorexia	6.94	2.78	23.5	0	Not available	42.22	Not available
Diarrhea	**2.78**	**5.56**	**5.9**	**3**	**30.52**	**8.88**	**30.9**
Leukopenia	2.78	8.33	70.6	Not available	45.26	31.11	47.1
Mucosal inflammation/stomatitis	0	2.78	11.8	3	Not available	8.88	17.6
Nausea	8.33	5.56	19.6	5	53.68	35.55	66.2
Neutropenia	**5.56**[e]	**12.5**[e]	**39.2**	**33**	**30.52**	**68.88**	**25**
HFS	**16.67**	**18.06**	**52.9**	**28**[f]	**38.95**	**31.11**	**69.2**
Thrombocytopenia	0	4.17	13.7	0	13.68	15.55	11.8

CR, complete response; HFS, hand-foot syndrome; PR, partial response; SD, stable disease.CR, complete response; PR, partial response; SD, stable disease.

[a] Best overall response is presented for the current study whereas the overall response rate is presented for the comparison studies except Harvey et al.

[b] The timepoints for DCR evaluation for the comparison studies is not clear.

[c] Harvey et al., study has presented grade ≥3 AEs only.

[d] AE reported as 'decreased hemoglobin'.

[e] Neutropenia and neutrophil count decreased were reported separately according to MedDRA but clubbed together in this manuscript.

[f] For HFS, grade ≥2 AE presented.

information precluding analysis of efficacy in biological subgroups, and the absence of a comparator arm like single agent capecitabine which could have allowed relevant comparisons of toxicity and efficacy. The eligibility criteria included an upper age limit of 65 years, which makes the study results less generalizable to elderly patients. Future studies will need to be performed to address these issues as well as need for data in other regulatory jurisdictions to make this combination more widely available.

In summary, the FDC of capecitabine (1800 mg per day) and cyclophosphamide (80 mg per day) is effective and well-tolerated in the management of patients with MBC who have been previously treated with anthracycline and/or taxane chemotherapy. Good disease control rate and safety profile, reduced pill burden and patient preference for oral drugs makes this FDC an attractive treatment option for metastatic breast cancer.

Availability of data and materials

The datasets used and/or analyzed during the current study are available on reasonable request.

Authors' contributions

Dr. Sudeep Gupta performed the research and was involved in the acquisition of data, critically revised the manuscript for important intellectual content, and approved the final manuscript. Drs. Mujtaba A. Khan, Piyush Patel, Nisarg Joshi and Vinay Bajaj supervised the study conduct, were involved in the data interpretation, critically revised the manuscript for important intellectual content, and approved the final manuscript. All authors performed the research and made substantial contributions to this study, reviewed and approved the manuscript and agree to be accountable for all aspects of the work. Employees of the Sponsor, as noted in Author Contributions, were involved in trial design, data analysis and interpretation, and/or other aspects pertinent to the study. Authors had full access to data, were involved in writing and/or revising the manuscript, and had final responsibility for the decision to submit for publication.

Funding support

Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India funded the study.

Declaration of competing interest

The FDC of capecitabine and cyclophosphamide was developed by Intas Pharmaceuticals Limited, Gujarat, India. Drs. Mujtaba A. Khan, Piyush Patel, Nisarg Joshi and Vinay Bajaj are employees of Intas Pharmaceutical Ltd., India.

Acknowledgments

We would like to thank Mr. Shreekant Sharma, ISMPP CMPP™ (Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India) for providing writing assistance and Dr. Venugopal Madhusudhana, ISMPP CMPP™ (Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India) for additional editorial assistance for the development of this manuscript. The authors would also like to thank the Department of Biostatistics, Lambda Therapeutic Research Limited, Ahmedabad, for statistical analysis.

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