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Sponsor: Sanofi **Drug substance(s):** SAR439281	**Study Identifiers:** U1111-1166-1149, NCT02664103 **Study code:** CAPCYR07568
Title of the study: A Phase II Open-label Randomized Study of a Fixed-dose Combination of Capecitabine and Cyclophosphamide Administered at Different Doses /Regimens with Metronomic Schedule in Patients with Metastatic Breast Cancer	
Study center(s): 2 Centers in India	
Study period: Date first subject/patient enrolled: 23/Jan/2016 Date last subject/patient completed: 06/Nov/2017	
Phase of development: Phase 2	

Objectives:

Primary objectives:

- Assess the 12-week safety for each treatment group of patients on a fixed dose combination tablet of capecitabine and cyclophosphamide administered at flat dose and with metronomic schedule (defined as continuous daily treatment without interruption) in patients with metastatic breast cancer
- Assess the PK and bioavailability of the fixed dose combination tablet of capecitabine and cyclophosphamide administered at different doses/regimens by metronomic schedule in patients with metastatic breast cancer

Secondary objectives:

- Assess anti-tumor activity of the fixed dose combination tablet of capecitabine and cyclophosphamide administered at different doses/regimens by metronomic schedule in patients with metastatic breast cancer given with 3 different doses and schedules (regimen 1= standard dose twice daily (BID), regimen 2= full dose once daily, regimen 3= low dose, once daily)
  - Disease control rate (DCR)
  - Overall response rate (ORR)
  - Time to progression (TTP)

  using the response evaluation criteria in solid tumors (RECIST) criteria (version 1.1)
- Evaluate the compliance under treatment at 12 weeks and all along the treatment
- Describe evolution of toxicities between week 4 and week 12
- Assess safety all along patient's treatment after the 12 first weeks of treatment.

Exploratory objective:

Explore potential biomarkers and their correlation with response to the metronomic schedule of a fixed dose combination tablet of capecitabine and cyclophosphamide at different doses/regimens in patients with metastatic breast cancer.

Methodology:

This was a phase 2, open-label, randomized, parallel-group study, in which patients were to be randomized in a 1:1:1 ratio to treatment groups 1, 2 and 3 which would run in parallel. The randomization list was centrally generated using interactive voice response system (ClinPhone) and this schedule was used to generate individual treatment assignments for eligible patients.

Approximately, 12 patients were to be enrolled in each treatment group. The treatment group 1 was to include standard regimen, 1 BID approximately 12 hours apart (total dose: capecitabine 1200 mg and cyclophosphamide 80 mg), treatment group 2 was to include once-a-day (OD) regimen, 2 OD (total dose: capecitabine 1200 mg and cyclophosphamide 80 mg) and treatment group 3 was to include low dose regimen 1 OD (once daily) (total dose: capecitabine 600 mg and cyclophosphamide 40 mg); all the dose regimen were to be given daily without interruption. In case of early drop outs (< 12 weeks), patients were to be replaced and randomization was to be extended to fit with the desired sample per treatment group. However, after 6 drop outs in the same treatment group, the treatment group was to be stopped and declared failure. This would have translated into maximal number of patients in the study of (12+6) × 3 = 54 patients.

An Independent data monitoring committee (IDMC) was to be formed to provide safety oversight for this study. The IDMC were to review the safety data on a regular basis and provide recommendations on the study conduct. A Steering committee (SC) included the study Chairman, Sponsor representatives, and non-Sponsor members; and made recommendations for the protocol. The SC would have been responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the IDMC in terms of study continuation with or without alterations, or of potential study termination.

Patients were treated until progression or unbearable toxicity; however, the primary evaluation was to be made on the first 12 weeks of treatment for each patient.

Number of subjects/patients**:** Planned: minimum of 36 patients and maximum of 54 patients

Randomized: 2

Treated: 2

Evaluated:

Efficacy/pharmacodynamics: 2

Safety: 2

Pharmacokinetics: 2

Diagnosis and criteria for inclusion:

Inclusion criteria

- Female ≥ 18 and ≤ 65 years old
- Patients with histologically or cytologically confirmed metastatic breast cancer (Human epidermal growth factor receptor 2 [HER2] negative, Estrogen receptor/Progesterone receptor [ER/PR] positive or negative), were candidates to receive capecitabine and cyclophosphamide as per the Investigator's judgment, and who met either one of the following characteristics:
  - Recurrence of the disease following at least 2 lines of chemotherapy failure for metastatic triple negative breast cancer
  - In ER/PR positive breast cancer, recurrence of the disease following at least 1 line of chemotherapy failure and 2 lines of hormonal therapy failure
- Patients who were previously treated with capecitabine were recruited in the study provided:
  - As per the Investigator's opinion, patients would be benefited from this chemotherapy and
  - 6 months washout period prior to administration of the Investigational medicinal product (IMP) when capecitabine was given as single chemotherapy or
  - 12 months washout period prior to administration of the IMP when capecitabine was given in combination with other chemotherapeutic agents
- At least one uni-dimensionally measurable lesion according to RECIST criteria version 1.1
- An Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2
- Life expectancy of >3 months
- Patients who were willing to undergo (oral) chemotherapy for the treatment of their disease and who were expected to comply with the treatment and study procedures, as per the Investigator's judgment
- For women of childbearing potential, documented negative pregnancy test and agreement to use acceptable birth control measures during the duration of the study
- Signed Informed consent was obtained prior to any study related procedures

Exclusion Criteria

- Patients who were HER2 positive
- Patients with 3 or more lines of chemotherapy failure for metastatic triple negative breast cancer
- In ER/PR positive breast cancer, recurrence of the disease following 2 or more lines of chemotherapy failure and/or 3 or more lines of hormonal therapy failure
- Patients who presented with de novo stage IV metastatic breast cancer, and not previously treated for their disease
- Patients who already had received any metronomic chemotherapy regimen
- Known hypersensitivity to capecitabine or to any of its components
- Known hypersensitivity to 5-fluorouracil
- Known hypersensitivity to cyclophosphamide or any of its components
- History of bladder carcinoma
- Systemic anticancer therapy (chemotherapy, hormone therapy or radiotherapy) within 4 weeks of randomization for the study
- History of unexplained hematuria
- History of dihydropyrimidine dehydrogenase deficiency
- Severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault])
- Concomitant warfarin treatment
- History of significant cardiac disease (e.g. unstable angina, congestive heart failure, myocardial infarction, ventricular arrhythmias) within the previous 6 months
- Conditions/situations such as:
  - Patient was the Investigator or any Sub-Investigator, research assistant, pharmacist, Study coordinator, other staff, or relative thereof, directly involved in the conduct of the protocol
  - Uncooperative patient or any condition that could make the patient potentially non-compliant to the study procedures
- Pregnant or breast-feeding female
- Women of childbearing potential not protected by effective contraceptive method of birth control and/or who were unwilling or unable to be tested for pregnancy
- Patients who had a possibility of active tuberculosis as suggested by:
  - Any signs or symptoms suggestive of active tuberculosis upon medical history or clinical examination
  - Chest radiograph within 3 months prior to the screening visit consistent with tuberculosis infection
  - Patients with close contact with a person with active tuberculosis
- Known history of Human Immunodeficiency Virus
- Any other significant medical conditions which was the judgment of the Investigator would preclude completion of the study
- Participation in a clinical research study evaluating another investigational drug or therapy within 30 days prior to the Screening Visit
- Presence of any of the following laboratory abnormalities at the Screening Visit:
  - Hemoglobin < 8.5g/L
  - White blood cells < 3000/µL;
  - Platelet count < 100000/µL;
  - Absolute neutrophil count < 1500/µL;
  - Aspartate aminotransferase or alanine aminotransferase >1.5x upper limit of normal [ULN] (or > 5×ULN in patients with liver metastasis)
  - Total Bilirubin > 1.5×ULN (or >2×ULN in patients with liver metastasis)
  - Patients who had a body surface area < 1.0 m² or > 1.8m²

Study treatments

Investigational medicinal product(s): capecitabine/cyclophosphamide

Formulation: Tablet, film-coated

Route(s) of administration: Oral

Dose regimen: One pill once daily, 2 pills once daily, 1 pill twice daily

Duration of treatment: Twelve weeks of open label treatment and extension treatment period (for patients who showed evidence of efficacy) until progression of disease.

Duration of observation: 2 weeks of screening, 12 weeks of treatment, followed by extension treatment period which included continuation of treatment for patients who showed evidence of efficacy at 12 weeks until progression of disease, and end of treatment visit 30 days after the last administration of the IMP.

The observation of safety data was from the time the informed consent was signed up to the end of the study.

Criteria for evaluation:

The current report is a synopsis style report because the study was terminated prematurely due to lower than expected recruitment, and as such, only the safety results are presented in full. The following safety criteria were evaluated, and analyzed using data listing.

Toxicities were to be graded and reported according to the National cancer institute- common terminology criteria for adverse events (NCI-CTCAE) version 4.03. Patient incidence rates of all Adverse Events (AEs) were to be tabulated by system organ class, preferred term, and severity. Tables cannot be evaluated for the "on-study" deaths, serious and significant AEs, including early withdrawals due to AEs, as well as toxicities between 4 weeks and 12 weeks. All AEs/serious AEs (SAEs) types and NCI-CTCAE grade after short and longer term treatment (4-12 weeks) were described. Safety all along patient's treatment after the 12 weeks (3 cycles) was assessed.

Statistical methods:

Sample size determination:
This was an estimation study and no statistical comparison between any of the dose groups was intended. For each treatment group (dose group), 12 patients were to be randomized to avoid any bias in patient selection. The sample size was decided based on clinical judgment. No formal statistical hypothesis was formulated for the sample size justification. Replacement of patients not evaluable at 12 weeks was planned for a maximum of 6 patients per treatment group.

Analysis population:
All-treated (AT) population: The AT population included patients who were randomized and took at least one dose of IMP. This population was to consider patients in the treatment actually received and was used for all safety and if applicable to all efficacy analyses.

Safety analyses:
Safety analyses were done on the AT population based on adverse events, physical examination (height, weight and systemic examination), vital signs (pulse rate, body temperature, and blood pressure), laboratory screenings and safety tests (Hematology, serum biochemistry, urine analysis).

Efficacy analyses:
All efficacy analyses were to be done on the AT population.

Efficacy endpoints:
A computed tomography scan was to be performed at Screening Visit and repeated every 12 weeks until progression to determine the following responses: Efficacy endpoints DCR, ORR, and TTP.

Interim and final analyses:
No formal interim analysis was performed. The safety data were to be reviewed for the first time by the IDMC and SC after the first 6 patients per treatment group completed their first month of treatment, for toxicities and compliance on treatment and then every 3 months or according to the study needs. However, there were only 2 patients recruited, and the study was terminated prematurely. The IDMC was not formed as the study was terminated before its formation.

Summary:

Efficacy/pharmacodynamic results:

The efficacy evaluation is performed in two patients from the AT population. However, due to lower than expected recruitment, only the safety results are presented in full in this report

In both the patients, blood samples were collected for the PK and the metronomic markers; however the analysis was not performed. The overall tumor assessment for the target lesion was assessed as stable disease, and the tumor assessment for the non-target lesion was assessed as non-complete response/non progressive disease in both the patients. Progression of disease

was recorded in patient A on 06-Oct-2017 (Day 484) and in the patient B on 14-Jun-2016 (Day 133) of the treatment. Patient A completed study on 06-Nov-2017 (Day 515); whereas, patient B discontinued from the study following disease progression on 14-Jun-2016. Safety results: Safety results from the two patients recruited in the study are included in this report. The safety parameters evaluated were, adverse events (AEs), including treatment-emergent AEs (TEAEs), and significant changes from baseline in clinical laboratory reports and vital signs. A total of 22 TEAEs were reported from the study (10 in Patient A and 12 in Patient B).
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