*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

| | |
|---|---|
| Sponsor / Company: Sanofi<br>Drug substance(s): SAR240550 (iniparib) | Study Identifiers: NCT00540358<br>Study code: TCD11485 |
| Title of the study: A Phase 2, Multicenter, Open-label, Randomized Trial of Gemcitabine/Carboplatin, With or Without BSI-201,in Patients With ER, PR and HER2-negative Metastatic Breast Cancer | |
| Study center(s): This study was conducted in 20 United States (US) oncology sites | |
| Study period:<br>Date first patient randomized: 16/Oct/2007<br>Data cut-off date: 16/Nov/2009<br>Database lock date: 24/Jun/2010 | |
| Phase of development: 2 | |

Objectives:

The primary objectives of the study were to:

- Assess the clinical benefit rate (complete response + partial response + stable disease ≥6 months) with gemcitabine/carboplatin with or without iniparib;
- Further evaluate the safety and tolerability of iniparib in adult patients with histologically documented (either primary or metastatic site) breast cancer that is estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and human epidermal growth factor receptor 2 (HER2) negative.

The secondary objectives of the study were to:

- Evaluate the overall response rate (ORR);
- Evaluate progression-free survival (PFS);
- Evaluate the toxicity associated with each arm.

The exploratory objectives were to:

- Characterize the inhibition of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) activity by iniparib in peripheral blood mononuclear cells (PBMCs);
- Characterize PARP gene expression and pharmacogenomics in archived tumor tissues samples;
- Study the status of the breast cancer gene (BRCA) in triple negative breast cancer (TNBC);
- Study the response in patients with cancer and known BRCA mutations compared to patients without these mutations;
- Classify breast cancer tissue as either basal or luminal.

Although overall survival, time to response, and duration of response were not prespecified endpoints in the study protocol, at the time the statistical analysis plan was prepared these end points were included for posthoc analyses.

Methodology: This was a Phase 2, open-label, 2-arm randomized trial to assess the safety and efficacy of iniparib in combination with gemcitabine and carboplatin versus a combination of gemcitabine and carboplatin.

Before randomization, the patients signed an informed consent and were screened with respect to medical history, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, prior treatments, hematology, serum biochemistries (including hepatic, renal, metabolism, and electrolyte parameters), urinalysis, electrocardiogram (ECG), and tumor measurement. After review of the screening assessments and the confirmation that the patients met eligibility criteria, the patients were randomly assigned (1:1) to one of the following treatments:

- Arm 1 (G/C): gemcitabine (1000 mg/m$^2$, 30 minute intravenous [IV] infusion) and carboplatin (area under the curve [AUC] 2; 60 minute IV infusion) on Days 1 and 8 of a 21-day cycle;
- Arm 2 (G/C/I): gemcitabine (1000 mg/m$^2$, 30 minute IV infusion) and carboplatin (AUC 2; 60 minute IV infusion) on Days 1 and 8 of a 21-day cycle with iniparib (5.6 mg/kg 1 hour IV infusion) on Days 1, 4, 8, and 11 of a 21-day cycle. Prior to the implementation of Amendment 2, the starting dose of iniparib was 4.0 mg/kg.

Patients who were randomized to the G/C arm could cross over to receive treatment with gemcitabine/carboplatin in combination with iniparib at the time of disease progression that had been confirmed by radiographic imaging such as magnetic resonance imaging (MRI) or computed tomography (CT) scan. Patients randomized to the G/C/I arm were to be discontinued from the trial at the time of disease progression.

Tumor response was evaluated by modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 every other cycle beginning at Cycle 2. After treatment discontinuation, patients were to be followed for survival only.

Vital signs, physical examinations, ECOG performance status, ECGs, and laboratory safety tests (including complete blood counts and serum chemistries) were obtained prior to drug administration and at designated intervals throughout the study. Adverse events were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0 during the study. All safety assessments were repeated at the end of each cycle (3 weeks), efficacy assessments were performed at the end of every even numbered cycle (6 weeks), and the final assessments were performed within 30 days following the final dose.

Number of patients: Planned: 120 (60 per arm)

Randomized (intent-to-treat [ITT] population): 123 (62 G/C; 61 G/C/I)

Treated (safety population): 116 (59 G/C; 57 G/C/I)

Crossover patients (G/C to G/C/I): 30

Efficacy analyses were done on the ITT population, which consisted of all randomized patients. All analyses using this population were based on the treatment group assigned at randomization.

The safety analysis was done on the safety population, which consisted of all patients who received at least 1 dose of any of the 3 study drugs. All analyses using this population were based on the treatment actually received. For patients who crossed over, analyses on the safety population included all data up to the crossover date. The crossover safety population included all patients from the G/C arm who crossed over to receive G/C/I. This population was used for analysis of exposure and safety data after the crossover date.

Diagnosis and criteria for inclusion: Patients had to be at least 18 years of age with metastatic breast cancer (Stage IV) measurable by RECIST criteria that was ER-negative, PR-negative, and HER2 nonoverexpressing by immunohistochemistry (0, 1) or non-gene amplification by fluorescence in situ hybridization (FISH). Patients had to have had 0 - 2 prior chemotherapy regimens in the metastatic setting. Prior adjuvant/neoadjuvant therapy was allowed. Patients also had to have an ECOG performance status of 0 or 1 with adequate organ function defined as: absolute neutrophil count (ANC) greater than or equal to 1500/mm$^3$, platelets greater than or equal to 100,000/mm$^3$, creatinine clearance greater than 50 mL/min, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) lower than 2.5 x upper limit of normal (ULN) (or lower than 5 x ULN in case of liver metastases) and total bilirubin lower than 1.5 mg/dL.

Study treatments

Investigational medicinal product(s): Iniparib (BSI-201, SAR240550)

Route(s) of administration: Intravenous

Dose regimen: Gemcitabine (1000 mg/m$^2$; 30 minute IV infusion) and carboplatin (AUC 2; 60 minute IV infusion) on Days 1 and 8 of a 21-day cycle with iniparib (5.6 mg/kg 1 hour IV infusion) on Days 1, 4, 8, and 11. The treatment cycle was repeated every 21 days. Prior to the implementation of Amendment 2, the starting dose of iniparib was 4.0 mg/kg.

Reference therapy: Gemcitabine and carboplatin (G/C)

Route(s) of administration: Intravenous

Dose regimen: Gemcitabine (1000 mg/m$^2$; 30 minute IV infusion) and carboplatin (AUC 2; 60 minute IV infusion) on Days 1 and 8 of a 21-day cycle. The treatment cycle was repeated every 21 days.

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity, Investigator's decision to discontinue, or withdrawal of consent. At the time of disease progression, patients in the G/C arm could crossover to the G/C/I arm.

Duration of observation: After treatment discontinuation, all patients were evaluated every 90 days after last dose of gemcitabine/carboplatin with or without iniparib, for up to 3 years or death or end of study, which ever occurred first.

Criteria for evaluation:

Efficacy: The primary efficacy variable, clinical benefit rate, was defined as the percentage of patients with complete response, partial response or stable disease ≥6 months. Tumor response was measured according to modified RECIST Version 1.0.

Secondary efficacy variables were PFS and ORR.

- Objective response rate was defined as the percentage of patients with confirmed complete response or partial response based on the Investigator tumor assessments.
- Progression-free survival was defined as the time interval from the date of randomization to the date of Investigator assessed disease progression based upon RECIST Version 1.0 or the date of death due to any cause, whichever came first. In the absence of disease progression or death before the analysis cut-off date, PFS was censored at the date of the last valid tumor assessment showing complete response, partial response, or stable disease performed before the cut-off date. If a patient received other therapy for breast cancer during this study before progression, the patient was censored at the date of the last tumor assessment before the start of the first such therapy. Patients who crossed over before disease progression were censored at the date of last tumor assessment before crossover.

Overall survival, duration of response, and time to response were not prespecified endpoints in the protocol but were added to the statistical analysis plan and performed for this study report as posthoc analysis:

- Overall survival was defined as the time interval from the date of randomization to the date of death due to any cause. In the absence of confirmation of death before the analysis cut-off date, overall survival was censored at the last date the patient was known to be alive, or at the analysis cut-off date, whichever was earlier.
- Duration of response was determined only for patients who had a confirmed complete response or partial response. Duration of response was defined as the time interval from the date of first documented complete response or partial response to the date of subsequent progressive disease or death, whichever was earlier. In the absence of disease progression or death before the analysis cut-off date, duration of response was censored at the date of the last valid tumor assessment before the cut-off date.
- Time to response was defined as the time from the date of randomization to the date of the first documented RECIST defined response (complete response or partial response). Time to response was determined only for patients who had a confirmed complete response or partial response.

PARP samples were to be collected in Arm 2 and crossover patients during Cycle 1, predose on Days 1, 4, 8, and 11 and postdose samples were to be collected on Days 1 and 11, for a total of 6 samples.

Safety: Safety was evaluated by summarizing clinical and laboratory adverse events (AEs) graded according to NCI-CTCAE Version 3 and coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0. In addition, vital signs (blood pressure, heart rate, and temperature); physical examinations, ECG parameters, ECOG performance status were evaluated periodically.

Statistical methods: Descriptive statistics for all demographic, safety, and efficacy variables were provided in tables. For continuous variables, descriptive statistics included number of observations, mean, standard deviation, median, and range (minimum and maximum). For categorical variables, descriptive statistics included frequency and percentage. Percentages were calculated using as the denominator the number of patients with nonmissing data in the considered population.

The number and percent of patients achieving clinical benefit were summarized with corresponding exact 2-sided 95% confidence intervals (CI). The difference between treatments, a 95% CI for the difference based on a normal distribution, and a p-value were based on the Pearson Chi-square test. Subgroup analysis was performed for the clinical benefit rate using line of chemotherapy, age category (<50 years; ≥ 50 years) race, ECOG performance status, time since diagnosis of TNBC, number of metastatic sites, and visceral disease. The potential influence of baseline characteristics and medical history on the clinical benefit rate was evaluated using the logistic regression model.

The analysis for overall response rate was similar to that described for clinical benefit rate.

Progression-free survival was analyzed using Kaplan-Meier method by treatment group. Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and the 95% CI of median were provided. In addition, probabilities of surviving at 3, 6, 9, and 12 months were provided for each treatment group. The hazard ratio and its 95% CI were estimated using the Cox proportional hazards regression model. The analysis for the endpoint overall survival was similar to that described for PFS and included separate analysis of crossover patients.

Duration of response and time to response were analyzed in the responders only. Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and the 95% CI were provided.

The safety analysis was based on the safety population and the crossover safety population. For patients who crossed over, analyses on the safety population included all data reported up to the crossover date.

Summary: A total of 123 patients were randomized (62 patients in G/C arm and 61 patients in the G/C/I arm) and 116 patients were included in the safety population (59 patients in G/C arm and 57 patients in the G/C/I arm).

The demographic and disease characteristics were generally well-balanced between the study arms.

Efficacy results: The addition of iniparib to the combination chemotherapy regimen of gemcitabine and carboplatin (G/C/I) resulted in an improvement in clinical benefit rate, ORR, PFS and overall survival compared to the control arm of gemcitabine and carboplatin (G/C) using the identical dose and schedule which is commonly used and has been shown to be active in patients with TNBC.

Best overall response among the 30 patients on the G/C arm who crossed over to receive iniparib was stable disease in 5 patients (16.7%).

Summary of key efficacy results prior to crossover - ITT population

| | Gemcitabine/ Carboplatin (N=62) | Gemcitabine/ Carboplatin/Iniparib (N=61) | p-value |
|---|---|---|---|
| | | | |
| | | | |
| Progression-free survival | | | |
| Number (%) of events | | | |
| Median (95% confidence interval [CI]) | | | 0.012[b] |
| Overall survival | | | |
| Number (%) of events | | | 0.014[b] |
| Median (95% CI) | | | |

[a] P-value is from the Pearsons chi-square test

[b] log-rank test, not adjusted for multiple interim analyses

Safety results: Prior to crossover, a total of 324 cycles were administered on the G/C arm compared with 485 on the G/C/I arm. The median number of cycles was 4 in the G/C arm with a range of 1 to 20 cycles and 7 in the G/C/I arm with a range of 1 to 28 cycles. The median duration of exposure in the G/C arm was 13 weeks (range: 3 to 73 weeks). In the G/C/I arm, the median duration of exposure was 24 weeks (range: 3 to 95 weeks). The relative dose intensity of gemcitabine and carboplatin was approximately 75% for each of the drugs on both treatment arms. Following crossover, the median number of cycles was 1 for gemcitabine, 2 for carboplatin and 1.5 for iniparib. The median duration of exposure was 3 weeks for gemcitabine 6 weeks for carboplatin, and 4.5 weeks for iniparib.

All patients from both arms reported at least 1 treatment-emergent adverse event (TEAE). The incidence of Grade 3-5 events was higher in the G/C/I arm (91.2% versus 84.7%), with hematological events comprising the greatest proportion of these Grade 3-5 events. The numbers (%) of patients who experienced at least 1 serious adverse event (SAE), 1 AE leading to treatment discontinuation, and fatal TEAE were comparable between the 2 arms.

The most frequent (≥5%) Grade 3-5 AEs in the G/C/I arm were neutropenia (66.7%), thrombocytopenia (36.8%), anemia (22.8%), leukopenia (12.3%), fatigue (7.0%), and ALT increase (5.3%). The most frequent (≥5%) Grade 3-5 TEAEs in the G/C arm were neutropenia (62.7%), thrombocytopenia (27.1%), fatigue (16.9%), anemia (15.3%), leukopenia (10.2%), and febrile neutropenia (5.1%).

During treatment per laboratory assessment, Grade 3-4 leukopenia (70.2% versus 59.3%), anemia (29.8% versus 15.3%), and thrombocytopenia (38.6% versus 32.2%) were reported more frequently on the G/C/I arm with a difference of at least 5 percentage points compared with the G/C arm. The incidence of Grade 3-4 elevated AST and bilirubin was similar on each arm, while Grade 3-4 elevated ALT was higher on the G/C/I arm (14.0% versus 0%). There were no cases of Grade 3-4 elevated creatinine.

Treatment-emergent serious adverse events (SAEs) were reported in 17 patients (28.8%) in the G/C arm and 16 patients (28.1%) in the G/C/I arm. The most frequently reported serious TEAEs on the G/C arm were febrile neutropenia (5.1%) and neutropenia (3.4%). In the G/C/I arm, the most frequent serious TEAEs were malignant neoplasm progression (5.3%), dyspnea (3.5%), and pneumonia (3.5%).

There were a total of 18 deaths (62.1%) up to crossover on the G/C arm and 33 deaths (57.9%) on the G/C/I arm. All deaths were due to disease progression. Of these, 2 deaths (6.9%) on the G/C arm and 4 deaths (7.0%) on the G/C/I arm occurred during the on-treatment period and were within 30 days of last dose of study treatment. The 2 patients in the G/C arm and 3 of the 4 patients in the G/C/I arm had fatal events of disease progression reported as adverse events because they occurred within 30 days of last dose of study drug. Nine patients (15.8%) on the G/C/I arm and 11 patients (18.6%) on the G/C arm discontinued treatment due to an AE.

On the crossover arm, the most frequent (≥20%) all grade TEAEs were anemia, thrombocytopenia, fatigue, nausea, neutropenia, and urinary tract infection. The most frequent (≥5%) Grade 3-5 TEAEs were neutropenia, thrombocytopenia, malignant disease progression, anemia, back pain, axillary pain, hypoxia, and pancytopenia. Four patients (13.3%) died within 30 days of last treatment, all due to progressive disease, 13 patients (43.3%) experienced treatment-emergent SAEs, and 6 patients (20.0%) discontinued treatment due to an AE. The most frequently reported Grade 3-4 laboratory abnormalities on the crossover arm were lymphopenia (30.0%), thrombocytopenia (20.0%), leukopenia (16.7%), and elevated bilirubin (10.0%).

Issue date: 18-May-2016