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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00938652, UTN U1111-1119-8208 Study code: EFC11486
Title of the study: A Phase 3, Multicenter, Open-label, Randomized Study 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 105 sites in the United States (US)	
Study period: Date first patient enrolled: 17/Jul/2009 Date last patient completed: 21/Nov/2010 (primary cut-off date for safety and efficacy data) 31/Jul/2011 (cut-off data for secondary analysis of overall survival) 07/Feb/2012 (final cut-off for safety data)	
Phase of development: Phase 3	

Objectives:

The primary objectives were:

- To evaluate overall survival (OS);
- To evaluate progression-free survival (PFS).

The secondary objectives were:

- To evaluate the objective response rate (ORR);
- To further evaluate the safety, tolerability, and pharmacokinetics of iniparib in combination with gemcitabine and carboplatin.

Methodology: This was an open-label, randomized, multicenter Phase 3 study conducted in adult patients with histologically documented metastatic breast cancer that was estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and human epidermal growth factor receptor 2 (HER2)-nonoverexpressing (ie, triple-negative breast cancer [TNBC]).

Prior to randomization, eligible patients were then classified into 1 of 2 strata according to the number of prior metastatic therapies:

- Stratum I: No previous chemotherapy in the metastatic setting for TNBC;
- Stratum II: One or 2 previous chemotherapies in the metastatic setting for TNBC.

Within each of the 2 strata, patients were randomized in a 1:1 ratio into 1 of 2 treatment arms:

- Arm A: G/C;
- Arm B: gemcitabine, carboplatin, and iniparib (G/C/I).

Treatment continued in the absence of disease progression, unacceptable toxicity, or other specified discontinuation reason.

Scans were sent to an independent radiologic review (IRR) committee for the assessment of disease response (partial response [PR], complete response [CR], stable disease [SD] and progressive disease [PD]). In addition, if clinical progression was suspected, all relevant clinical documentation was to be submitted to the IRR committee to confirm clinical progression.

Upon confirmed disease progression by the committee, patients in the G/C treatment arm could cross over to the G/C/I treatment arm.

During the follow-up period all randomized patients were followed for OS every 45 days (±10 days), whether or not study treatment was administered, until death or the study cut-off date. All randomized patients who discontinued study treatment before documented disease progression and patients who were randomized but not treated, were followed for PFS every 45 days (±10 days) until end of study, death, or receipt of new anticancer therapy, whichever was first.

Safety was assessed prior to and at intervals subsequent to study drug administration by standard clinical and laboratory tests (hematology, blood chemistry, and urinalysis) and by adverse event (AE) reporting, with toxicity grade defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 3.0. In addition, safety was assessed by physical and neurological examination, vital signs, electrocardiogram (ECG), and Eastern Cooperative Oncology Group performance status (ECOG PS) assessment.

The primary analysis was to occur after 260 OS events (effectively, 261 OS events had occurred as of the database cutoff on 21 November 2010). Due to over enrollment, 261 deaths represented only 50% of patients had survival events. A post hoc protocol amendment was implemented to obtain survival information when approximately 70% of patients had survival events. This exploratory analysis was planned at 360 OS events (effectively, 365 OS events had occurred as of the database cutoff on 31 July 2011). No PFS or ORR information was collected for this updated analysis. Efficacy and safety analyses were performed on data from the first cut off and only survival was analyzed on data from the second cut off. In addition, safety data through study completion were also analyzed.

Number of patients:	Planned: Approximately 420 (210 in each study arm)
	Randomized: 519 (G/C: 258, G/C/I: 261)
	Treated: 499 (G/C: 244, G/C/I: 255)
Evaluated:	
	Efficacy: 519
	Safety: 499
	Crossover: 152 at the primary cut-off date; 161 at updated analysis cut-off date

Diagnosis and criteria for inclusion: Eligible patients were female ≥18 years of age with histologically documented metastatic breast cancer that was ER-negative, PR-negative (<10%), and HER2-nonoverexpressing by immunohistochemistry (0, 1) or fluorescence in situ hybridization (FISH)+ as measured at the local laboratory. Patients were not to have had prior treatment with gemcitabine, carboplatin, cisplatin, or iniparib, and were to have had 0-2 prior chemotherapy regimens in the metastatic setting. Prior adjuvant/neoadjuvant therapy was allowed. Any other systemic anticancer therapy was not to have been administered within 14 days of the first dose of study drug. Patients were to have an ECOG-PS of 0 or 1 and organ and marrow function as follows:
absolute neutrophil count (ANC) ≥1500 µL, platelets ≥100,000/µL, hemoglobin ≥9 g/dL, bilirubin ≤1.5 mg/dL, serum creatinine ≤1.5 mg/dL or creatinine clearance ≥60 mL/min, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN) if no metastatic liver involvement (or ≤5 times the ULN with liver involvement).

Study treatments

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

Dose: On Days 1, 4, 8, and 11, iniparib 5.6 mg/kg IV infusion (60 ± 10 minutes) followed by a 1-week treatment-free period in each 21-day cycle.

Route(s) of administration: Intravenous (IV)

Background chemotherapy/Reference therapy: Gemcitabine/carboplatin

Dose: gemcitabine (1000 mg/m^2) as an IV infusion over 30 ± 10 minutes and carboplatin (AUC 2) as an IV infusion over 30 ± 10 minutes or 60 ± 10 minutes both on Days 1 and 8 of each 21 day cycle

Route(s) of administration: IV

Duration of treatment: Treatment continued every cycle in the absence of disease progression, unacceptable toxicity, or consent withdrawal. Upon confirmed disease progression by IRR, patients in the G/C treatment arm could cross over to receive treatment with G/C/I. At the time of disease progression, patients in the G/C/I treatment arm were discontinued from the treatment Phase of the study.

Duration of observation: All randomized patients were followed every 45 days (±10 days) after the end-of-treatment visit (for treated patients) or after randomization (for patients not treated) until end of study or death, whichever was first. The estimated length of the study was 24 months.

Criteria for evaluation:

Efficacy:

The primary endpoints for this study were OS and PFS.

- Overall survival was defined as the time from randomization to death from any cause. In the absence of confirmation of death before the analysis cut off date, OS was censored at the last date of follow up when the patient was known to be alive or at the analysis cut off date, whichever occurred first.
- Progression-free survival was defined as the time interval from the date of randomization to the date of first IRR documented disease progression (based upon RECIST v 1.1 for radiological progression or clinical data for clinical progression), or the date of death due to any cause, whichever occurred first. In the absence of confirmation of IRR, documented disease progression, or death before the analysis cut off date, PFS was censored at the date of the last valid tumor assessment showing CR, PR, or SD performed before the cut off date. If a patient received new anticancer therapy during this study before progression, the patient was censored at the date of the last tumor assessment before the start of the new therapy. Patients who crossed over to the G/C/I treatment arm before confirmation of disease progression were censored at the date of last tumor assessment before crossover.

The secondary endpoint of objective response rate (ORR) and was determined based on Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 by IRR. ORR was defined as the percentage of patients with confirmed PR or CR prior to disease progression or starting other tumor therapy per IRR evaluations. Confirmation of a partial response (PR) or complete response (CR) was required at least 4 weeks after initial documentation of a response. Best overall response and duration of response were also evaluated. Best overall response was defined as the best IRR evaluation observed from the start of treatment through the entire study, excluding any time following crossover or the start of new anticancer therapy. Duration of response was defined as the time interval from the date of first IRR-documented CR or PR to the date of subsequent disease progression or death.

Safety: Safety was assessed by standard clinical and laboratory tests (hematology, blood chemistry, and urinalysis), physical and neurological examination, vital signs, ECOG-PS assessment, electrocardiogram (ECG), and by AE reporting. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v12.0 and with toxicity grade defined by the NCI-CTCAE v 3.0.

Pharmacokinetics: A subset of patients in the G/C/I treatment arm at pharmacokinetic (PK)-capable study sites were to participate in the PK portion of this study for determination of plasma concentrations of iniparib and 2 metabolites.

Pharmacokinetic sampling times and bioanalytical methods: Pharmacokinetic samples were taken in 2 consecutive treatment cycles (eg, Cycles 1 and 2 or Cycles 4 and 5), with PK samples taken on Days 1 and 4 of the first PK sampling cycle and on Day 1 of the second PK sampling cycle. Samples were taken predose, 30 minutes after initiation of iniparib infusion, 5 minutes prior to end of iniparib infusion, and between 1 to 3 hours after the end of iniparib infusion. Iniparib, 4-iodo-3-nitrobenzamide (IABM) and 4-iodo-3-nitrobenzoic acid (IABA) concentrations were to be measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS method).

Statistical methods: Descriptive statistics for all demographic, safety, and efficacy variables were provided in tables.

Cutoff Dates:

The following cut-off dates were utilized for the analyses.

Demography
Primary: 21 November 2010 (261 deaths)

Efficacy
Primary: 21 November 2010 (261 deaths)
Update (OS only): 31 July 2011 (365 deaths)

Exposure and Safety
Primary: 21 November 2010 (261 deaths)
End of study safety update: 07 February 2012 (date last patient completed study)

Analysis of primary efficacy variables:

The primary efficacy variables were PFS and OS. The study was to be considered positive if either endpoint met the stated significance criteria from the unstratified log-rank test in the intent-to-treat (ITT) population (ie, all randomized patients): 0.04 for OS and 0.01 for PFS. The primary efficacy analysis was to be performed when 260 deaths had occurred.

OS was analyzed using the Kaplan-Meier method by treatment group in the ITT population. Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associated 95% confidence intervals (CIs) were provided. In addition, probabilities of surviving at 3, 6, 9, and 12 months with 95% CIs (Hall and Wellner simultaneous intervals) were provided for each treatment group. The hazard ratio (HR) and its 95% CI were estimated using the Cox proportional hazards regression model. Kaplan-Meier curves were plotted. The 2 sided unstratified log rank test for the ITT population was used to compare treatment groups.

The analysis for the co-primary endpoint PFS was similar to that for OS.

Secondary and exploratory analyses of primary efficacy variables included analyses of OS and PFS by randomization strata (Stratum I: no chemotherapy in the metastatic setting/Stratum II: 1 to 2 chemotherapies in the metastatic setting) and the use of the stratified log-rank test in the ITT population for comparison of PFS and OS between the 2 arms.
Updated OS information was presented similarly to that for the primary cut off.

Analysis of secondary efficacy variables:

Best overall response was summarized with descriptive statistics for the ITT population. Within the CR, PR, SD, and PD categories, the difference between treatments and 95% CI for the difference based on a normal distribution were provided.

ORR was assessed for the ITT population and within each stratum (no chemotherapy in the metastatic setting and 1 to 2 chemotherapies in the metastatic setting). The number and percentage of patients achieving an objective response was summarized with corresponding exact 2-sided 95% CIs. In addition, the difference between treatments and 95% CI for the difference based on a normal distribution were provided. ORR between the 2 arms was compared with the Pearson chi-square test and the Cochran-Mantel-Haenszel (CMH) test adjusted for stratification factor.

Duration of response was analyzed in the same manner as the primary analysis of OS.

Analysis of safety variables:

Safety analyses were 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:

Efficacy results: This study did not meet its primary efficacy objectives at the pre-specified significance levels for OS and PFS in the primary efficacy analysis (after 261 OS events). At the primary analysis cut off date when 261 patients had OS events, the differences between treatment arms for both primary endpoints (OS and PFS) were not significant (OS: HR=0.88 [95% CI 0.69–1.12], p=0.28; and PFS: HR=0.79 [95% CI 0.65–0.98], p= 0.027), although the HRs showed reductions in the risk of death or progression with the G/C/I treatment arm for both parameters (12% and 21% reductions, respectively).

The secondary endpoint of ORR was not significantly different in the G/C and G/C/I groups (30.2% versus 33.7%; p=0.379).

In the secondary/exploratory analyses of the primary endpoints based on the predefined subgroups by number of lines of prior chemotherapy for mTNBC suggested an efficacy benefit restricted to patients receiving G/C/I as second or third-line therapy. This was reflected in both of the primary outcomes (OS and PFS), but not in the secondary efficacy endpoint (ORR).

Risk of death was decreased by 35% in the second or third-line therapy patients compared with an 11% increase in risk in patients receiving iniparib in first-line therapy; the PFS risk was reduced by 22% and 12% in patients receiving second or third-line therapy and first-line therapy, respectively.

Because only 50% of patients had experienced an OS event at the primary analysis cut-off date and 55 patients were continuing to receive treatment, an updated survival analysis was performed after 365 deaths had occurred. Results of this updated analysis were similar to those at the primary cut-off date. Among all patients, risk of death was reduced by 15% with G/C/I. In the analyses based on prior chemotherapy, risk of death increased by 7% in patients receiving first-line therapy and decreased by 40% in patients receiving second or third-line therapy.

A post hoc multivariate analysis was performed to evaluate the impact of imbalances in specific demographic/baseline characteristics and prognostic factors on the updated OS results in the 2 treatment arms. In the ITT population, the adjusted HR for OS was 0.75 (95% CI, 0.61 to 0.92). The HR adjusted for imbalances in the baseline factors in the first-line patients was 0.87 (95% CI, 0.65 to 1.17) and was 0.62 (95% CI, 0.46 to 0.84) in the second/third-line patients.

Safety results:

Before crossover, a total of 1518 and 1863 cycles were administered in the G/C and G/C/I treatment arms, respectively, with patients receiving a median of 5.0 and 6.0 cycles, respectively. In both arms, over 60% of patients had dose reductions of gemcitabine and/or carboplatin due to toxicity, while only 5.1% of patients had an iniparib dose reduction.

In the safety population, all except 1 patient in the G/C/I treatment arm reported at least 1 TEAE before crossover. The incidence of Grade 3 or 4 TEAEs was similar between the 2 arms (G/C: 82.4%, G/C/I: 81.2%).

The most frequent TEAEs (all grades) before crossover were generally similar in the 2 treatment arms and included fatigue, neutropenia, nausea, anemia, thrombocytopenia, constipation, vomiting, headache, dyspnea, ALT increased, diarrhea, leukopenia, peripheral edema, cough, AST increased, and pyrexia. Nearly all of the most frequently reported TEAEs occurred at a higher incidence in the G/C/I treatment arm. The most frequent Grade 3 or 4 TEAEs (≥10% incidence) in both arms were neutropenia, thrombocytopenia, anemia, and leukopenia, but only TEAEs of neutropenia (52.9% and 61.2% in the G/C and G/C/I treatment arms, respectively) occurred at a >5% difference between the treatment arms. When normalized for exposure, the incidence and severity of TEAEs as analyzed per cycle, the trend remained toward greater incidence of TEAEs and Grade 3 or 4 TEAEs in the G/C/I treatment arm compared with the G/C treatment arm, but the difference was smaller.

Before crossover, nausea (2.9%) and breast cancer metastatic, thrombocytopenia, pyrexia, and vomiting (2.5% each) were the most frequently reported serious TEAEs in the G/C treatment arm, and breast cancer metastatic (6.3%), pleural effusion (3.1%), anemia and metastases to central nervous system (2.7% each), and thrombocytopenia (2.4%) were the most frequently reported serious TEAEs in the G/C/I treatment arm.

The most frequent TEAEs leading to treatment discontinuation before crossover were thrombocytopenia (12.3% in the G/C treatment arm and 15.3% in the G/C/I treatment arm) and neutropenia (7.0% and 12.2%).

During the on-treatment period (up to 30 days after last dose), 8 patients in the G/C treatment arm who did not crossover died and an additional 31 patients died after crossover. Most of the deaths were due to disease progression. One crossover patient died of treatment-emergent respiratory failure 14 days after the last dose of study treatment, which the Investigator attributed to G/C background chemotherapy. In the G/C/I treatment arm, 16 patients died during the on-treatment period and most deaths were due to disease progression. One patient in the G/C/I treatment arm died 12 days after the last dose of study treatment due gastrointestinal hemorrhage which the investigator attributed to G/C background chemotherapy.

During the follow-up period, 21 patients in the G/C treatment arm who did not crossover died and an additional 63 patients died after crossover. All except for one death in a patient who did not crossover were due to disease progression. In the G/C/I treatment arm, 108 patients died during the follow-up period. One patient died of non-treatment emergent pneumonitis 123 days after the last dose of study treatment, which the investigator attributed to iniparib.

As with TEAEs reported, the most frequent Grade 3-4 clinical laboratory abnormalities were hematologic (leukopenia, neutropenia, thrombocytopenia, and lymphopenia) and these events were reported more frequently in the G/C/I treatment arm. The incidence of creatinine abnormalities was low in both arms.

Post-crossover, a total of 400 cycles of iniparib were administered to patients who crossed over from G/C to G/C/I, with a median 2 cycles received. Among 152 patients who crossed over, 148 (97.4%) had at least one TEAE and 69 (45.4%) had at least 1 serious TEAE. The most frequently reported TEAEs were generally similar to precrossover population: thrombocytopenia, anemia, neutropenia, fatigue, nausea, vomiting, and leukopenia). The most frequently reported Grade 3-4 TEAEs were hematologic (lymphopenia, neutropenia, thrombocytopenia, and leukopenia) as were those leading to treatment discontinuation (thrombocytopenia and neutropenia). The most frequently reported serious TEAEs were metastatic breast cancer, pleural effusion, and pneumonia.

In the supplemental analyses of safety data from first dose through the end of study, no new safety signals were observed.

Pharmacokinetic results: However, as only 4 patients participated in PK sampling, drug concentration data are presented by patient in the bioanalytical report.

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