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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01130259 Study code: EFC11614
Title of the study: An open-label, expanded access protocol of iniparib in combination with gemcitabine/carboplatin in patients with ER-, PR-, and HER2-negative metastatic breast cancer	
Study center(s): 150 centers in the United States	
Study period: Date first patient enrolled: 21/Jun/2010 Date last patient completed: 08/Apr/2013	
Phase of development: Phase 3b	
Study background: Study EFC11614 was initiated after the announcement of the positive results of the Phase 2 study TCD11485 (20070102) (gemcitabine + carboplatin versus gemcitabine + carboplatin + iniparib [GCI] in metastatic triple negative breast cancer [TNBC]) and while the Phase 3 study EFC11486 (20090301) was still ongoing. In February 2011, Sanofi announced that the Phase 3 study did not meet its primary endpoint for the intent-to-treat [ITT] population, although there was some clinical benefit for patients receiving GCI as second- or third-line treatment. Consequently, Sanofi closed to enrollment study EFC11614 and recommended that patients be discontinued from treatment; however, Investigators were given discretion to permit patients to continue treatment if a patient was already receiving clinical benefit. In April 2013, the study was closed when the last of the remaining patients still receiving benefit was transferred to the treatment extension study LTS12674.	
Objectives: Primary: To offer pre-approval drug access to iniparib in combination with gemcitabine and carboplatin in adult patients with histologically documented breast cancer that is estrogen receptor (ER)-negative, progesterone receptor (PR) negative, and human epidermal growth factor-2 (HER2)-nonoverexpressing. Secondary: To further evaluate the safety and tolerability of iniparib in combination with gemcitabine and carboplatin. No efficacy information was to be collected per protocol.	
Methodology: This was an open-label, expanded-access, multicenter, nonrandomized, single-arm clinical study designed to offer pre-approval drug access in the United States to iniparib in combination with gemcitabine and carboplatin for patients with metastatic TNBC. Patients were to be administered a fixed study treatment regimen in 21-day cycles as follows: • Gemcitabine 1000 mg/m^2 as a 30 ± 10-minute intravenous (IV) infusion once weekly on Days 1 and 8 of each 21-day cycle (immediately prior to iniparib administration); • Carboplatin area under the plasma concentration-time curve (AUC)=2 mg/mL/min as a 30 ± 10-minute or 60 ± 10-minute IV infusion (per institutional standard) once weekly on Days 1 and 8 of each 21-day cycle (immediately prior to iniparib administration); • Iniparib 5.6 mg/kg as a 60 ± 10-minute IV infusion twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle.	

Number of patients:	Planned: up to 1500 Treated: 994 Safety: 994
Diagnosis and criteria for inclusion: Eligible patients were females ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 and adequate organ and marrow function who had metastatic (stage IV), histologically documented breast cancer that was ER-negative, PR-negative, and HER2-negative; and who had received 0 to 3 prior chemotherapy regimens in the metastatic setting (this criterion was changed to 1 to 3 previous lines per study protocol amendment 3 after the communication of the results of the Phase 3 study EFC11486, which suggested that the observed progression-free survival [PFS] and overall survival [OS] benefit was restricted to patients with 2 to 3 previous lines of chemotherapy).	
Study treatments Investigational medicinal product: iniparib (SAR240550; BSI-201) Formulation: 10 mg/mL iniparib in 25% hydroxypropylbetacyclodextrin/10 mM phosphate buffer at a pH of 7.4 Route(s) of administration: IV infusion (over 60 minutes) Dose regimen: 5.6 mg/kg on Days 1, 4, 8, and 11 of each 21-day cycle	
Noninvestigational medicinal product: gemcitabine Formulation: commercially available marketed formulation Route(s) of administration: IV infusion (over 30 minutes) Dose regimen: 1000 mg/m^2 once weekly on Days 1 and 8 of each 21-day cycle.	
Noninvestigational medicinal product: carboplatin Formulation: commercially available marketed formulation Route of administration: IV infusion (over 30 or 60 minutes per institutional standard) Dose regimen: AUC = 2 mg/mL/min on Days 1 and 8 of each 21-day cycle. Dose was calculated according to local institutional standard	
Duration of treatment: Treatment was to continue in 21-day cycles in the absence of disease progression, unacceptable toxicity, or withdrawal of consent. Patients were discontinued at the time of disease progression as determined by the Investigator based on clinical signs and symptoms and/or radiologic evaluations. Duration of observation: The final follow-up assessments were performed within 30 days (± 5 days) of the date of administration of the last dose of study treatment (iniparib, gemcitabine, or carboplatin). Medically significant adverse events (AEs) considered by the Investigator to be related to study treatment were to have been followed until they had resolved or were considered stable.	

Criteria for evaluation: Safety was based on the incidence of AEs and on changes in physical examinations, neurologic examinations, clinical laboratory tests (hematology and serum chemistry panel), vital signs, electrocardiograms (ECG), ECOG PS, and use of concomitant medications. The only concomitant medications that were not allowed during the study were those contraindicated for gemcitabine or carboplatin. Use of additional antitumor chemotherapy within 30 days following the last dose of study treatment was collected. Efficacy, pharmacodynamics (PD), pharmacogenomics (PGx), and pharmacokinetics (PK) were not evaluated in this study.

Eastern Cooperative Oncology Group PS assessment was performed at screening, Day 1 of Cycle 1 and Cycle 2, and on Day 1 of every subsequent even cycle, and at 30 (±5) days after last dose. Blood samples were obtained for clinical laboratory tests at screening, on Day 1 and Day 8 of each 21-day cycle, and at 30 (±5) days after last dose. Vital signs were measured at screening; pre- and postdose on Days 1, 4, 8, and 11 of the first cycle; and 30 (±5) days after the last dose. A 12-lead electrocardiogram (ECG) was obtained at screening and at the end of study (30 [±5] days after the last dose).

Deaths that occurred >30 days after administration of the last dose of study treatment that were considered by the Investigator to be definitely, possibly, or probably related to study treatment (ie, gemcitabine, carboplatin, or iniparib) were to be reported as serious adverse events (SAEs).

Statistical methods:

Sample size calculation:

No formal statistical methods were performed for the determination of sample size.

Analysis population:

The safety population included all patients who received at least 1 dose (or a partial dose) of any of the study treatments. All analyses of patient demographic and baseline characteristics, safety, and extent of study exposure were performed on the safety population.

Analyses of patient characteristics and safety:

Descriptive statistics and listings were used to summarize patient demographic and baseline characteristics, disposition, extent of exposure, and safety variables. Tabulated summaries were presented by a single arm (all patients).

Concomitant medications (other than other anticancer therapies) were summarized for the safety population. Medications were summarized according to the World Health Organization-drug dictionary (WHO-DD) version 2009 March 01. All anatomical therapeutic chemical (ATC) codes corresponding to a medication were summarized.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0 and were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The number (%) of patients who had AEs were summarized by MedDRA terms, by all grades and Grade $\geq$3 (using worst grade) for the safety population. Separate summary tables were produced for AEs, SAEs, and drug-related SAEs. Deaths, SAEs, and AEs leading to treatment discontinuation are presented in listings. Cause of death was summarized by study period (the on-treatment period, which included the time from the first administration of any study treatment through 30 ± 5 days following the last administration of study treatment, and the on-study period, which included the time from the start of treatment until the end of the study [ie, the last protocol-planned visit]). Hematology and serum chemistry results were graded according to NCI-CTCAE, Version 3.0, when applicable. The number (%) of patients with laboratory abnormalities (ie, all grades and Grade $\geq$3) using the worst grade were provided for the safety population.

Vital signs were summarized as the incidence of potentially clinically significant abnormalities (PCSAs).

Summary:

Patient disposition:

A total of 994 patients were enrolled and treated in this study (safety population).

A total of 21 patients receiving gemcitabine and carboplatin in Phase 3 study EFC11486 and 4 patients receiving gemcitabine and carboplatin in Phase 2 study TCD11485 were rolled over into this study to add iniparib to their treatment regimen.

Reasons for treatment discontinuation are summarized in Table 1. The most common reason for treatment discontinuation was disease progression (743/994, 74.7%); 7.6% of patients (76/994) were discontinued from treatment due to AEs.

A pregnancy was reported for 1 patient during the study but could not be confirmed, as the patient was lost to follow-up.

Table 1 - Summary of reasons for treatment discontinuation – Safety population

	ALL (N=994)
Patients End of Treatment	994 (100.0 %)
Reason for patient ending treatment	
Withdrawal of consent	50 (5.0 %)
Administrative decision by the investigator or sponsor0	50 (5.0 %)
Pregnancy (report on Pregnancy Notification Worksheet/CRF)0	1 (0.1 %)
Ineligibility determined after enrollment	1 (0.1 %)
Patient Noncompliance	6 (0.6 %)
Adverse Event (disease progression is not considered an AE)	76 (7.6 %)
Progression of disease (clinical and/or radiological)	743 (74.7 %)
Other	67 (6.7 %)

AE = adverse event; CRF = case report form
Includes primarily patients receiving iniparib as first-line treatment whose treatment was discontinued following the communication of the results of Phase 3 study EFC11486
A pregnancy was reported during the study but could not be confirmed, as the patient was lost to follow up.

Demographics and baseline characteristics:

The median age of the safety population was 54.0 years (range, 23 to 88 years) with 83.0% <65 years old. Per the protocol entry criteria, nearly all patients had an ECOG PS of 0 (52.4%, 521/994) or 1 (44.9%, 446/994) at baseline, and 76.0% (755/994) of patients were white.

Overview of adverse events:

Overall, of the 994 patients, 99.0% had at least 1 AE and 85.1% had at least 1 Grade ≥3 AE. Adverse events considered by the Investigator to be related to the study drugs were reported in 95.2% of patients, and 76.0% of patients had a Grade ≥3 AE considered to be related to study drugs. Serious adverse events were reported in 36.0% of patients, with 31.8% of patients having a Grade ≥3 SAE. Adverse events leading to permanent treatment discontinuation were reported in 19.4% of patients, with 13.1% of patients having a Grade ≥3 AE leading to treatment discontinuation.

Adverse events with a fatal outcome, including events due to disease progression, were reported in 9.2% of patients; 1.2% of patients died due to AEs that were reported during the on-treatment period (ie, the time from the first administration of any study treatment through 30 ± 5 days following the last administration of study treatment).

Analysis of adverse events:

The AEs occurring in ≥20% of patients (all grades by preferred term [PT]) were neutropenia (56.5%), fatigue (52.5%), thrombocytopenia (50.8%), anemia (44.5%), nausea (44.2%), constipation (28.4%), dyspnea (23.6%), vomiting (21.3%), and headache (20.7%).

The Grade ≥3 AEs occurring in ≥10% of patients (by PT) were neutropenia (48.4%), thrombocytopenia (30.2%), and anemia (19.1%).

Drug-related AEs occurring in ≥20% of patients (all grades by PT) were neutropenia (56.1%), thrombocytopenia (49.8%), fatigue (45.8%), anemia (43.2%), and nausea (37.3%).

Drug-related Grade ≥3 AEs occurring in ≥10% of patients (by PT) were neutropenia (48.2%), thrombocytopenia (29.2%), and anemia (18.4%).

Deaths

Table 2 summarizes the deaths by cause by study period. Disease progression was the most common cause of death across the entire study period, including the on-treatment period.

Table 2 - Summary of deaths – Safety population

	ALL (N=994)
Deaths during on-study period[a]	
Due to disease progression	92 (9.3%)
Due to AE	16 (1.6%)
Due to other reasons	2 (0.2%)
Deaths during on-treatment period[b]	
Due to disease progression	69 (6.9%)
Due to AE	12 (1.2%)
Due to other reasons	2 (0.2%)

AE = adverse event

a Defined as the time from the start of treatment until the end of the study (ie, the last protocol-planned visit)

b Defined as the time from the first administration of any study treatment through 30 ± 5 days following the last administration of study treatment

Adverse events leading to death:

Adverse events leading to death as recorded on the AE eCRF were reported in 9.2% of patients (91/994). The most common TEAEs leading to death (by PT) were disease progression (3.6%), breast cancer metastatic (1.6%), respiratory failure (0.6%), and hepatic failure and pneumonia (0.4% each).

Serious adverse events:

At least 1 SAE all grades was reported in 36.0% of patients; 31.8% of patients had at least 1 Grade ≥3 SAE. The most frequently reported SAEs (by PT) were disease progression (all grades: 3.8%; Grade ≥3: 3.7%), dyspnea (all grades: 3.5%; Grade ≥3: 3.1%), thrombocytopenia (all grades: 3.2%; Grade ≥3: 3.1%), anemia (all grades: 2.9%; Grade ≥3: 2.6%), pneumonia (all grades: 2.6%; Grade ≥3: 2.2%), and pleural effusion (all grades: 2.6%; Grade ≥3: 2.0%).

Adverse events leading to discontinuation of study treatment:

Adverse events leading to treatment discontinuation were reported in 19.4% of patients, and 13.1% of patients had a Grade ≥3 AE leading to treatment discontinuation. The most common AEs (by PT) leading to treatment discontinuation were thrombocytopenia (as classified under the Blood and Lymphatic System Disorders system organ class [SOC]) (all grades: 6.4%; Grade ≥3: 3.7%), neutropenia (all grades: 2.7%; Grade ≥3: 2.4%), and platelet count decreased (as classified under the Investigations SOC) (all grades: 1.5%; Grade ≥3: 0.7%).

Analysis of laboratory results

Hematologic laboratory parameters:

Consistent with the AEs presented above, Grade 3-4 hematologic laboratory abnormalities during the on-study period included neutropenia (54.8%), leukopenia (46.9%), lymphopenia (33.6%), thrombocytopenia (24.8%), and anemia (19.2%).

Nonhematologic laboratory parameters:

Grade 3-4 nonhematologic laboratory abnormalities during the on-study period included the liver and renal function abnormalities of elevated ALT (6.3%), AST (4.6%), total bilirubin (3.2%), alkaline phosphatase (2.6%), and creatinine (2.0%); the metabolic abnormalities of hypoalbuminemia (4.3%), hyperglycemia (3.9%), and hypoglycemia (1.4%); and the electrolyte abnormalities of hyponatremia (6.5%), hypokalemia (3.6%), hypocalcemia (2.7%), hypercalcemia (1.8%), hyperkalemia (1.6%), and hypernatremia (0.2%).

Analysis of vital signs

The following vital signs PCSAs for blood pressure were observed during the treatment period: systolic blood pressure (SBP) ≤95 mmHg and decrease from baseline ≥20 mmHg (6.9%), SBP ≥160 mmHg and increase from baseline ≥20 mmHg (9.7%), diastolic blood pressure (DBP) ≤45 mmHg and decrease from baseline ≥10 mmHg (1.2%), and DBP ≥110 mmHg and increase from baseline ≥10 mmHg (0.6%).

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