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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01173497 Study code: TCD11608
Title of the study: A Phase II study of the PARP inhibitor, iniparib (BSI-201), in combination with chemotherapy to treat triple negative breast cancer brain metastasis	
Study center(s): 14 study centers in the USA	
Study period: Date first patient enrolled: 21/Jul/2010 Date last patient completed: 29/Jul/2013	
Phase of development: Phase 2	
Study background: This study was initiated under BiPar Sciences standard operating procedures that allowed the University of North Carolina, Lineberger Comprehensive Cancer Center (Chapel Hill, North Carolina USA) to be entirely responsible for the conduct of this study. University of North Carolina published their results of the study (referenced above) prior to Sanofi's receipt of the database. The findings presented herein represent a separate analysis performed by Sanofi. This accounts for any potential discrepancies between the publication's results and the findings described herein. Following Sanofi's decision to discontinue this compound, it was decided that this study would be reported as a synoptic report containing only the safety data. The efficacy data is available in the publication by Anders et al.	
Objectives: Primary Objective: To evaluate the efficacy of iniparib in combination with irinotecan in the treatment of brain metastasis (BM) arising from triple negative breast cancer (TNBC) as measured by intracranial or extracranial, whichever occurred first, time to progression (TTP) as defined using the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria or the RECIST 1.1 criteria, respectively. Secondary objectives: • To further evaluate the safety and tolerability of iniparib in combination with chemotherapy. • To evaluate the efficacy of iniparib in combination with chemotherapy on intracranial tumor as measured by intracranial objective response rate (ORR) determined by modified RECIST criteria, volumetric analysis, and central nervous system (CNS) Composite Response Criteria. • To evaluate time to intracranial progression after administration of iniparib in combination with chemotherapy as defined via volumetric analysis and CNS Composite Response Criteria. • To evaluate the extracranial response rate as determined by RECIST 1.1 criteria after administration of iniparib in combination with chemotherapy. • To evaluate progression-free survival (PFS) and overall survival (OS) after administration of iniparib in combination with chemotherapy. • To evaluate the impact of iniparib on quality of life as measured by the FACT-B (Functional Assessment of Cancer Therapy-breast) and FACT-Br (brain) questionnaires.	

Exploratory/correlative objectives:

- To correlate intracranial vascular morphologic changes measured via magnetic resonance angiography (MRA) with clinical response to iniparib plus irinotecan.
- To correlate the intrinsic breast cancer subtype (eg, basal-like) with therapeutic response to iniparib and irinotecan.
- To correlate tumor biomarkers discovered in other trials with iniparib in patients with metastatic TNBC with the clinical outcome of the patients participating in the present study.
- To examine the influence of germ line polymorphisms (eg, BRCA mutation and functional status) on response to iniparib and chemotherapy.

Methodology: This was a multicenter, single-arm, open-label, nonrandomized Phase 2 study in patients with TNBC and BM.

Patients were enrolled into 1 of 2 cohorts based on prior history of intracranial radiation (ICR) therapy (yes or no).

Eligible patients received intravenous (IV) iniparib plus irinotecan administered in 21-day cycles as follows:

- Iniparib as a 1-hour IV infusion (± 10 min) on Days 1, 4, 8, and 11 at a dose of 5.6 mg/kg or 8.0 mg/kg, as described below under Study Treatments;
- Irinotecan as a 90-minute IV infusion on Days 1 and 8 at a dose of 125 mg/m^2 immediately prior to iniparib administration.

Patients responding to iniparib and irinotecan continued on Study Treatment until either intracranial or extracranial progression, unacceptable toxicity, study withdrawal, or death.

Safety, tolerability, and development of potential toxicity were assessed on an ongoing basis.

Efficacy (intracranial and extracranial tumor lesions) and quality of life (patient reported outcomes) assessments were performed every 3 cycles. Intracranial tumor lesions were evaluated via gadolinium-enhanced brain magnetic resonance imaging and intracranial response (complete response [CR], partial response, progressive disease [PD], and stable disease [SD]) was determined using modified RECIST criteria. Extracranial tumor lesions were evaluated by computed tomography. Extracranial response was determined using the RECIST 1.1 criteria.

Number of patients:	Planned: 40 with 32 evaluable
	Treated: 37
Evaluated:	
	Efficacy/pharmacogenomics: Efficacy = Not performed
	Safety: 37

Diagnosis and criteria for inclusion: Patients eligible for inclusion were females ≥21 years old with histologically confirmed, estrogen-receptor (ER) negative, progesterone receptor (PR) negative (ER or PR negative: <10% immunohistochemical staining of tumor), and human epidermal growth factor receptor 2 (Her2) negative (0 to 1 + or fluorescence in situ hybridization nonamplified; by clinical assay on either primary or metastatic tumor) adenocarcinoma of the breast, with brain lesion on radiographic imaging, with or without prior ICR, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2, and with no limit to prior therapies with last prior anticancer treatment ≥2 weeks from initiation of protocol-based therapy.

Study treatments

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

Formulation: 10 mg/mL iniparib in 25% hydroxypropylcyclodextrin/ 10 mM phosphate buffer at a pH of 7.4

Route(s) of administration: IV (over 60 minutes)

Dose regimen: 5.6 mg/kg (for patients enrolled prior to protocol amendment 7) or 8.0 mg/kg (for patients enrolled following implementation of protocol amendment 7; patients on 5.6 mg/kg dose could have had their dose increased to 8.0 mg/kg) on Days 1, 4, 8, and 11 of each 21-day cycle.

Noninvestigational medicinal product(s): irinotecan (Camptosar®)

Formulation: 0.12 to 2.8 mg/mL final concentration in dextrose 5% (commercially available marketed formulations of 40 mg/2 mL or 100 mg/5 mL).

Route(s) of administration: IV over 90 minutes.

Dose regimen: 125 mg/m^2 on Days 1 and 8 of every 21-day cycle.

Duration of treatment: Treatment continued for all patients in 21-day cycles until study withdrawal, disease progression, unacceptable toxicity, or death, whichever occurred first.

Duration of observation: After treatment discontinuation, follow-up visits were to have been performed at local physician's office every 60 days (± 15 days) starting 60 days (± 15 days) after the last dose of iniparib and continuing for up to 3 years or until death, whichever was first. The final analyses were to have been performed when all patients had been followed for 12 months after treatment discontinuation or had a TTP event.

Criteria for evaluation:

Efficacy: The primary efficacy endpoint was intracranial or extracranial TTP, whichever occurred first. Tumors were assessed every 3 cycles and at the end of treatment for determination of response. Time to progression was defined as the time from treatment initiation to documented disease progression.

The secondary efficacy endpoints were intracranial best ORR, time to intracranial progression determined by volumetric analysis and CNS composite response criteria, extracranial response rate progression-free survival (PFS), overall survival (OS), and impact on quality of life using the Fact-B (Breast) and Fact-Br (Brain) subscales.

The exploratory endpoints included correlation of intrinsic breast cancer subtype and other important predictive biomarker with therapeutic response, correlation of intracranial vascular morphologic changes with clinical response and examination of the influence of germ line polymorphisms on response to iniparib and chemotherapy.

Although efficacy parameters were collected during the course of the study, they were not included in this analysis and are not reported in this abbreviated clinical study report (CSR).

Safety: Safety was based on the incidence of adverse events (AEs) as reported by the patient or noted by the Investigator, changes in vital signs, neurological examinations, physical examinations, ECOG PS, and clinical laboratory tests (including complete blood count [CBC] with differential and platelets, chemistry panel).

Pharmacodynamics sampling times and bioanalytical methods: Fixed paraffin-embedded blocks were obtained from the original diagnostic specimen in all patients at baseline. Research core biopsies were obtained at study entry and approximately 14 to 21 days of treatment with iniparib and irinotecan for those patients who had accessible tumor tissue. Blood samples for pharmacogenomics and BRCA mutation testing were obtained pretreatment.

Statistical methods:

Sample size calculation: The sample size for this single arm study was 40 patients to allow for a 20% dropout rate (yielding 32 evaluable patients). Under the assumption that the intracranial/extracranial TTP was approximately exponentially distributed and that patients came onto the study uniformly during the accrual period, a sample size of 32 evaluable patients achieved 80% power to detect the difference between the null hypothesis that the mean TTP was equal to 2.0 months (based on historical control) and the alternative hypothesis that the mean TTP was equal to 3.15 months (57.5% improvement) at a 0.05 significance level using a two-sided likelihood ratio χ^2 test for a study with 12.0 months follow-up.

Analysis populations: The safety population included all enrolled patients who received at least 1 (or any portion of 1 dose) of the either of the Study Treatments. This population was used for all safety analyses.

Analysis of patient characteristics and safety: Descriptive statistics and data listings were used to summarize patient characteristics and extent of exposure variables.

Analysis of safety: Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All hematologic and serum chemistry test results were graded by NCI-CTCAE version 4.0.

The number (%) of patients with treatment-emergent AEs (TEAEs) was summarized by MedDRA system organ class and preferred terms (PT), by all grades and Grade $\geq$3 for the safety population. Separate summary tables were produced for TEAEs, serious AEs (SAEs), and drug-related TEAEs and 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 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]). The number (%) of patients with laboratory abnormalities (ie, all grades and Grade $\geq$3) using the worst grade were provided for the safety population.

Summary:

Patient disposition: A total of 37 patients were enrolled and treated in this study (safety population).

The most common reason for treatment discontinuation was disease progression, (28 [75.7%] patients). One patient died during the on-treatment period and 1 patient withdrew from treatment but continued on to follow-up. Seven (18.9%) patients were classified under "other" as reason for treatment discontinuation.

Demographics and baseline characteristics: The median age of the safety population was 47.0 years (range: 34 to 80 years). Most patients (33 [89.2%]) were white and 4 (10.8%) African-Americans. Median body surface area was 1.86 m^2 (range: 1.5 to 3.0 m^2). Per the protocol entry criteria, 36 patients had an ECOG PS of 0 to 2 (0: 13 [36.1%] patients, 1: 14 [38.9%] patients, or 2: 9 [25.0%] patients) at baseline.

At diagnosis, breast cancer stage was I or II for the majority of patients (28 of 36 [77.8%] patients), stage III for 6 of 36 (16.7%) patients and stage IV for 2 of 36 (5.6%) patients.

Efficacy results: Efficacy analyses for this study were not performed for this report.

Safety results:

Extent of exposure: The median number of cycles administered per patient was 3.0 (range: 1 to 38 cycles). Twenty-four (64.9%) patients received at least 3 cycles and 12 (32.4%) patients received at least 6 cycles. The median number of weeks on-treatment (ie, the time from the first administration of any Study Treatment through 30 days following the last administration of Study Treatment) for the safety population was 9.1 weeks (range: 3 to 120 weeks).

Overview of adverse events: All 37 (100%) patients had at least 1 TEAE and 23 (62.2%) patients had at least 1 Grade ≥3 TEAE. Treatment-emergent AEs considered by the Investigator to be related to the study drugs were reported in 36 (97.3%) patients, and 11 (29.7%) patients reported related events of Grade ≥3. Treatment-emergent SAEs were reported in 16 (43.2%) patients, and SAEs Grade ≥3 were reported in 13 (35.1%) patients.

Adverse events leading to permanent treatment discontinuation were reported in 10 (27.0%) patients, with 5 (13.5%) patients having an AE leading to treatment discontinuation of Grade ≥3.

Four (10.8%) patients died during the on-treatment period.

Analysis of adverse events: The TEAEs occurring in ≥20% of patients (all grades by preferred term [PT]) were diarrhea (21 [56.8%] patients), fatigue (19 [51.4%] patients), nausea (19 [51.4%] patients), headache (18 [48.6%] patients), neutrophil count decreased (13 [35.1%] patients), vomiting (12 [32.4%] patients), constipation (10 [27.0%] patients), abdominal pain (9 [24.3%] patients), anemia (8 [21.6%] patients), and dyspnea (8 [21.6%] patients). The only Grade ≥3 TEAE occurring in ≥10% of patients (by PT) was neutrophil count decreased (5 [13.5%] patients).

Treatment-related TEAEs reported in ≥20% of patients (all grades by PT) were diarrhea (20 [54.1%] patients), nausea (17 [45.9%) patients], fatigue (13 [35.1%] patients), neutrophil count decreased (13 [35.1%] patients), and constipation (8 [21.6%] patients). The only treatment-related TEAE of Grade ≥3 reported in ≥10% of patients (by PT) was neutrophil count decreased (5 [13.5%] patients).

Deaths: Twenty-nine (78.4%) patients died during the on-study period including 4 (10.8%) deaths during the on-treatment period. Disease progression was the most common cause of death (all but 1 patient). The cause of death for 1 patient was listed as other (death not otherwise specified [NOS]/respiratory failure).

Adverse events leading to death: There were 4 patients with AE that led to death: the reported PT was death NOS for 2 patients, death NOS/respiratory failure for 1 patient and hypoxia for another patient.

Serious adverse events: At least 1 SAE (all grades) was reported in 16 (43.2%) patients; 13 (35.1%) patients had at least 1 Grade ≥3 SAE. The most frequently (≥2 patients) reported SAEs (by PT) were death NOS (all grades: 3 [8.1%] patients; Grade ≥3: 3 [8.1%] patients), abdominal pain (all grades: 2 [5.4%] patients; Grade ≥3: 1 [2.7%] patients), depressed level of consciousness (all grades: 2 [5.4%] patients; Grade ≥3: 1 [2.7%] patients), dyspnea (all grades: 2 [5.4%] patients; Grade ≥3: 0), headache (all grades: 2 [5.4%] patients; Grade ≥3: 2 [5.4%] patients), and thromboembolic event (all grades: 2 [5.4%] patients; Grade ≥3: 1 [2.7%] patients).

At least 1 treatment-related SAEs (all grades) was reported in 2 [5.4%] patients (abdominal pain, edema limbs, and thromboembolic event was reported by 1 patient each) and 1 [2.7%] patients had at least 1 treatment-related SAE of Grade ≥3 (thromboembolic event). Outcomes of related treatment-emergent SAEs are available with the patients' narratives.

Adverse events leading to discontinuation of Study Treatment: Adverse events leading to treatment discontinuation were reported in 10 (27.0%) patients, and AEs leading to treatment discontinuation of Grade ≥3 were reported in 5 (13.5%) patients (1 patient with flank pain, 1 patient with cognitive disturbance and confusion, 1 patient with depressed level of consciousness, 1 patient with hematoma and 1 patient with intracranial hemorrhage). No event (by PT) occurred more than once except for 2 events of intracranial hemorrhage which occurred in the same patient.

Analysis of laboratory results:

Hematologic laboratory parameters: Hematologic laboratory abnormalities during the on-treatment period included: anemia (all grades: 33 of 36 [91.7%] patients; Grade ≥3: 2 of 36 [5.6%] patients), leukopenia (all grades: 29 of 36 [80.6%] patients; Grade ≥3: 5 of 36 [13.9%] patients), neutropenia (all grades: 15 of 36 [41.7%] patients; Grade ≥3: 4 of 36 [11.1%] patients), and thrombocytopenia (all grades: 7 of 36 [19.4%] patients; Grade ≥3: 0).

Nonhematologic laboratory parameters (liver and renal function): Liver and renal function laboratory abnormalities during the on-treatment period included: alkaline phosphatase (all grades: 13 of 36 [36.1%] patients; Grade ≥3: 0), elevated alanine aminotransferase (all grades: 19 of 36 [52.8%] patients; Grade ≥3: 0), elevated aspartate aminotransferase (all grades: 18 of 36 [50.0%] patients; Grade ≥3: 1 of 36 [2.8%] patients), hyperbilirubinemia (all grades: 2 of 36 [5.6%] patients; Grade ≥3: 0), and creatinine (all grades: 1 of 36 [2.8%] patients; Grade ≥3: 0).

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