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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00687765 Study code: TCD11616
Title of the study: A Phase 1/2 Study of Iniparib (SAR240550/ BSI-201) in Patients with Newly Diagnosed Malignant Glioma	
Study center(s): 9 study centers	
Study period: Date first patient enrolled: 28/Jul/2008 Date last patient completed: 12/Nov/2011	
Phase of development: Phase 1/2	
Objectives: Primary Objective for Phase 1: • Study Group 1: To determine the maximum tolerated dose (MTD) of iniparib administered as an intravenous (IV) infusion in patients with newly diagnosed malignant glioma when given with standard dose temozolomide (TMZ) after the completion of standard radiation therapy (RT) and concomitant TMZ. • Study Group 2: To determine the MTD of iniparib administered as an IV infusion in patients with newly diagnosed malignant glioma when given with metronomic TMZ after the completion of standard RT and concomitant TMZ. Secondary Objectives for Phase 1: • To assess the toxicity associated with the 2 treatment regimens. • To assess and describe the pharmacokinetics (PK) of iniparib in these 2 treatment regimens and potentially correlate with biologic markers of activity.	
Methodology: This was a multicenter, open-label, nonrandomized Phase 1/2 study in patients with newly diagnosed malignant glioma. In Phase 1, the MTD of iniparib in combination with either standard dose or metronomic TMZ was determined in a dose-escalating fashion using a modified continual reassessment method (CRM). All patients were assessed on an ongoing basis for safety and followed for survival. Safety assessments followed the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v. 3.0) guidelines until 01 January 2011.The protocol was then amended to include the NCI CTCAE v. 4.0 guidelines. In Phase 1, patients were assigned to 1 of 2 study groups. Each group had a maximum of 5 patients per cohort to ensure that 3 patients were evaluable for safety. Iniparib was administered to patients as a 1-hour IV infusion at a starting dose of 5.1 mg/kg in both groups. Patients were evaluable for dose-limiting toxicities (DLTs) if they had received at least 1 dose of iniparib.	
Number of patients:	Planned: Cohorts of 5 per Study Group (Phase 1) Treated: 43 (23 in Group 1; 20 in Group 2) Evaluated: 43 (23 in Group 1; 20 in Group 2)
Evaluated:	Safety: 43 (23 in Group 1; 20 in Group 2)

Diagnosis and criteria for inclusion: All patients had to be ≥18 years old; have a Karnofsky performance status ≥60%; and have adequate hematologic, renal, and liver function.

In addition to the criteria for all patients enrolled in the study noted above, patients enrolled in Phase 1 must have had the following: histologically proven supratentorial malignant glioma; received at least 80% of planned TMZ and RT with no Grade 3 or Grade 4 toxicity attributed to TMZ; received planned treatment with RT and concomitant TMZ at least 28 days but no more than 49 days prior to starting treatment in this study; and gadolinium MRI or contrast computerized tomography (CT) scan within 28 days of starting treatment. No prior repeat craniotomy for tumor therapy after receiving RT and TMZ was permitted. Patients must not have had chemotherapeutics or investigational agents in addition to RT and TMZ; however, prior treatment with carmustine (Gliadel) wafers was permitted.

Study treatments

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

Formulation: 10 mg/mL iniparib in a betahydroxypropylcyclodextrin/phosphate buffer, pH 7.4

Route(s) of administration: Intravenous

Dose regimen for Phase I:

Study Group 1: Iniparib 5.1 mg/kg (starting dose) over 1 hour twice weekly (on 2 consecutive days at least 24 hours apart) of a 4-week cycle. Iniparib was administered in combination with TMZ (Days 1 through 5) of each cycle. A maximum of 6 cycles was allowed.

Study Group 2: Iniparib 5.1 mg/kg (starting dose) over 1 hour twice weekly (2 consecutive days at least 24 hours apart) for Weeks 1 through 6 of a 10-week cycle. Iniparib was administered in combination with TMZ (daily). A maximum of 6 cycles was allowed.

Noninvestigational medicinal product(s): temozolomide (Temodar®, Merck)

Formulation: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules

Route(s) of administration: Oral

Dose regimen for Phase I:

Study Group 1: TMZ 150 mg/m^2 on Days 1 through 5 of Cycle 1 and 200 mg/m^2 on Days 1 through 5 of Cycle 2 of a 4-week cycle.

Study Group 2: TMZ 75 mg/m^2 daily for Weeks 1 through 6 of a 10-week cycle.

Duration of treatment: Patients were treated until disease progression, unacceptable toxicity, patient's refusal to continue treatment under the study (withdrawal of informed consent), or Investigator's decision to withdraw the patient either due to extraordinary medical circumstance or failure to comply with protocol.

Duration of observation in Phase I: Patients were observed during a Run-in Period of up to 28 days prior to initiation of treatment; a Study Treatment Period of at least 2 cycles (8 weeks) for Study Group 1, and at least 1 cycle (10 weeks) for Study Group 2; and a posttreatment follow-up period defined as the End-of-Treatment (EOT) visit until the date of death.

Criteria for evaluation:

Efficacy: Not applicable for Phase 1

Safety: Safety was assessed by examining data for adverse events (AEs) and serious adverse events (SAEs) including type, frequency, relationship to study treatment, and severity for each event; clinical examinations including vital signs; laboratory tests (including complete blood count [CBC] with differential, platelet count, and chemistry panel); and concomitant medications. The NCI CTCAE v. 4.0 was used in this study to grade the severity of AEs.

Dose-limiting toxicities were defined by NCI CTCAE v.4.0 as any of the following events determined by the Investigator to be possibly, probably, or definitely related to study treatment (iniparib and/or TMZ), regardless of outcome:

- Grades 3 or 4 severity (except nausea and vomiting without sufficient antiemetic prophylaxis; Grade 3 radionecrosis [central nervous system necrosis]; and Grade 3 neurologic toxicity responding within 2 weeks to steroids, anticonvulsants, or electrolyte correction.);
- Absolute neutrophil count (ANC) ≤500 cells/$mm^{3;}$
- Platelets ≤25 000 cells/$mm^{3;}$
- White blood cells (WBC) <1 000 cells/$mm^{3;}$
- Any toxicity that prevented administration of >80% of the planned TMZ and iniparib doses for the first cycle;
- Any DLT (as defined above) causing delay in treatment of >7 days in the Initiation cycle or over 21 days in Maintenance cycles without recovery to a ≤Grade 1 or baseline status would result in taking the patient off treatment.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Phase 1 (Group 1 and Group 2):

To assess the pharmacokinetic (PK) profile of iniparib and to evaluate potential poly (ADP-ribose) polymerase (PARP) inhibition on peripheral lymphocytes in pharmacodynamics (PD) studies, 2 blood samples were collected from all patients before and after infusions of Cycle 1, Cycle 2, and Cycle 3, and 30 days (±7 days) after the last dose of study treatment. Analyses of the PK samples for iniparib and metabolite concentrations were performed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

Biomarker Testing:

Tumor (paraffin-embedded) tissue samples were collected for biomarker testing prior to enrollment. All samples were to be analyzed for certain biomarkers including O6-methylguanine-DNA methyltransferase (MGMT) repair enzyme and PARP receptor status. Samples for biomarker testing were collected but not analyzed or reported.

Statistical methods:

Sample size calculation for Phase 1 (Group 1 and Group 2): No formal statistical methods were performed for the determination of sample size. Each group required 5 patients per dose cohort to ensure at least 3 evaluable patients for DLT assessment.

Analysis populations for Phase 1: The Safety Population included all patients who received at least 1 dose (or a partial dose) of iniparib or TMZ. The Evaluable for DLT Population included all patients who received at least 1 dose of iniparib and completed the DLT observation period. Patients were evaluable for the cohort if they had completed ≥80% their expected dose of combined treatment for Cycle 1.

General Statistical Approach: Statistical analyses were only performed for Phase 1 (Group 1 and Group 2). Descriptive statistics and listings were used to summarize and present patient demographics, baseline characteristics, treatment administration, and safety outcomes. Tables were presented by group and overall. Phase 2 analysis will be performed at a later date.

Analysis of pharmacokinetics: Plasma concentrations of iniparib are provided in a Bioanalytical report that is found in Appendix 16.2.5.2.

Summary:

Patient disposition: A total of 43 patients were enrolled and treated in this study (safety population); 23 patients were enrolled into Group 1 and 20 patients were enrolled into Group 2. Eighteen patients completed treatment and 25 patients discontinued treatment. The most common reason for treatment discontinuation was disease progression (15 [34.9%] patients overall; 7 [30.4%] patients in Group 1; 8 [40.0%] patients in Group 2). Three (7.0%) patients (all in Group 1 [13.0%]) discontinued treatment due to toxicity. Six (14.0%) patients refused further treatment (3 [13.0%] patients in Group 1; 3 [15.0%] patients in Group 2), and 1 [2.3%] patient (in Group 2 [5.0%]) was noted as having withdrawn consent.

Demographics and baseline characteristics: The median age of the safety population was 54.0 years (range: 19.0 to 73.0); patients in Group 1 (median age: 55.0 years; range: 40.0 to 73.0 years) tended to be older than those in Group 2 (median age: 49.5 years; range: 19.0 to 72.0 years). Most patients were male (32 [74.4%] patients overall; 18 [78.3%] patients in Group 1; 14 [70.0%] patients in Group 2), and all but 1 Black/African American patient (in Group 1 [4.3%]) were White. Median weight and height in the safety population were 85.26 kg and 177.00 cm, respectively, and were similar between groups. All but 1 patient (in Group 2 [5.0%]) had a Karnofsky performance status score of 80 to 100 at baseline.

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

Safety results:

Extent of Exposure:

The overall median number of cycles of treatment administered per patient was 3.0 (range: 1.0 to 6.0), with more cycles administered in Group 1 (median: 5.0; range: 1.0 to 6.0) than Group 2 (median: 2.0; range: 1.0 to 3.0). More than half the patients in the safety population received at least 3 cycles of treatment (24 [55.8%] patients overall; 16 [69.6%] patients in Group 1; 8 [40.0%] patients in Group 2); 10 (23.3%) patients (all in Group 1 [43.5%]) received at least 6 cycles. The median number of weeks on-treatment (i.e, the time from first administration of any study treatment through last administration of study treatment) for the safety population was 20.14 weeks (20.14 weeks for Group 1; 20.50 weeks for Group 2).

Adverse events:

Overview of adverse events:

All 43 (100%) patients experienced at least 1 treatment-emergent adverse event (TEAE), and 19 (44.2%) patient experienced at least 1 Grade ≥3 TEAEs (8 [34.8%] patients in Group 1; 11 [55.0%] patients in Group 2). Forty (93.0%) patients experienced at least 1 TEAE considered by the Investigator to be related to study treatment (22 [95.7%] patients in Group 1; 18 [90.0%] patients in Group 2); 11 (25.6%) patients experienced at least 1 Grade ≥3 treatment-related TEAEs (5 [21.7%] patients in Group 1; 6 [30.0%] patients in Group 2).

One (2.3%) patient (in Group 2 [5.0%]) died due to an SAE during the on-treatment period.

Treatment-emergent SAEs (all grades) were reported in 12 (27.9%) patients overall (7 [30.4%] patients in Group 1; 5 [25.0%] patients in Group 2); 9 (20.9%) patients experienced Grade ≥3 SAEs (5 [21.7%] patients in Group 1; 4 [20.0%] patients in Group 2).

One (2.3%) patient (in Group 1 [4.3%]) experienced a TEAE that led to permanent treatment discontinuation; this was assessed as a Grade 3 event.

Analysis of adverse events:

The most commonly reported TEAEs (in ≥20% of patients overall, all grades, by preferred term [PT]) were fatigue (29 [67.4%] patients overall, 15 [65.2%] patients in Group 1; 14 [70.0%] patients in Group 2), headache (20 [46.5%] patients overall; 10 [43.5%] patients in Group 1; 10 [50.0%] patients in Group 2), nausea (19 [44.2%] patients overall; 10 [43.5%] patients in Group 1; 9 [45.0%] patients in Group 2), constipation (18 [41.9%] patients overall; 9 [39.1%] patients in Group 1; 9 [45.0%] patients in Group 2), memory impairment (16 [37.2%] patients overall; 8 [34.8%] patients in Group 1; 8 [40.0%] patients in Group 2), rash maculopapular (12 [27.9%] patients overall; 6 [26.1%] patients in Group 1; 6 [30.0%] patients in Group 2); insomnia (10 [23.3%] patients overall; 5 [21.7%] patients in Group 1; 5 [25.0%] patients in Group 2), dizziness (10 [23.3%] patients overall; 8 [34.8%] patients in Group 1; 2 [10.0%] patients in Group 2), oedema peripheral (10 [23.3%] patients overall; 4 [17.4%] patients in Group 1; 6 [30.0%] patients in Group 2), confusional state (9 [20.9%] patients overall; 2 [8.7%] patients in Group 1; 7 [35.0%] patients in Group 2), vomiting (9 [20.9%] patients overall; 6 [26.1%] patients in Group 1; 3 [15.0%] patients in Group 2), muscular weakness (9 [20.9%] patients overall; 4 [17.4%] patients in Group 1; 5 [25.0%] patients in Group 2), and pain in extremity (9 [20.9%] patients overall; 4 [17.4%] patients in Group 1; 5 [25.0%] patients in Group 2). The only Grade ≥3 TEAE reported in at least 10% of patients overall was lymphocyte count decreased (6 [14.0%] patients overall; 1 [4.3%] patient in Group 1; 5 [25.0%] patients in Group 2).

Treatment-related adverse events:

The most commonly reported treatment-related TEAEs (in ≥20% of patients overall, all grades, by PT) were fatigue (26 [60.5%] patients overall; 13 [56.5%] patients in Group 1; 13 [65.0%] patients in Group 2), nausea (18 [41.9%] patients overall; 9 [39.1%] patients in Group 1; 9 [45.0%] patients in Group 2), and constipation (16 [37.2%] patients overall; 9 [39.1%] patients in Group 1; 7 [35.0%] patients in Group 2). The only Grade ≥3 treatment-related TEAE reported in at least 10% of patients overall was lymphocyte count decreased (6 [14.0%] patients overall; 1 [4.3%] patient in Group 1; 5 [25.0%] patients in Group 2).

Deaths:

Thirty-eight (88.4%) patients died during the on-study period (18 [78.3%] patients in Group 1; 20 [100.0%] patients in Group 2), including 2 (4.7%) patients (both in Group 2 [10.0%]) who died during the on-treatment period. A majority of deaths were due to disease progression (27 [62.8%] patients overall; 15 [65.2%] patients in Group 1; 12 [60.0%] patients in Group 2). Ten (23.3%) patients died due to unknown reasons (3 [13.0%] patients in Group 1; 7 [35.0%] patients in Group 2). One (2.3%) patient (in Group 2 [5.0%]) was listed as dying due to other reasons (SAE of small intestinal perforation, described below).

Adverse events leading to death:

One (2.3%) patient (in Group 2 [5.0%]) died due to small intestinal perforation on-treatment; this TEAE was not considered by the Investigator to be treatment-related.

Serious adverse events:

Twelve (27.9%) patients experienced ≥1 SAE (all grades) (7 [30.4%] patients in Group 1; 5 [25.0%] patients in Group 2); 9 (20.9%) patients experienced Grade ≥3 SAEs (5 [21.7%] patients in Group 1; 4 [20.0%] patients in Group 2). The most commonly reported SAEs (in ≥2 patients overall; all grades) were embolism (4 [9.3%] patients overall; 2 [8.7%] patients in Group 1; 2 [10.0%] patients in Group 2), central nervous system necrosis (2 [4.7%] patients overall; 1 [4.3%] patient in Group 1; 1 [5.0%] patient in Group 2), and headache (2 [4.7%] patients overall; both in Group 2 [10.0%]). All SAEs of embolism were assessed as Grade ≥3.

Adverse events leading to discontinuation of study treatment:

One (2.3%) patient (in Group 1 [4.3%]) experienced a TEAE of hypersensitivity that led to permanent discontinuation of study treatment; this was a Grade 3 treatment-related event.

Analysis of laboratory results:

Hematologic laboratory parameters:

Hematologic laboratory abnormalities (all grades) noted at baseline included: leukopenia (3 [7.0%] patients overall; 1 [4.3%] patient in Group 1; 2 [10.0%] patients in Group 2); thrombocytopenia (5 [11.6%] patients overall; 4 [17.4%] patients in Group 1; 1 [5.0%] patient in Group 2); anemia (9 [20.9%] patients overall; 6 [26.1%] patients in Group 1; 3 [15.0%] patients in Group 2); none of these abnormalities were assessed as Grade 3-4.

Hematologic laboratory abnormalities (all grades) during the on-treatment period included: anemia (29 [67.4%] patients overall; 17 [73.9%] patients in Group 1; 12 [60.0%] patients in Group 2), leukopenia (24 [55.8%] patients overall; 13 [56.5%] patients in Group 1; 11 [55.0%] patients in Group 2), thrombocytopenia (22 [51.2%] patients overall; 15 [65.2%] patients in Group 1; 7 [35.0%] patients in Group 2), and neutropenia (3 [7.0%] patients overall; 1 [4.3%] patient in Group 1; 2 [10.0%] patients in Group 2). Of these abnormalities, 1 (2.3%) patient each had Grade 3-4 neutropenia (Group 1 [4.3%]), anemia (Group 2 [5.0%]), and thrombocytopenia (Group 1 [4.3%]).

Non-hematologic laboratory parameters (liver and renal function):

Liver and renal function abnormalities noted at baseline included: alanine aminotransferase (ALT) (13 [30.2%] patients overall; 6 [26.1%] patients in Group 1; 7 [35.0%] patients in Group 2), aspartate aminotransferase (AST) and total bilirubin (2 [4.7%] patients overall; 1 [4.3%] patient in Group 1; 1 [5.0%] patient in Group 2), and alkaline phosphatase (1 [2.3%] patient overall; in Group 1 [4.3%]). Only 1 [2.3%] patient (in Group 2 [5.0%]) had a Grade 3-4 abnormality (ALT) at baseline.

Liver and renal function abnormalities during the on-treatment period included: ALT (18 [41.9%] patients overall; 8 [34.8%] patients in Group 1; 10 [50.0%] patients in Group 2), AST (12 [27.9%] patients overall; 7 [30.4%] patients in Group 1; 5 [25.0%] patients in Group 2), alkaline phosphatase and total bilirubin (5 [11.6%] patients overall; 3 [13.0%] patients in Group 1; 2 [10.0%] patients in Group 2), and creatinine (4 [9.3%] patients overall; 1 [4.3%] patient in Group 1; 3 [15.0%] patient in Group 2). Grade 3-4 abnormalities were noted for ALT (2 [4.7%] patients overall; both in Group 1 [8.7%]) and total bilirubin (1 [2.3%] patient overall; in Group 2 [5.0%]).

Non-hematologic laboratory parameters (metabolic function):

Metabolic function abnormalities noted at baseline included: hyperglycemia 16 [37.2%] patients overall; 9 [39.1%] patients in Group 1; 7 [35.0%] patients in Group 2), and hypoalbuminemia (3 [7.0%] patients overall; all in Group 1 [13.0%]). None of these abnormalities were assessed as Grade 3-4.

Metabolic function abnormalities during the on-treatment period included: hyperglycemia (30 [69.8%] patients overall; 15 [65.2%] patients in Group 1; 15 [75.0%] patients in Group 2), hypoglycemia (5 [11.6%] patients overall; 4 [17.4%] patients in Group 1; 1 [5.0%] patient in Group 2), and hypoalbuminemia (8 [18.6%] patients overall; 5 [21.7%] patients in Group 1; 3 [15.0%] patients in Group 2). None of these abnormalities were assessed as Grade 3-4.

Non-hematologic laboratory parameters (electrolytes):

Electrolyte abnormalities noted at baseline included: hyponatremia (3 [7.0%] patients overall; 1 [4.3%] patient in Group 1; 2 [10.0%] patients in Group 2), and hypokalemia (1 [2.3%] patient overall; in Group 2 [5.0%]). One (2.3%) patient (in Group 2 [5.0%]) had hyponatremia at baseline that was assessed as Grade 3-4.

Electrolyte abnormalities during the on-treatment period included: hypokalemia (8 [18.6%] patients overall; 5 [21.7%] patients in Group 1; 3 [15.0%] patients in Group 2), hyponatremia (6 [14.0%] patients overall; 2 [8.7%] patients in Group 1; 4 [20.0%] patients in Group 2), hypocalcemia (6 [14.0%] patients overall; 4 [17.4%] patients in Group 1; 2 [10.0%] patients in Group 2), hyperkalemia (3 [7.0%] patients overall; 2 [8.7%] patients in Group 1; 1 [5.0%] patients in Group 2), hypernatremia (2 [4.7%] patients overall; both in Group 1 [8.7%]), and hypercalcemia (1 [2.3%] patient overall; in Group 2 [5.0%]). One (2.3%) patient had Grade 3-4 hyponatremia (in Group 2 [5.0%]), and 1 (2.3%) patient had Grade 3-4 hyperkalemia (in Group 1 [4.3%]).

Analysis of vital signs: Potentially clinically significant increases in systolic blood pressure (≥160 mmHg and increase from baseline ≥20 mmHg) were observed in 3 (7.0%) patients overall (2 [8.7%] in Group 1; 1 [5.0%] in Group 2). One (2.3%) patient each was noted as having a potentially clinically significant decrease in systolic blood pressure (≤95 mmHg and decrease from baseline ≥ 20 mmHg; 1 [5.0%] patient in Group 2), decrease in diastolic blood pressure (≤45 mmHg and decrease from baseline ≥10 mmHg; 1 [4.3%] patient in Group 1), and decrease in heart rate (≤50 bpm and decrease from baseline ≥20 bpm; 1 [5.0%] patient in Group 2). Pharmacokinetics/Pharmacodynamics: Pharmacokinetic and pharmacodynamic parameters are provided in a bioanalytical report.
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