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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01213381, UTN U1111-1117-3152 Study code: TED11451
Title of the study: A Phase I study evaluating the safety and pharmacokinetics of SAR240550 (iniparib, BSI-201) administered twice weekly in patients with advanced solid tumors	
Study center(s): 2 centers in Japan	
Study period: Date first patient enrolled: 27/Aug/2010 Date last patient completed: 06/Feb/2013	
Phase of development: Phase 1	

Objectives:

The primary objective of the study was to determine a dose of iniparib to be further studied in combination with chemotherapy regimens.

The secondary objectives were:

- To determine a Dose Limiting Toxicity (DLT) of iniparib and iniparib in combination with chemotherapy (gemcitabine and carboplatin).
- To assess safety profiles: significant laboratory changes and adverse events (AEs).
- To make a preliminary assessment of antitumor effect of study subjects (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) with measurable disease.
- To characterize iniparib and metabolites, 4-iodo-3-amino-benzamide (IABM) and 4-iodo-3-amino-benzoic acid (IABA) pharmacokinetics.
- To collect glutathione S-transferase (GST) genotypes at baseline.

Methodology: This was a multicenter, open-label, non-randomized, Phase 1 study evaluating iniparib given twice weekly for 2 consecutive weeks in each 21-day cycle as single agent or combined with chemotherapy regimen (gemcitabine and carboplatin).The study was designed to assess the safety of the dose of iniparib previously used in Phase 2 and 3 outside Japan and to generate the corresponding pharmacokinetic (PK) profiles of iniparib in approximately 21 adult Japanese patients with histologically documented advanced solid tumors. For this reason, the only dose of iniparib to be tested is 5.6 mg/kg administered on Days 1, 4, 8, and 11 without any dose-escalation.

The planned dose levels were as followed:

- Iniparib single agent: 5.6 mg/kg (Dose level 1) on Days 1, 4, 8, and 11.
- Combination therapy: 5.6 mg/kg of iniparib on Days 1, 4, 8, and 11 combined with 1000 mg/m^2 of gemcitabine and AUC2 of carboplatin both on Days 1 and 8 (Dose level 2, iniparib plus gem/carb2).

- Combination therapy: 5.6 mg/kg of iniparib on Days 1, 4, 8, and 11 combined with 1000 mg/m^2 of gemcitabine on Days 1 and 8 and AUC5 of carboplatin only on Day 1 using Calvert formula with calculated creatinine clearance by Cockroft-Gault formula (Dose level 3, iniparib plus gem/carb5).
- Combination therapy: 5.6 mg/kg of iniparib on Days 1, 4, 8 and 11 combined with 1000 mg/m^2 of gemcitabine only on Days 1 and 8, and AUC5 of carboplatin only on Day 1 using Calvert formula with a modified formula to calculate the estimated Glomerular Filtration Rate (eGFR) validated specifically for Japanese patients (Dose level 3A, iniparib plus gem/carb5A). This dose level was incorporated in protocol amendment 3.

Initially, 3 patients were to be enrolled starting with Dose level 1 and assessed predefined dose-limiting toxicities (DLTs) during Cycle 1.

After evaluation of safety data of 3 patients in Cycle 1, if none of the first 3 patients experienced a DLT, then the next dose level could start enrolling patients. If 1 patient showed DLT, an additional 3 patients were to be enrolled at the same level. In this case, if no more than 1 out of 6 patients showed DLTs, patient enrollment to the next dose level could start. When more than 1 patient experienced a DLT, the dose level was considered above the maximum tolerated dose (MTD) and a Steering Committee meeting was to be held to discuss next steps (for instance, amending the protocol to enroll additional patients in the lower dose level). Because the objective of the trial was the confirmation of the safety in Japanese patients of doses and combinations of iniparib already in use in efficacy trials in Western countries, there was no true dose-escalation. For each dose level it was a requirement to have none or 1 DLT out of 3 or 6 patients to confirm the safety.

Although the dose testing process was guided by the safety evaluation during Cycle 1, the overall safety profile during the treatment with iniparib at dose level was to be considered and reviewed by Steering Committee to confirm the absence of safety concerns before moving into the next cohort.

This dose-escalation scheme was provided as guidance and any suggestion of toxicity (especially compound specific toxicity) was to be discussed within the Steering Committee including the medical expert, the Investigators and the Sponsor, and the Efficacy and Safety Evaluation Committee if needed.

Dose escalation of iniparib

Dose Levels	Iniparib (mg/kg)	Gemcitabine/Carboplatin	Patients
-1	2.8	-	
1	5.6	-	3-6
2 (iniparib plus gem/carb2)	5.6	1000 mg/m^2 / AUC2 D1, 8	6
3 (iniparib plus gem/carb5)	5.6	1000 mg/m^2 / AUC5 D1[1]	6
3A (iniparib plus gem/carb5A)	5.6	1000 mg/m^2 / AUC5A D1[2]	6

1 Calvert formula using calculated creatinine clearance by Cockroft-Gault formula

2 Calvert formula using the estimated glomerular filtration rate with a formula validated for Japanese patients

DLT was defined as follows:

- Grade 3 or 4 neutropenia with fever >38.5°C.
- Grade 4 neutropenia (absolute neutrophil count [ANC] <0.5 x 10^9/L) for more than 7 days.
- Grade 4 thrombocytopenia (platelet count <25.0 x 10^9/L).
- Grade 3 thrombocytopenia with bleeding requiring transfusion.
- Any Grade 3 or greater nonhematological adverse event except for nausea. For fatigue, diarrhea, vomiting, and transaminases elevations, the following criteria were applied;
  - Grade 3 fatigue, persistent for more than 7 days.
  - Grade 4 diarrhea, and/or vomiting.
  - Aspartate aminotransferase (AST) or alanine aminotransfease (ALT) >2 grade change from baseline.

Number of patients:	Planned: 24
	Enrolled: 18
	Treated: 18
Evaluated:	
	Efficacy: 18
	Safety: 18
	Pharmacokinetics: 18

Diagnosis and criteria for inclusion:

Patients meeting all of the following inclusion criteria were to be considered for enrollment in the study:

- Presence of histologically or cytologically documented advanced solid tumor that had become refractory to standard therapy or for which no standard therapy.
- Patients with signed IRB-approved informed consent form (ICF) before any study-specific procedure.

Study treatments

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

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

Route(s) of administration: intravenous (IV) infusion in 60 minutes.

Dose regimen: Patients were to receive 5.6 mg/kg of iniparib as single agent or combined with chemotherapy (gemcitabine and carboplatin) given twice weekly (Days 1, 4, 8, and 11) every 21 days in all dose levels.

Investigational medicinal product(s): Gemcitabine

Formulation: Solution

Route(s) of administration: IV infusion

Dose regimen: Gemcitabine was to be administered at 1000 mg/m^2 as an approximately 30 min IV infusion once weekly (Days 1 and 8) every 21 days.

Investigational medicinal product(s): Carboplatin

Formulation: Solution

Route(s) of administration: IV infusion

Dose regimen: Carboplatin was to be administered at AUC2 as a more than 30 min IV infusion once weekly (Days 1 and 8) at the Level 2, or AUC5 as an approximately 60 min IV infusion every 21 days (Day 1) at the Level 3 and 3A. For AUC2 and AUC5 carboplatin dose was calculated using Calvert formula with creatinine clearance obtained with the Cockroft-Gault formula. For AUC5A glomerular filtration rate was estimated using a creatinine clearance formula validated specifically for Japanese patients.

Duration of treatment: The study treatment was administered every 3-week until a definitive treatment discontinuation criterion was met.

Duration of observation: The duration of the study for each patient included up to a 28-day screening phase, study treatment in the study phase, and a follow-up period of 30±5 days after the last administration. For an AE to meet DLT criteria must be observed during Cycle 1.

Criteria for evaluation:

Efficacy: The RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria were followed for assessment of tumor response. Objective response information was to be obtained if patients have disease which can readily be measured and re-assessed.

Tumor evaluation: imaging for measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI), or bone scintigraphy was to be recorded within 28 days prior to the enrollment.

Safety: Safety parameters included collection of treatment-emergent adverse events (TEAEs), serious TEAEs, laboratory tests (including hematology, chemistry, and urinalysis), and other tests as clinically indicated, 12-lead electrocardiogram (ECG), physical examinations, concomitant medications and treatment, and number of patients with treatment withdrawal and reason. Clinical and laboratory adverse events (AEs) were assessed and reported using terminology of the National Cancer Institute - Common Terminology Criteria (NCI CTCAE) version 4.0.

Pharmacokinetics: Plasma concentrations of iniparib, IABA and IABM on Cycle 1 Day 1 were used to determine the following PK parameters using noncompartmental methods:

Iniparib: maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve calculated from time zero to the real time t_{last} corresponding to the last concentration above the lower limit of quantification (AUC_{last}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), clearance (CL), apparent volume of distribution at steady state (V_{ss}) and terminal half-life ($t_{1/2z}$).

IABA and IABM: C_{max}, AUC_{last} , AUC and $t_{1/2z}$.

Other assessments

Genotyping:

For those subjects who signed the specific pharmacogenetic analysis informed consent form, a single blood sample (on Day 1 of Cycle 1) was to be collected to investigate genetic variants of GST which was involved in the metabolism of iniparib.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples were collected at the following time points:

Cycle 1 Day 1:

- Predose and 30 minutes, 55 minutes (prior to the end of the infusion,EOI), 10, 15, and 30 minutes after EOI, and 1, 2, 3, and 7 hours after EOI.

Cycle 1 Day 4 and Day 8:

- 30 and 55 (prior to EOI) minutes after the start of infusion.

Cycle 1 Day 15:

- Predose

Cycle 2 Day 15

- Predose

Plasma concentration of iniparib, IABA and IABM were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL for iniparib and 0.4 ng/mL for IABA and IABM.

Statistical methods:

The primary objective of the study was to confirm the safety of the dose of 5.6 mg/kg of iniparib as single agent and in combination with 2 schedules of gemcitabine and carboplatin in Japanese patients. This objective is accomplished by the analysis of DLTs during Cycle 1 as described previously using a "3+3" dose escalation method.

Demographic and baseline characteristics

Demographic and baseline characteristics' variables including age, race, sex, ECOG performance status, medical and surgical history, and cancer diagnosis were to be summarized by dose level on safety population using descriptive statistics. Individual data listings related to demographics and baseline characteristics were to be provided by patient.

Prior or concomitant medications

Prior anti-cancer therapies and concomitant medications were to be summarized by dose level on the safety population.

Extent of study treatment exposure and compliance

The extent of IP exposure was to be assessed and summarized by dose level on the safety population.

Analyses of safety data

Safety analyses were performed on the all treated population unless otherwise specified. Percentages were calculated using the number of treated patients as the denominator. All tables were presented by dose level.

Analysis of dose-limiting toxicities

Dose-limiting toxicities were reported for Cycle 1 and displayed in a listing by each dose level in evaluable for DLT population.

Analysis of adverse events

Adverse event data were to be assessed by summarizing the number (%) of patients with TEAE by system organ class (SOC) and preferred term (PT) or by the 4 level terms of Medical Dictionary of Regulatory Activities (MedDRA), presenting maximum Grade, seriousness, relationship to investigational product. Summary tables of TEAEs, of related TEAEs, of serious TEAEs, of TEAEs leading to delay/reduction were to be presented. All AEs were to be listed by patient.

Analysis of laboratory variables

Clinical laboratory tests were collected over the course of the study and include hematology, chemistry, and urinalysis. Primary laboratory safety parameters (hematology and biochemistry) were programmatically categorized into one of four severity grades of the CTCAE version 4.0. The parameters of all vital signs variables were listed for each visit by dose level.

Summary:

Population characteristics:

Overall, 18 patients were included in the study. Four patients were treated with iniparib single agent regimen at 5.6 mg/kg. In the combination cohort, 6 patients were treated with iniparib 5.6 mg/kg plus gemcitabine and carboplatin AUC2 (iniparib plus gem/carb2), 5 patients were treated with iniparib 5.6 mg/kg plus gemcitabine and carboplatin AUC5 (iniparib plus gem/carb5) and 3 patients were received to iniparib 5.6 mg/kg plus gemcitabine and carboplatin AUC5 (iniparib plus gem/carb5A) with a calculation of carboplatin dose based in a creatinine clearance estimation adapted to Japanese population.

One patient in the iniparib single agent level was excluded from DLT evaluable population due disease progression during Cycle 1, therefore leaving 17 patients evaluable for the primary objective.

The median age of patients was 52.0 years (range, 22 to 67 years). Most of patients (88.9%) were female, and all patients (100%) were of Asian/Oriental (Japanese). Eleven patients (61.1%) had an ECOG performance status of 0 and 7 (38.9%) had a performance status of 1.

Primary tumors were located in breasts (10 patients, 55.6%), ovaries (5 patients, 27.8%) and lungs (3 patients, 16.7%). Histologically, the tumors were adenocarcinomas (12 patients, 66.7%). The median (range) number of previous regimens for the metastatic disease was 2.5 (0 to 7).

Efficacy results: All 18 patients were evaluable for response per RECIST 1.1. Best overall response was PR in 4 patients treated with iniparib in combination with gemcitabine and carboplatin. Eight patients had SD as best response sustained for ≥4 cycles (range 4-24).

Safety results:

No DLTs were observed with the iniparib single agent and with iniparib plus gem/carb2, while 2 out of 5 patients treated with iniparib plus gem/carb5 and 2 out of 3 patients with iniparib plus gem/carb5A using the Japanese estimate of glomerular filtration rate level, experienced AEs meeting the DLT definition (4 events of thrombocytopenia and 1 event of upper respiratory infection) that were considered to be related to investigational product. For this reason the MAD of iniparib 5.6 mg/kg in combination with gemcitabine and carboplatin AUC5 was considered above a maximum tolerated dose for Japanese patients.

The median number of cycles was 3.0 cycles (range: 1 to 5 cycles) for the iniparib single dose level, 9.0 cycles (range: 2 to 16 cycles) for the iniparib plus gem/carb2, 4.0 cycles (range: 1 to 24 cycles) for the iniparib plus gem/carb5 and 4.0 cycles (range: 1 to 4 cycles) for the iniparib plus gem/carb5A with adjusted estimation of GFR, respectively.

Median relative dose intensity (RDI) for iniparib was greater than 90% for iniparib given as single agent or iniparib plus gem/carb2. When iniparib was given with gem/carb5 or iniparib plus gem/carb5A, median RDI of iniparib was 68% approximately. Median RDI for gemcitabine was 88% for iniparib plus gem/carb2, and 63% and 69% for iniparib plus gem/carb5 and iniparib plus gem/carb5A, respectively. Median RDI for carboplatin was 92% for iniparib plus gem/carb2, and 73% and 92% for iniparib plus gem/carb5 and iniparib plus gem/carb5A, respectively.

The number of patients with at least one cycle delayed was 1 patient (1/3, 33.3%) at iniparib single agent, 3 patients (3/6, 50.0%) with iniparib plus gem/carb2, 4 patients (4/4, 100.0%) with iniparib plus gem/carb5 and 2 patients (2/2, 100.0%) with iniparib plus gem/carb5A.

All 18 patients experienced at least 1 TEAE or 1 related TEAE on study except 2 patients at the iniparib single agent. One of 4 patients at the iniparib single agent, and 5 of 6 patients at iniparib plus gem/carb2 and all 8 patients treated with iniparib plus gem/carb5 and gem/carb5A experienced at least one Grade 3/4 TEAEs.

The most common TEAEs (reported in ≥ 9 patients) in all dose levels (all grades) were fatigue (13 patients), neutropenia (12 patients), thrombocytopenia (11 patients), anaemia (11 patients), constipation (11 patients), decreased appetite (10 patients), nausea (10 patients), vomiting (10 patients), leukopenia (9 patients). Majority of these TEAEs occurred across the gemcitabine/carboplatin combination groups, except for constipation. The Grade 3/4 TEAEs reported more than 1 patient were neutropenia (8 patients), thrombocytopenia (7 patients), anaemia (6 patients), leukopenia (5 patients).

No in-study death was observed.Two of 5 patients (40.0%) at the iniparib plus gem/carb5 and 1 of 3 patients (33.3%) at the iniparib plus gem/carb5A experienced serious TEAEs. One patient at the iniparib plus gem/carb5 discontinued study treatment due to a TEAE.

TEAEs leading to dose reduction or delay did not occur in the iniparib single agent, while dose reduction or delay occurred in the gemcitabin/carboplatin combination groups. Majority of adverse events leading to dose reduction or delay were neutropenia and thrombocytopenia.

In the iniparib single agent, no Grade 3/4 hematological abnormalities were observed. In the dose levels of gemcitabine/carboplatin combination, Grade 3-4 abnormalities included leukopenia, neutropenia, anaemia, thrombocytopenia, and lymphopenia.

In the iniparib single agent, no Grade 3/4 biochemical abnormalities were observed. In the dose levels of gemcitabine/carboplatin combination, Grade 3-4 abnormalities included ALT increased, hyperuricemia, and hypophosphatemia.

Overall, the changes in vital signs and ECG were small and not clinically meaningful.

Pharmacokinetic results:

Mean ± SD (Geometric Mean) [CV%] of pharmacokinetic parameters of iniparib in plasma on Cycle 1 Day 1

Parameter	Dose Level 1 (N = 4)	Dose Level 2 (N = 6)	Dose Level 3 (N = 5)	Dose Level 3A (N = 3)
C_{max} (ng/mL)	2460 ± 476 (2420) [19.4]	2350 ± 712 (2250) [30.3]	2270 ± 452 (2230) [19.9]	2800 ± 922 (2700) [32.9]
AUC_{last} (ng•h/mL)	2080 ± 391 (2050) [18.8]	1790 ± 568 (1710) [31.7]	1920 ± 338 (1890) [17.6]	2150 ± 326 (2130) [15.2]
AUC (ng•h/mL)	2080 ± 392 (2050) [18.8]	1800 ± 568 (1710) [31.6]	1920 ± 338 (1890) [17.6]	2150 ± 326 (2130) [15.2]
CL (mL/h/kg)	2810 ± 507 (2770) [18.1]	3360 ± 1200 (3200) [35.7]	3060 ± 657 (3000) [21.5]	2650 ± 393 (2630) [14.9]
V_{ss} (mL/kg)	472 ± 139 (458) [29.5]	664 ± 480 (543) [72.3]	520 ± 133 (508) [25.6]	638 ± 170 (621) [26.7]
$t_{1/2z}$ (h)	0.180 ± 0.0284 (0.178) [15.8]	0.188 ± 0.0236 (0.187) [12.6]	0.194 ± 0.0346 (0.191) [17.9]	0.146 ± 0.0153 (0.145) [10.5]

Mean ± SD (Geometric Mean) [CV%] of pharmacokinetic parameters of metabolite IABA in plasma on Cycle 1 Day 1

Parameter	Dose Level 1 (N = 4)	Dose Level 2 (N = 6)	Dose Level 3 (N = 5)	Dose Level 3A (N = 3)
C_{max} (ng/mL)	20.1 ± 11.0 (17.4) [54.7]	21.1 ± 10.0 (19.6) [47.5]	26.4 ± 23.6 (20.4) [89.3]	15.5 ± 6.23 (14.8) [40.1]
AUC_{last} (ng•h/mL)	52.6 ± 32.2 (45.6) [61.3]	63.4 ± 34.6 (57.7) [54.6]	71.3 ± 58.6 (56.4) [82.2]	44.3 ± 15.9 (42.1) [35.8]
AUC (ng•h/mL)	55.3 ± 33.9 (48.1) [61.2]	66.7 ± 37.1 (60.5) [55.6]	75.7 ± 64.4 (59.0) [85.1]	47.4 ± 16.6 (45.2) [35.0]
$t_{1/2z}$ (h)	1.77 ± 0.154 (1.77) [8.7]	1.66 ± 0.0543 (1.66) [3.3]	1.62 ± 0.169 (1.62) [10.4]	1.91 ± 0.0489 (1.91) [2.6]

Mean ± SD (Geometric Mean) [CV%] of pharmacokinetic parameters of metabolite IABM in plasma on Cycle 1 Day 1

Parameter	Dose Level 1 (N = 4)	Dose Level 2 (N = 6)	Dose Level 3 (N = 5)	Dose Level 3A (N = 3)
C_{max}	7.09 ± 3.40	6.45 ± 1.81	6.86 ± 2.32	5.52 ± 0.306
(ng/mL)	(6.56) [48.0]	(6.24) [28.0]	(6.55) [33.8]	(5.51) [5.5]
AUC_{last}	10.8 ± 6.38	11.6 ± 4.27	10.3 ± 3.70	8.64 ± 0.381
(ng•h/mL)	(9.73) [58.9]	(10.9) [37.0]	(9.87) [35.7]	(8.63) [4.4]
AUC	11.8 ± 6.54	12.3 ± 4.50	11.1 ± 3.72	9.31 ± 0.284
(ng•h/mL)	(10.7) [55.5]	(11.6) [36.6]	(10.6) [33.5]	(9.30) [3.0]
$t_{1/2z}$	0.830 ± 0.0650	0.800 ± 0.0994	0.706 ± 0.0847	0.859 ± 0.263
(h)	(0.829) [7.8]	(0.795) [12.4]	(0.702) [12.0]	(0.833) [30.6]

Dose Level 1 = iniparib at 5.6 mg/kg
Dose Level 2 = iniparib at 5.6 mg/kg plus Gemcitabine 1000 mg/m^2 / Carboplatin AUC2
Dose Level 3 = iniparib at 5.6 mg/kg plus Gemcitabine 1000 mg/m^2 / Carboplatin AUC5

Dose Level 3A = iniparib at 5.6 mg/kg plus Gemcitabine 1000 mg/m^2 / Carboplatin AUC5 based on adjusted eGFR

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