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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01033292 Study code: TCD11504
Title of the study: A Phase 2, Multi-Center, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination with BSI-201 in Patients with Platinum-Resistant Recurrent Ovarian Cancer	
Study center(s): This study was conducted at 3 locations in the United States (US)	
Study period: Date first patient enrolled: 11/Dec/2009 Date last patient completed: 16/Dec/2012	
Phase of development: Phase 2	
Objectives: The primary objective of this study was to evaluate the objective response rate (ORR) of gemcitabine/carboplatin in combination with iniparib (GCI). The secondary objectives of this study were to determine the nature and degree of toxicity of gemcitabine/carboplatin in combination with iniparib and to evaluate progression-free survival (PFS). The exploratory objective of this study was to evaluate the relationship between breast cancer gene (BRCA) status and response. Additional exploratory objectives were to include identification of biologic correlates using tumor blocks from prior surgery; evaluation of tumor and peritoneal tissue, staining for poly(ADP-ribose) polymerase (PARP), Ki-67, and annexin V; and evaluation of surrogate markers of response in peripheral blood mononuclear cells (PBMCs) and in circulating tumor cells (CTCs). These exploratory objectives were not evaluated. In addition, cancer antigen-125 (CA-125) response was added in the statistical analysis plan as an exploratory endpoint. <u>Biomarkers</u> Optional tumor samples were planned to be collected during the study at screening and at the time of disease progression for the purpose of staining for PARP, Ki-67, and annexin V as an exploratory analysis; this endpoint was not evaluated. Surrogate markers of response were to be evaluated in CTCs and PBMCs as an exploratory analysis; this endpoint was also not evaluated.	
Methodology: In this Phase 2, multicenter, single-arm, open-label, nonrandomized safety and efficacy study, up to 48 patients with platinum-resistant, recurrent ovarian cancer were to be enrolled at several sites in the US and were to receive a fixed-study treatment regimen as follows: • iniparib 5.6 mg/kg intravenously (IV) on Days 1, 4, 8, and 11 of each 21-day cycle • carboplatin area under the curve (AUC) = 4 mg/mL*min IV on Day 1 of each 21-day cycle • gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of each 21-day cycle Based on historical data (low end of 95% confidence intervals [CIs]), the assumed ORR for the gemcitabine plus carboplatin regimen in this patient population was 0.15. The objective of the study was to be able to detect an improvement in the ORR of 100% (from 0.15 to 0.3).	

This study used a Simon 2-stage minimax design.

The first scheduled tumor assessment for measurable disease was to be performed after 2 cycles of treatment and every 2 cycles (ie, approximately every 6 weeks) thereafter. Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0, was to be used to establish disease progression and to determine tumor response. For nonmeasurable disease, best medical practices were to be used to determine disease progression. CA-125 response also was to be evaluated as an exploratory efficacy endpoint at the same time points described for tumor response assessment.

Adverse events (AEs) were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECGs), and laboratory tests (including chemistry, hematology, coagulation parameters, and urinalysis) were performed prior to drug administration and at designated intervals throughout the study.

Number of patients:	Planned: 48
	Treated: 45
Evaluated:	
	Efficacy: 42
	Safety: 45

Diagnosis and criteria for inclusion: Eligible patients must have had a histological diagnosis of epithelial ovarian carcinoma, fallopian tube cancer, or primary peritoneal carcinoma; must have completed only 1 previous course of cytotoxic chemotherapy, which must have contained a platinum therapy, with resistance to that regimen defined as a relapse within 2 to 6 months after the last dose of platinum-based chemotherapy. Date of relapse was determined using 1 of the following criteria:

- Rise in CA-125 to >35, confirmed by radiographic evaluation prior to study entry; the date of the CA-125 test was the date of relapse.
- Clinical signs or symptoms, confirmed by radiographic evaluation prior to study entry; the date of clinical evidence was the date of relapse.
- Radiographic evaluation with no pre-existing signs or symptoms; the date of radiographic scan was the date of relapse.

Study treatments

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

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

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

Dose regimen: 5.6 mg/kg on Days 1, 4, 8, and 11 of each 21-day cycle

Noninvestigational medicinal product(s): carboplatin

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

Dose regimen: AUC = 4 mg/mL*min on Day 1 of each 21-day cycle

Noninvestigational medicinal product(s): gemcitabine

Route(s) of administration: IV (over 30 minutes)

Dose regimen: 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle

Duration of treatment: Treatment with GCI was to continue for at least 6 cycles in the absence of disease progression or unacceptable toxicity. Patients could continue for an additional 4 cycles, up to a maximum of 10 cycles, at physician discretion. Single-agent iniparib could be continued beyond the 10th cycle as maintenance therapy, at physician discretion, until progressive disease (PD).

Duration of observation: End-of-treatment assessments were performed within 30 (±5) days after the last dose of study treatment. Patients who discontinued treatment before PD were to undergo regular staging evaluation for ORR every 90 (±10) days until PD or death.

Criteria for evaluation:

Efficacy: Tumor response was evaluated according to RECIST, Version 1.0. Tumors were to be assessed at screening, approximately every 6 weeks thereafter in the absence of clinically evident progression of disease, and at the end-of-treatment visit if not done within 30 days prior to the last dose of study drug.

The primary efficacy endpoint was ORR, which was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) relative to the total number of patients in the efficacy population with measurable disease at study entry (ie, at least 1 target lesion at baseline).

Progression free survival (PFS), defined as the number of months from the date of first dose to the date of progression (ie, radiological progression or clinical progression) or the date of death (from any cause), whichever was earlier, was evaluated as a secondary efficacy endpoint.

CA-125 was to be evaluated at the same time points described for tumor response assessment. CA-125 response was added in the SAP as an exploratory efficacy endpoint and was defined as at least a 50% reduction in CA-125 levels compared with a pretreatment sample (sample must have been taken within 2 weeks prior to starting treatment, and the CA-125 value must have been at least 2 times the upper limit of normal [ULN] at this time point); the response must have been confirmed and maintained for at least 28 days.

Safety: Safety was based on the incidence of AEs and changes in vital signs, physical examinations, laboratory tests (including chemistry, hematology, coagulation parameters, and urinalysis), ECG, and ECOG performance status.

Statistical methods:
Sample size calculation: The objective of the study was to detect an improvement in the ORR of 100% (from 0.15 to 0.30).

The sample size was calculated using a Simon minimax 2-stage design. Twenty-three patients were to be treated in the first stage, and 4 or more responses were required to proceed to Stage 2. Then an additional 25 patients were to be treated in Stage 2 to complete the study (N = 48). If 12 or more responses were observed out of the required 48 patients, then the null hypothesis was to be rejected. This design was based on the use of a 1-sided test at the 5% level of significance and provided 80% power.

Analysis population: The efficacy population consisted of all patients who completed at least 1 cycle of treatment and who had a baseline and posttreatment tumor size assessment and no major protocol deviation.

The safety population included all patients who received at least 1 of the study drugs.

The CA-125 response-evaluable population included all patients who had a pretreatment sample that was at least twice the ULN and was collected within 2 weeks prior to starting treatment.

Analyses of patient characteristics, efficacy, and safety: Descriptive statistics and listings were used to summarize patient characteristics and extent of exposure variables.

Best overall response (CR, PR, stable disease [SD], PD, not evaluable [NE]) and ORR were summarized using descriptive statistics; 95% CI were also calculated for ORR. A waterfall plot of maximum percent reduction from baseline in tumor burden of target lesions was produced. Progression-free survival was analyzed using the Kaplan-Meier method and summarized with median and 95% CIs of the median. In addition, probabilities of PFS at 3, 6, and 12 months were provided. Events contributing to the PFS (ie, radiological disease progression, clinical progression, or death without progression) were described. A Kaplan-Meier curve of PFS was also provided.

Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0, and were graded using CTCAE Version 3.0 criteria. The number (%) of patients with treatment-emergent AEs (TEAEs) by primary system organ class (SOC) and preferred term (PT) were summarized by all grades and Grade 3 or 4 (using worst grade during the TEAE period) for the safety population. Separate summary tables were provided for TEAEs, drug-related TEAEs, and treatment-emergent serious adverse events (SAEs). By-patient listings were provided for deaths, SAEs and TEAEs leading to treatment discontinuation.

Hematology and biochemistry results were graded according to NCI-CTCAE, Version 3.0, when applicable. The number (%) of patients with laboratory abnormalities (ie, all grades and Grade 3 or 4) using the worst grade during the on-treatment period were provided for the safety population.

Summary:

Patient disposition: A total of 45 patients were enrolled in the study; all 45 were treated and comprised the safety population (Table 1). Three patients were excluded from the efficacy population, resulting in a total of 42 patients in the efficacy population (2 patients had a platinum-free interval shorter than 2 months, which was deemed a major efficacy-related protocol deviation for both patients; 1 patient had no postbaseline tumor assessment). Twenty-three patients comprised the CA-125 population. Enrollment was closed before completion on 31 July 2012 due to slow enrollment (2 patients had enrolled in the prior 7 months), despite extension of the accrual period by 1 year.

Eight (17.8%) of the 45 patients in the safety population entered into the maintenance phase and received single-agent iniparib after completion of 10 cycles with GCI.

Table 1 - Summary of analysis populations

	All (N=45)	
Enrolled patients	45	(100%)
Safety population	45	(100%)
Patients with maintenance phase	8	(17.8%)
Efficacy population	42	(93.3%)
CA-125 population	23	(51.1%)

Reasons for treatment discontinuation are summarized in Table 2.

Table 2 - Summary of reasons for treatment discontinuation - Safety population

	All (N=45)	
Patients off treatment	45	(100%)
Disease progression - radiological	25	(55.6%)
Disease progression - clinical	12	(26.7%)
Investigator judgment	2	(4.4%)
Subject withdrew consent	5	(11.1%)
Adverse event1	1	(2.2%)

Demographics and baseline characteristics: The median age of the safety population was 60 years (range, 37 to 85 years), and approximately half (51.1%) of the patients had an ECOG performance status score of 1 at baseline.

Four patients had BRCA mutation (present or absent) assessed by both the Myriad and AltheaDX assays, while the remaining 22 patients were assessed by the Myriad method only. Due to inconsistencies between the BRCA mutation analysis data sets from Myriad Genetics, Inc. and AltheaDX Laboratories for patients whose samples were analyzed using both assays, only the Myriad Genetics, Inc. data set was used for the statistical analysis, as this is the only approved (by CLIA) method of analysis.

BRCA 1 or 2 mutations as assessed by the Myriad assay were recorded as present in 12 (26.7%) patients, absent in 14 (31.1%) patients, and unknown in 19 (42.2%) patients.

Epithelial ovarian carcinoma (unilateral or bilateral) was reported as the primary site at initial diagnosis in 36 (80.0%) of the patients in the safety population. The predominant histological subtype was serous in 28 (62.2%) patients. The time from last platinum treatment to relapse/recurrence was between 2 and 6 months inclusive for all but 3 patients; for 2 of these patients for whom the interval was shorter than 2 months, this was considered to be a major protocol deviation and these patients were excluded from the efficacy population The median time from last platinum treatment to relapse/recurrence was 4.57 months (range, 0.6 to 6.0 months for the 45 enrolled patients).

Most (71.1%) patients had at least 3 organs involved at baseline. Approximately half (51.1%) of patients had solid organ metastases (at least 1 lesion of the liver, lung, or bone) at baseline. The majority (64.4%) of patients had a baseline CA-125 level of >70.

All patients received chemotherapy and surgery prior to study entry. Because prior treatments were not coded, no summary by drug/procedure is provided.

Efficacy results:

Investigator-assessed best overall response:

Efficacy information for the 42 evaluable patients is summarized in Table 3. Among the 42 patients in the efficacy population, the best overall response was partial response (PR) for 11 (26.2%) patients. No complete response (CR) was observed. Twenty-eight (66.7%) patients had SD, and 3 (7.1%) patients had PD. The ORR was 26.2% (95% CI, 13.9% to 42.0%).

Table 3 - Best overall response and objective response rate - Efficacy population

	All
	(N=42)
Best overall response rate	
Partial response	11 (26.2%)
Stable disease	28 (66.7%)
Progressive disease	3 (7.1%)
Objective response rate (ORR)	11 (26.2%)
95% confidence interval (CI) for ORR[a]	(13.9% to 42.0%)

[a] Estimated by Clopper-Pearson exact method.

Among the 14 patients for whom BRCA mutation (Myriad assay only) was reported as absent, the best overall response was PR in 4 (28.6%) patients. Among the 11 patients for whom BRCA mutation was reported as present, the best overall response was PR in 5 (45.5%) patients.

Progression-free survival:

Thirty-eight (90.5%) patients had a PFS event (ie, had clinical or radiological progression or died). Median PFS was 6.8 months (range, 5.7 to 7.7 months).

CA-125 response:
Among the 6 CA-125-response-evaluable patients who achieved tumor response (ie, best overall response of PR or CR), all 6 (100%) patients had a CA-125 response.

Among the 17 CA-125-response-evaluable patients who did not achieve tumor response, 7 (41.2%) patients had a CA-125 response and 10 (58.8%) did not have a CA-125 response.

Safety results:

Extent of exposure

The median number of cycles administered was 6.0 (range, 1.0 to 10.0) for gemcitabine and carboplatin. For iniparib, the median number of cycles administered was higher (8.0 [range, 1.0 to 16.0]) because of the 8 patients who received single-agent iniparib as maintenance treatment after completion of 10 cycles of GCI.

Overview of treatment-emergent adverse events

All treated patients had at least 1 TEAE, and most (95.6%) patients had at least 1 event of Grade 3 or 4. About half (48.9%) of the patients had treatment-emergent SAEs, and 4 (8.9%) patients had a TEAE leading to study drug discontinuation. There were no TEAEs leading to death during the study.

Analysis of adverse events

Those TEAEs occurring in ≥20% of patients (all grades, by PT) included fatigue (88.9%), nausea (84.4%), neutropenia (80.0%), anemia (68.9%), constipation (64.4%), thrombocytopenia (62.2%), vomiting (60.0%), abdominal pain (44.4%), diarrhea (42.2%), drug hypersensitivity (33.3%), headache (31.1%), neuropathy peripheral (24.4%), pyrexia (20.0%), back pain (20.0%), and hypomagnesemia (20.0%). The most frequent Grade 3 or 4 TEAEs were neutropenia (73.3%) and thrombocytopenia (37.8%).

Those drug-related TEAEs occurring in ≥20% of patients (all grades, by PT) included fatigue (88.9%), neutropenia (80.0%), nausea (75.6%), anemia (64.4%), thrombocytopenia (62.2%), vomiting (51.1%), constipation (35.6%), drug hypersensitivity (31.1%), and diarrhea (20.0%). The most frequent Grade 3 or 4 drug-related TEAEs were neutropenia (73.3%) and thrombocytopenia (37.8%).

Deaths

Seventeen (37.8%) patients died before the study safety cutoff date. The cause of death was disease progression for all of these patients, and all events occurred more than 30 days after the last dose (ie, during the follow-up period).

Treatment-emergent serious adverse events

Twenty-two (48.9%) patients had at least 1 treatment-emergent SAE. The most frequently reported treatment-emergent SAEs were thrombocytopenia (15.6% all grades; all were Grade 3 or 4), nausea (11.1% all grades; 8.9% Grade 3 or 4), and small intestine obstruction (11.1% all grades; 8.9% Grade 3 or 4).

Treatment-emergent adverse events leading to discontinuation of study drug

Four (8.9%) patients had at least 1 TEAE leading to treatment discontinuation. For 3 patients, the event leading to treatment discontinuation was related to disease progression (reason for treatment discontinuation was clinical disease progression).
One patient discontinued study treatment due to serious Grade 4 neutropenia and thrombocytopenia during Cycle 5, both of which were considered related to study treatment.

Hematologic laboratory parameters

Consistent with the TEAEs presented above, Grade 3 or 4 hematologic abnormalities during the treatment period included neutropenia (71.8 %), leukopenia (40.0%), thrombocytopenia (37.8%), lymphopenia (21.1%), and anemia (15.6%).

Nonhematologic laboratory parameters

Grade 3 or 4 nonhematologic abnormalities during the treatment period included hypokalemia (6.8%), hyponatremia (4.5%), and hypernatremia (2.3%); elevated ALT (11.1%), elevated AST (6.7%), elevated alkaline phosphatase (2.2%), and hyperbilirubinemia (2.2%); and hypoglycemia (4.4%). There were no Grade 3 or 4 abnormalities in renal function parameters.

The following on-treatment PCSAs in renal creatinine clearance were identified: mild renal impairment (≥50 to ≤80 mL/min) in 23 (51.1%) patients and moderate renal impairment (≥30 to <50 mL/min) in 4 (8.9%) patients. No patient had severe renal impairment (<30 mL/min) while on treatment.

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