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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01033123 Study code: TCD11503
Title of the study: A Phase 2, Multi-Center, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination with BSI-201 in Patients with Platinum-Sensitive Recurrent Ovarian Cancer	
Study center(s): 3 centers in the United States	
Study period: Date first patient enrolled: 09/Dec/2009 Date last patient completed: 28/Feb/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. 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 determine the relationship between breast cancer gene (BRCA) status and response. In addition, cancer antigen-125 (CA-125) response was added in the statistical analysis plan as an ad hoc analysis. Additional exploratory analyses 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).	
Methodology: In this Phase 2, multicenter, single-arm, open-label, nonrandomized safety and efficacy study, up to 41 patients with platinum-sensitive, recurrent ovarian cancer were to be enrolled at several sites in the United States 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. This study used a Simon 2-stage design. In order to proceed to Stage 2, a response must have been achieved in at least 8 patients out of the first 17 treated patients in Stage 1. In Stage 2, a response must have been achieved in 22 or more patients in order to reject the null hypothesis. The first scheduled tumor response 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 safety tests (including chemistry, hematology, coagulation parameters, and urinalysis) were to be obtained prior to drug administration and at designated intervals throughout the study.	

Number of patients:	Planned: 41
	Treated: 41
Evaluated:	
	Efficacy: 41
	Safety: 41

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 sensitivity to that regimen ("platinum sensitivity" was defined by a relapse greater than 6 months after the last dose of platinum-based chemotherapy); and must have met all other inclusion criteria and failed to meet all other exclusion criteria.

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: Until drug intolerance or disease progression

Duration of observation: Approximately 18-30 weeks (6 to 10 cycles) of treatment with study medication and 30 days of follow-up; at the discretion of the Investigator, after completion of 10 cycles of GCI, patients could continue receiving single-agent iniparib until disease progression.

Criteria for evaluation:

Efficacy: Tumor response was evaluated according to RECIST version 1.0 criteria. Tumors were to be assessed by standard methods (eg, CT, MRI) at screening, approximately every 6 weeks thereafter in the absence of clinically evident progression of disease, and at the end of study (EOS) visit if not done within 30 days prior to the last dose of iniparib. The same technique used during screening was to be used for all subsequent tumor assessments. Measurable target lesions, measurable nontarget lesions, and nonmeasurable nontarget lesions were evaluated. To be assigned a status of complete response (CR) or partial response (PR), changes in tumor measurements were to be confirmed by repeat assessments during the study. In the case of stable disease (SD), follow-up measurements were to meet the SD criteria at least once after enrollment during the study.

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

Progression-free survival, 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 response was to be evaluated as an exploratory efficacy endpoint at the same time points described for tumor response assessment. CA-125 response 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 x ULN at this time point); the response must have been confirmed and maintained for at least 28 days.

Safety: Safety evaluations were to include vital signs, physical examinations, laboratory safety tests (including chemistry, hematology, coagulation parameters, and urinalysis), ECG, ECOG performance status, and recording of concomitant medications. AEs were collected and graded according to the NCI-CTCAE, Version 3.0.

Statistical methods:

Sample size calculation:

The objective of the study was to detect an improvement in the ORR of 50% (from 0.4 to 0.6).

The sample size was calculated using a modified Simon optimal 2-stage design. Seventeen patients were to be treated in Stage 1, and 8 or more responses were required to proceed to Stage 2. Then an additional 24 patients were to be treated in Stage 2 to complete the study (N=41). If 22 or more responses were observed, 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:

All efficacy and safety variables were to be analyzed using the safety population. This population included all patients who received at least 1 of the study drugs.

Statistical methods:

Descriptive statistics and listings were used to summarize patient characteristics and extent of exposure variables.

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

Adverse events were to be classified by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0. Number (%) of patients experiencing TEAEs by primary SOC and PT were to be summarized by all grades and Grade 3/4 (using the worst grade during the TEAE period) for the safety population. Separate tables were to be issued for TEAEs, drug-related TEAEs, and serious TEAEs. Deaths and TEAEs leading to treatment discontinuation were to be presented in listings. Hematology and biochemistry results were to be graded according to NCI-CTCAE, Version 3.0, when applicable. Number (%) of patients with laboratory abnormalities (ie, all grades and Grade 3/4) using the worst grade during the on-treatment period were to be provided for the safety population.

Summary: Population characteristics: A total of 41 patients were enrolled and treated during the study. Sixteen patients (39.0%) entered into the maintenance phase and received single-agent iniparib after completion of 10 cycles of GCI. All 41 patients (100.0%) were female, as expected for the studied disease. The median age of patients was 59 years (range, 35 to 82 years), and most patients (95.1%) were of white race. Twenty-one patients (51.2%) presented at baseline with metastases in the liver, lung, and/or bone. The median time from last platinum treatment to relapse/recurrence was 12.6 months (range, 6.7 to 73.8 months), with 46.3% of patients experiencing relapse/recurrence 6-12 months following last platinum treatment and 53.7% experiencing relapse/recurrence >12 months following last platinum treatment. The predominant histological subtype was serous in 34 (82.9%) of the patients. The most common prior ovarian cancer treatments were surgery (97.6%) and chemotherapy (100% [78.0% adjuvant, 14.6% neoadjuvant, 4.9% adjuvant plus neoadjuvant, and 2.4% metastatic]).

Efficacy results: Among all treated patients, best overall response (BOR) was PR for 27 (65.9%) patients. Stable disease was achieved in 13 (31.7%) patients. CR was not observed in any patient. The ORR was 65.9% (95% CI, 49.4% to 79.9%). Since the number of responses was >22, the null hypothesis was rejected.

Breast cancer gene status (Myriad assay only) was available for 30 of 41 patients. Among the 15 patients for whom BRCA mutation was present, BOR was PR in 11 (73.3%) patients. Stable disease was achieved in 4 (26.7%) patients. Results were identical in the 15 patients for whom BRCA mutation was absent.

Twenty-five (61.0%) patients had a PFS event: 10 (24.4%) patients had clinical progression and 15 (36.6%) had radiological progression. Median PFS was 9.9 months (95% CI, 8.2 to 11.3).

Of the 18 patients considered evaluable for CA-125 response, 14 (77.8%) had a CA-125 response and 4 (22.2%) did not have a CA-125 response. Among the 12 CA-125-response-evaluable patients who also achieved tumor response, 11 (91.7%) patients also had a CA-125 response and 1 (8.3%) patient did not have a CA-125 response. Among the 6 CA-125-response-evaluable patients who did not achieve tumor response, 3 (50.0%) had a CA-125 response and 3 (50.0%) did not have a CA-125 response.

Safety results: The median number of cycles of GCI administered per patient was 9.0 (range, 3.0 to 22.0).

All 41 (100%) patients experienced a TEAE, and 38 (92.7%) patients experienced a TEAE ≥Grade 3; of note, 35 (85.4%) patients had Grade 3-4 TEAEs pertaining to hematological laboratory abnormalities in the blood and lymphatic system disorders SOC. The 5 most common TEAEs were fatigue, neutropenia, nausea, constipation, and thrombocytopenia. The most common TEAEs ≥Grade 3 were neutropenia and thrombocytopenia.

All 41 (100%) patients experienced a TEAE that was considered related to study drug by the Investigator, of which 38 (92.7%) were ≥Grade 3 (35 [85.4%] patients had treatment-related Grade 3-4 TEAEs pertaining to hematological laboratory abnormalities in the blood and lymphatic system disorders SOC). The 5 most common drug-related TEAEs were fatigue, nausea, neutropenia, thrombocytopenia, and anemia.

No patient died during the treatment period of the study. Eight (19.5%) patients died during the follow-up period (ie, >30 days after the last dose of study drug). All of the deaths were due to progression of cancer.

Twelve (29.3%) patients experienced 26 serious TEAEs. Ten of the patients experienced 14 serious TEAEs that were considered drug related by the Investigator, as follows (in 1 patient each, except where noted otherwise): urinary tract infection and drug hypersensitivity (both Grade 3); and anaphylactic reaction, pulmonary embolism, thrombocytopenia (in 5 patients), and neutropenia (all Grade 4). The most common serious TEAEs were thrombocytopenia in 5 (12.2%) patients (all ≥Grade 3) and small intestinal obstruction in 3 (7.3%) patients (2 [4.9%] ≥Grade 3).

One (2.4%) patient permanently discontinued treatment due to a serious TEAE (Grade 3 small intestinal obstruction, not related to study drug). Thirty-one (75.6%) patients had a TEAE leading to dose reduction of study treatment, and 22 (53.7%) patients had a TEAE leading to dose delay of study treatment.

Grade 3-4 hematological laboratory abnormalities during the study treatment period included leukopenia (41.5% of patients), neutropenia (68.4%), thrombocytopenia (46.3%), lymphopenia (15.8%), and anemia (7.3%). The incidence of Grade 3-4 nonhematological laboratory abnormalities was low (<5%) for all parameters tested. Potentially clinically significant abnormalities (PCSAs) in creatinine clearance during the treatment period included mild renal impairment in 24 (58.5%) patients and moderate renal impairment in 4 (9.8%) patients; at baseline, mild renal impairment had been observed in 18 (43.9%) patients and moderate renal impairment in 2 (4.9%) patients. No patient had severe renal impairment at baseline or during the treatment period.

No patient had an abnormal and clinically significant ECG at the end of treatment. One patient experienced a cardiac-related, nonserious TEAE of Grade 2 tachycardia during Cycle 6 of treatment, which was considered related to treatment.

Biomarker results: Optional tumor samples were planned to be collected during the trial at screening and at 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.

Data from exploratory biologic correlate/gene expression microarray analysis of archival tumor samples or unstained slides (primary or metastatic) are not included in this CSR but are available on file.

Issue date: 18-May-2016