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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00687687 Study code: TCD11615
Title of the study: A phase 2 evaluation of paclitaxel (Taxol®, NSC #673089), carboplatin (paraplatin, NSC #241240), and BSI-201 (NSC #746045, IND #71,677) in the treatment of advanced, persistent, or recurrent uterine carcinosarcoma	
Study center(s): This study was conducted at 20 centers in the United States by the Gynecologic Oncology Group (GOG)	
Study period: Date first patient enrolled: 19/Feb/2008 Date last patient completed: 30/Apr/2010	
Phase of development: Phase 2	
Objectives: • To estimate the antitumor activity of iniparib in combination with paclitaxel and carboplatin in patients with recurrent or advanced uterine carcinosarcoma and no prior chemotherapy. • To assess the safety profile of the combination regimen of iniparib in combination with paclitaxel and carboplatin in this cohort of patients.	
Methodology: This study was initiated under BiPar Sciences guidance in 2007 which was acquired by Sanofi in April 2009. Gynecologic Oncology Group was entirely responsible for the conduct of this study. Gynecologic Oncology Group published their results of the study (see reference above) prior to Sanofi's receipt of the database. The findings presented herein represent a separate analysis using the conventions described in the statistical analysis plan (SAP). This accounts for any potential discrepancies between the publication's results and the findings described herein. This was a Phase 2, single-arm, prospective, open-label, multicenter study. Eligible patients with recurrent or advanced uterine carcinosarcoma not previously treated with chemotherapy received paclitaxel 175 mg/m^2 intravenous (IV) followed by carboplatin area under the time concentration curve (AUC) = 6 mg/mL• min on Day 1 of 21-day cycles plus iniparib 4 mg/kg IV twice weekly beginning on Day 1. Treatment continued until progressive disease or adverse effects prohibited further therapy. Patients were intended to be followed every 3 months for the first 2 years and then every 6 months for the next 3 years. The study used a Simon 2-stage design[1]. A total of 20 eligible and evaluable patients were to be enrolled in the first stage. The primary endpoint of the study was tumor response. If more than 9 patients had a response (defined as complete or partial response) and medical judgment indicated, accrual to the second stage of the study was to be initiated. Otherwise, the study was to be stopped and the treatment regimen would be classified as clinically uninteresting. If the study advanced to the second stage, then an overall study accrual of 45 eligible and evaluable patients would be targeted. If not more than 24 out of 45 patients had a response, then the regimen would be considered clinically uninteresting. A synopsis-style clinical study report was written with only efficacy and safety results presented because the study was terminated at Simon's stage 1 due to futility because only 5 of 17 evaluable patients responded and indication discontinued.	

Number of patients:	Planned: 45 patients maximum (Stage 1: 20 patients – Stage 2: 25 additional patients) Treated: 22
Evaluated:	Efficacy: 17 Safety: 22

Diagnosis and criteria for inclusion: Patients must have had advanced (Stage III or IV per International Federation of Gynecology and Obstetrics [FIGO] classification), persistent or recurrent uterine carcinosarcoma with documented disease progression with histologic confirmation of the original primary tumor.

- Patients must have had at least 1 "target lesion" at baseline as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0). A target lesion was defined as a lesion that could be accurately measured in at least 1 dimension (longest dimension to be recorded) and must have been ≥20 mm when measured by conventional techniques, including palpation, plain x-ray, computed tomography (CT), and magnetic resonance imaging (MRI), or ≥10 mm when measured by spiral CT. Tumors within a previously irradiated field were to be designated as "non-target" lesions unless progression was documented or a biopsy was performed to confirm persistence at least 90 days following completion of radiation therapy.
- Patients must have had a GOG (Zubrod) Performance Status (PS) of 0, 1, or 2.
- Patients must have had adequate bone marrow, renal, hepatic, and neurologic function.

Study treatments

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

Formulation: Iniparib was supplied as a liquid sterile product in 10 mL single-entry vials formulated in 25% hydroxypropylbetacyclodextrin/10 mM phosphate buffer, pH 7.4, with an active ingredient concentration of 10 mg/mL.

Route(s) of administration: One-hour IV infusion

Dose regimen: Following administration of paclitaxel and carboplatin on Day 1, iniparib was administered at 4 mg/kg (based on patient's weight) twice weekly for 21 days. This 3-week period of time was considered 1 treatment cycle. Doses of iniparib were required to be separated by at least 2 days. Subsequent cycles of chemotherapy were delivered if ANC ≥1500 cells/μL and platelets ≥100,000/μL. Therapy was delayed for a maximum of 2 weeks until these values were achieved. Subsequent doses were modified for febrile neutropenia and Grade 4 neutropenia persisting ≥7 days (first occurrence) and by adding filgrastim or pegfilgrastim (second occurrence); Grade 4 thrombocytopenia; and Grade 2 (or greater) peripheral neuropathy, renal and/or ≥Grade 3 hepatic toxicity.

Noninvestigational medicinal product(s): Paclitaxel

Formulation: Paclitaxel was supplied as a sterile solution concentrate, 6 mg/mL in 5 mL vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50% (Bristol-Myers Squibb Company).

Route(s) of administration: IV

Dose regimen: Paclitaxel 175 mg/m^2 was administered as a 3-hour infusion

Noninvestigational medicinal product(s): carboplatin

Formulation: Carboplatin was supplied as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin. Each vial contained equal parts by weight of carboplatin and mannitol (Bristol-Myers Squibb Company).

Route(s) of administration: IV

Dose Regimen: Following paclitaxel, carboplatin will be administered to an AUC = 6 over 30 minutes, on Day 1, every 21 days, plus iniparib twice weekly beginning on Day 1.

Duration of treatment: Treatment continued until disease progression or adverse effects prohibited further therapy. Patients with CR received additional cycles at the discretion of the treating physician. Patients not meeting the criteria for progression of disease ([PR] or stable disease [SD]) were continued on study treatment provided there was no unacceptable toxicity.

Duration of observation: Patients were intended to be followed every 3 months for the first 2 years and then every 6 months for the next 3 years.

Criteria for evaluation: The primary efficacy endpoint was objective response rate (ORR), which was defined as the proportion of patients with confirmed CR or PR relative to the total number of patients in the efficacy population. Tumor response was evaluated according to RECIST Version 1.0 criteria. Tumor assessments were performed every other cycle. Other efficacy endpoints included overall survival (OS) and progression-free survival (PFS).

Safety assessments included treatment-emergent adverse events (TEAEs), physical examinations, chest imaging, electrocardiogram (ECG), and radiographic tumor measurements. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Statistical methods: This study was designed using a Simon's optimum 2-stage design with early stopping guidelines intended to limit patient accrual to inactive treatment, using ORR as the primary endpoint. The study was designed to detect an improvement in the ORR from 0.45 to 0.65 with a type 1 error of 10% and 90% power. In the first stage of the study, accrual of 20 eligible and evaluable patients was planned. The minimum number of responses to proceed to the second stage was 9. A cumulative total sample size of 45 was planned to be targeted if the study went to the second stage, requiring at least 25 responders before the regimen was deemed of interest. Only those patients who were deemed ineligible on central pathology review or who received no therapy were excluded from the efficacy population.

The primary efficacy endpoint was ORR, which was defined as the proportion of patients with confirmed CR or PR according to RECIST Version 1.0 criteria relative to the total number of patients in the efficacy population. Objective response rate was summarized using descriptive statistics and 95% confidence interval (CI).

Secondary endpoints included PFS and OS.

Overall survival time was defined as the time from entry into the study (ie, date of first dose) to death. If death was not observed, OS was censored at the date of last contact. Progression-free survival was the period from study entry (ie, date of first dose) until disease progression or death. If death or progression was not observed, PFS was censored at the date of last tumor assessment without evidence of progression.

Progression-free survival and OS were analyzed using the Kaplan-Meier method and summarized with median and 95% CI of the median. The PFS and OS curves were estimated using the Kaplan-Meier estimates.

Adverse events were classified by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). The proportion of patients experiencing TEAEs by primary SOC and PT were to be summarized by all grades and Grade 3/4 (using the worst grade reported during the TEAE period) for the safety population. Separate tables were to be provided for TEAEs, drug-related TEAEs, and serious TEAEs. Deaths and TEAEs leading to treatment discontinuation were to be presented in listings.

Summary: This study was designed to investigate the combination of iniparib with paclitaxel and carboplatin in patients with histologically documented advanced, persistent, or recurrent uterine carcinosarcoma. The selection of dosing of this regimen was based on the interim results of BiPar Study Part 1 that included 8 patients of whom 2 received 4.0 mg/kg twice weekly. In the current study, 22 patients received iniparib plus paclitaxel and carboplatin study treatment and were evaluated for safety. Seventeen patients were evaluable for efficacy. The remaining 5 (23%) patients were excluded because of not meeting central pathology review criteria.

The median age of the safety population was 61.5 years (range 47 to 84 years), with 15 (68.2%) patients less than 65 years old. Ten (45.5%) patients had a Zubrod performance status (PS) of 0; 10 (45.5%) of 1; and 2 (9.1%) of 2. Eleven patients (52.4%) were stage FIGO stage IV at initial diagnosis. The most frequent metastatic sites were lymph nodes (10 patients, 45.5%), uterus (7 patients, 31.8%), lung (6 patients, 27.3%), and peritoneum (4 patients, 18.2%).

The ORR at the end of stage 1 was 29.4% (90% CI = 10.3% to 56.0%). Two (11.8%) patients had confirmed CR; 3 (17.6%) patients had confirmed PR; and 7 (41.2%) patients achieved a best response of SD. Three (17.6%) patients had increasing (progressive) disease and 2 (11.8%) patients did not have repeat tumor assessments and therefore were not evaluable. The study was terminated at Simon's stage 1 due to futility because only 5 of 17 evaluable patients responded. The minimal number of responses required to proceed to stage 2 was 9 of 20 evaluable patients. Eighty-two percent of patients had a PFS and OS event. The median PFS in the efficacy population was 3.7 months (95% CI = 2.00 to 8.48 months) and the median OS of the efficacy population was 11.0 months (95% CI = 5.55 to 26.51 months).

The median duration of study treatment was 12.0 weeks (range 3 to 51 weeks). The median number of cycles of treatment per patient was 4.0 (range 1 to 16 cycles). Patients in the safety population had median relative dose intensity (RDI) of 84% for iniparib, 90% for carboplatin, and 94% for paclitaxel.

The most frequent Grade 3/4 treatment-emergent SAEs were nausea, dehydration, and vomiting, (2 patients, 9.1% each). One patient had Grade 3 febrile neutropenia. The most frequently reported Grade 3/4 TEAEs (ie, occurring in at least 3 [13.6%] patients) were neutrophil count decreased (20 patients, 90.9%), white blood cell count decreased (14 patients, 63.6%), and lymphopenia, hypokalemia, dehydration, fatigue, hemoglobin decreased, and platelet count decreased (3 patients, 13.6% each). Fifteen of the 22 patients in the safety population died; all were due to progressive disease. One patient died while on treatment due to progressive disease. Narratives of deaths and serious adverse events (SAEs) are provided in 15-3-3-list-narratives.

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