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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00813956 Study code: TCD11487
Title of the study: A Phase II Study of Gemcitabine, Carboplatin and Poly (ADP-Ribose) Polymerase (PARP) Inhibitor Iniparib in the Neoadjuvant Treatment of Triple-Negative or BRCA Mutation-Associated Breast Cancer	
Study center(s): Multicenter study (7 centers in the United States)	
Study period: Date first patient enrolled: 28/Apr/2009 Date last patient completed: 24/Oct/2012	
Phase of development: Phase 2	

Objectives:

Primary

To determine whether the neoadjuvant combination therapy regimen of gemcitabine, carboplatin, and iniparib would result in a 40% or greater proportion of patients with Stage I-IIIA triple-negative or BRCA 1/2 mutation-associated breast cancer achieving a pathologic complete response (pCR).

Secondary

- To determine radiographic response by breast magnetic resonance imaging (MRI);
- To determine rate of breast conservation eligibility;
- Assess safety of the combination regimen.

Correlative Objectives

- To determine whether baseline functional deoxyribonucleic acid (DNA repair activity and/or expression of DNA repair genes correlate with response to neoadjuvant therapy in patients with triple-negative or BRCA mutation-associated breast cancer.
- To correlate DNA repair gene expression (PARP1, PARP2, BRCA1, BRCA2, ERCC1, RRM1, p63, p73, RAD51) with treatment response.

Given that during the course of the study it was discovered that iniparib is not a bona fide PARP inhibitor, PARP1 and PARP 2 immunohistochemistry assessment was abandoned; however, the exploratory analyses of BRCA1, BRCA2, ERCC1, RRM1, p63, and p73, are ongoing and will be reported at a later date. Analysis of RAD51 will not be pursued.

Methodology:

This was a Phase II, open-label, single-arm nonrandomized trial to assess the efficacy and safety of iniparib in combination with gemcitabine and carboplatin in patients with triple-negative or BRCA mutation-associated breast cancer. The study initially opened in early 2009 at Stanford as a 4-treatment-cycle protocol. After positive data from a randomized Phase II study of gemcitabine, carboplatin, and iniparib in metastatic triple-negative breast cancer were reported in 2009, the protocol was amended to a 6 cycle protocol and accrual was expanded to include 80 additional patients in order to evaluate this combination regimen as a definitive treatment in a larger group of patients. These modifications were done in conjunction with the trial's activation in PrECOG. A total of 93 patients were enrolled, 13 patients to the 4 cycle protocol and 80 patients to the 6 cycle protocol.

Within 4 weeks prior to registration, the patients signed an informed consent and were screened with respect to medical history, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status (PS), prior treatments, hematology, serum chemistry (including hepatic, renal, and electrolyte parameters), urinalysis, electrocardiogram (ECG), tumor assessment, breast MRI, and digital mammogram. After review of the screening assessments and the confirmation that the patients met eligibility criteria, the patients were treated with gemcitabine (1000 mg/m^2, 30-min intravenous [IV] infusion) and carboplatin (area under plasma concentration curve [AUC] 2; 60-min IV infusion) on Days 1 and 8 of a 21-day cycle followed by iniparib (5.6 mg/kg 60-min IV infusion) on Days 1, 4, 8 and 11 of a 21-day cycle. Tumor assessment, breast MRI and digital mammogram were collected at the end of treatment.

Patients underwent definitive surgery as standard of care during weeks 20-22. Surgery was to be completed within 4 weeks of completing neoadjuvant therapy. Participants with a positive pretreatment sentinel lymph node biopsy or fine needle aspiration were to undergo axillary lymph node dissection as per standard of care. Participants with a baseline negative sentinel lymph node biopsy did not require further axillary surgery and were considered ypN0. Breast tissue and axillary lymph nodes were to be examined for residual invasive cancer. Following completion of participation in this trial, patients were to receive additional adjuvant therapies (chemotherapy, radiotherapy) as per standard of care.

Vital signs, physical examinations, ECOG PS, and laboratory safety tests (including complete blood count [CBC] and serum chemistry parameters) were obtained on Days 1 and 8. Adverse events (AEs) were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI CTCAE v.3.0) during the study.

Number of patients:	Planned: 80
	Enrolled: 93 (13 received 4 cycles, 80 received 6 cycles)
	Withdrawn: 11
	Completed: 82
	ITT population: 93
	Safety population: 93

Diagnosis and main criteria for admission:

- Histologically confirmed adenocarcinoma of the breast that was estrogen receptor (ER)-negative (≤5%), progesterone receptor (PR)-negative (≤5%) and HER2-negative (0,1 by immunohistochemistry [IHC] or fluorescent in situ hybridization [FISH] ratio 2.2) or BRCA 1/2 mutation-associated adenocarcinoma of the breast;
- Clinical Stage I-IIIA disease (T ≥1 cm);
- No prior therapy for current breast cancer;
- Age 18 years or greater;
- Adequate organ function as evidenced by the following, obtained within 4 weeks prior to registration;
- ECOG performance status of 0 or 1;
- Patients must have agreed to undergo definitive breast surgery including total mastectomy and axillary dissection (modified radical mastectomy), total mastectomy and sentinel lymph node biopsy, lumpectomy and axillary dissection, or lumpectomy and sentinel node biopsy.

Study treatments

Test product, dose and mode of administration: iniparib

Gemcitabine (1000 mg/m^2; 30-min IV infusion) and carboplatin (AUC 2; 60-min IV infusion) on Days 1 and 8 of a 21-day cycle with iniparib (5.6 mg/kg as a 60-min IV infusion) on Days 1, 4, 8, and 11.

Gemcitabine and carboplatin were commercially supplied.

Duration of treatment:

The first 13 patients on trial were assigned to treatment with four 21-days cycles (12 weeks) and the 80 remaining patients on trial were assigned to treatment with six 21-day cycles (18 weeks) prior to definitive surgery. Patients were to be followed AEs for 30 days after the last dose of neoadjuvant therapy.

- Duration of screening period: 7 days;
- Duration of treatment period: 12 or 18 weeks;
- Duration of follow-up: 30 days after the completion of neoadjuvant therapy.

Criteria for evaluation:

Efficacy: Pathologic complete response (breast and axilla, RCB0), objective response rate by breast MRI, eligibility rate for breast conservation surgery among patients not eligible for breast conservation surgery at baseline.

Safety: Adverse events, vital signs, physical examinations, ECG, hematology, clinical chemistry, urinalysis and concomitant medications.

Pharmacokinetics (substudy): Plasma samples were collected from patients on Day 1 – 2 (n=16 timepoints; 13, samples for gemcitabine/carboplatin concentration analysis and 4 samples for iniparib, 4-iodo-3-benzamide [IABM] and 4-iodo-3-benzoate [IABA] concentration analysis), Day 4 (12 timepoints; 1 sample for gemcitabine/carboplatin analysis and 12 samples for iniparib/IABM/IABA analysis), and Day 8 – 9 (20 timepoints; 13 samples for gemcitabine/carboplatin analysis and 14 samples for iniparib/IABM/IABA analysis). The pharmacokinetic (PK) analysis was to be performed ideally in cycle 1, though could be performed on the appropriate treatment days (Days 1-2, Day 4, and Days 8-9) of subsequent cycles as necessary to accommodate patient schedules.

Translational: correlation of DNA repair gene expression (PARP1, PARP2, BRCA1, BRCA2, ERCC1, RRM1, p63, p73,) with treatment response. Given that during the course of the study it was discovered that iniparib is not a bona fide PARP inhibitor, PARP1 and PARP 2 immunohistochemistry assessment was abandoned; however, the analyses of BRCA1, BRCA2, ERCC1, RRM1, p63, and p73, are ongoing and will be reported at a later date. Analysis of RAD51 will not be pursued.

Statistical methods:

Per protocol, the primary analysis was to combine patients enrolled to receive 4- or 6- cycles. Descriptive analyses were to also report results separately for the 4 and 6 cycle groups. At the time the study was expanded, the revised design was based solely on the patients to be treated at 6 cycles. Therefore, both the 6-cycle cohort alone and the combined cohorts are reported.

The proportion of participants achieving a pCR (breast and axilla, RCB0) was calculated and reported with its exact binomial 90% confidence interval (CI). The null hypothesis of a 25% pCR rate was to be rejected if the 90% CI did not include the null rate of 25%.

The proportion of participants achieving objective response as measured by MRI at baseline and after therapy was estimated using stated criteria, and was reported with its 90% CI. The proportion of participants down-staged to eligibility for breast conservation was estimated and reported with the associated 90% CI.

Safety results were reported using summary tables, figures, and data listings. Continuous variables were summarized using mean, SD, median, minimum, and maximum. Categorical variables were summarized by presenting the number (frequency) and percentage in each category.

Summary:

Patient demographics: Among the 93 females treated in the study, most were white (67 patients, 72.0%). The median age at screening was 48 years with a range of 26 to 74 years. All patients but three had triple-negative breast cancer according to the protocol definition. The three remaining patients were ER- and/or PR-positive, HER2-negative, but BRCA1 (1) and BRCA2 (2) mutant.

Efficacy results:

- Among the 80 patients who received 6 cycles of treatment, 29 patients achieved pCR, resulting in a pCR rate of 36.3% (90% exact binomial confidence interval 27.3 to 46.0%). Fifty-eight (72.5%) patients achieved an objective response by MRI. Among the 23 patients not eligible for breast conservation surgery at baseline, 14 (60.9%) became eligible for breast conservation.
- For the primary endpoint of pCR in the total population of 93 patients, 31 (33.3%) patients achieved a pCR (90% exact binomial CI, 25.3 to 42.2%). Sixty-eight (73.1%) patients achieved an objective response by MRI. Among the 27 patients not eligible for breast conservation surgery at baseline, 15 (55.6%) became eligible for breast conservation.
- Among the patients treated with 4 cycles, none discontinued due to progressive disease. Among the 80 patients treated with 6 cycles, 5 (6.3%) discontinued due to progressive disease.

Safety results:

- All patients had at least 1 treatment emergent adverse event (TEAE).
- The most common treatment-related TEAEs among all 93 patients were fatigue (84.9%), nausea (81.7%), neutropenia/neutrophil count decreased (49.5%), alopecia (46.2% [41.9% Grade 1,4.3% Grade 2]), anemia (33.3%), dysgeusia (25.8%), diarrhea (24.7%), and rash (20.4%).
- Among the 80 patients who received 6 cycles of treatment, the most common treatment-related TEAEs fatigue (85.0%), nausea (81.3%), neutropenia/neutrophil count decreased (53.8%), alopecia (51.3% [46.3% Grade 1, 5.0% Grade 2]), anemia (35.0%), dysgeusia (28.8%), diarrhea (26.3%), and rash (23.8%).
- All grade 4 TEAEs occurred in patients receiving 6 cycles of treatment.
- There were no deaths during the study.
- Eleven (11.8%) patients had serious adverse events (SAEs), all of whom received 6 cycles of treatment. The most common SAEs were pulmonary embolism and thrombocytopenia, each of which occurred in 3 (3.2%) patients.
- Five (5.4%) patients discontinued study treatment due to an AE, all of which were considered treatment-related by the Investigator. These 5 patients received 6 cycles of treatment.
- Most hematology, clinical chemistry, urinalysis, and vital sign values were within normal ranges. In general, values that were outside the normal ranges were not clinically significant. Mean changes from baseline at each visit and at the end of the study were generally small and not clinically significant.

Issue date: 18-May-2016