SYNOPSIS

Title of the study: Multicenter, randomized, open label study evaluating a poly(ADP-ribose) polymerase-1(PARP-1) inhibitor, SAR240550 (BSI-201), administered twice weekly or weekly, in combination with gemcitabine/carboplatin, in patients with metastatic triple negative breast cancer

Investigator(s): [redacted]

Study center(s): 20 centers in 6 countries

Publications (reference):

Diéras V, Bonnefoi H, Alba E, et al. A Phase 2, Randomized Open-Label Study of Iniparib, Administered Either Weekly or

Twice-Weekly in Combination with Gemcitabine Plus Carboplatin in Patients with mTNBC. Cancer Res December 15, 2011; 71(24 Supplement): P3-16-08.

Verweij, J, Dieras, V, Rockich, K, Su Y, Mery-Mignard D, Pham, N, and Emmons G. Pharmacokinetics and metabolism of iniparib for the treatment of metastatic triple-negative breast cancer. A134, Poster presented at AACR-NCI-EORTC International Conference, Molecular Targets and Cancer Therapeutics (November 12-16, San Francisco, CA).

Study period:

Date first patient enrolled: 25 February 2010

Date last patient completed: 08 November 2012

Phase of development: Phase 2

Objectives:

Primary Objective:

- To assess the objective response rate (ORR) of iniparib administered as a 60-minute intravenous (IV) infusion twice weekly (tw)-iniparib or weekly (w)-iniparib in combination with gemcitabine/carboplatin (GC) chemotherapy regimen in patients with metastatic triple-negative breast cancer (mTNBC)

Secondary Objectives:

- To assess the safety profile in both study arms
- To assess the clinical benefit rate (CBR), defined as the rate of complete response (CR), partial response (PR), and stable disease (SD) lasting at least 24 weeks, in both study arms
- Progression-free survival (PFS) and overall survival (OS) in both study arms (disease progression assessed per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1)
- To evaluate the pharmacokinetic (PK) profile of iniparib in both study arms (substudy)
- To assess the biological activity of the study treatment in tumor tissue in both study arms (substudy)
- To characterize the molecular and biological profile of tumors (substudy)
- To assess the effect of iniparib on poly(ADP)-ribose (PAR) level in peripheral blood mononuclear cells (PBMC) in both arms (substudy)

Methodology: This was a multicenter, randomized, open-label, Phase 2 study to assess the ORR of 2 regimens of iniparib (weekly and twice-weekly) in combination with gemcitabine and carboplatin in female patients with mTNBC.

After confirmation of eligibility criteria, patients were randomly assigned via a central interactive voice response system (IVRS) in a 1:1 ratio to 1 of the 2 treatment arms, with stratification based on prior chemotherapies for metastatic disease (0 versus 1 to 2):

- GC+tw-iniparib: iniparib 5.6 mg/kg (IV over 60 minutes) on Days 1, 4, 8, and 11, plus gemcitabine 1000 mg/m² (IV over 30 minutes) and carboplatin area under the curve (AUC) = 2 mg•mL/min (IV over 60 minutes), both on Days 1 and 8, every 3 weeks
- GC+w-iniparib: iniparib 11.2 mg/kg (IV infusion over 60 minutes) on Days 1 and 8, plus gemcitabine 1000 mg/m² (IV over 30 minutes) and carboplatin AUC = 2 (IV over 60 minutes), both on Days 1 and 8, every 3 weeks

Tumor response at each time point (partial response [PR], complete response [CR], stable disease [SD] and progressive disease [PD]) was determined using RECIST criteria (version 1.1) by an Independent Radiology Review Committee (IRRC) based on central review of scans in a blinded manner. The first scheduled tumor assessment was to be performed after 2 cycles of treatment and every 2 cycles (ie, approximately every 6 weeks) thereafter. To be assigned a status of CR or PR, changes in tumor measurements were to be confirmed by repeat assessments at least 4 weeks after initial documentation.

Cumulative safety and tolerability was to be assessed on an ongoing basis. Adverse events (AEs) were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECGs), and laboratory tests (including chemistry, hematology, and coagulation parameters) were performed prior to drug administration and at designated intervals throughout the study.

Molecular-biological and pharmacodynamic sampling was to be performed in at least 15 patients in each treatment arm with evaluable tumor samples (tissue blocks or unstained slides [local relapse and/or metastatic] collected within 1 month before patient's inclusion and biopsies collected in Cycle 1). Peripheral blood mononuclear cells were to be isolated at baseline and during Cycles 1 and 2 (Days 1 and 11 in the GC+tw-iniparib arm and Days 1 and 8 in the GC+w-iniparib arm). Pharmacokinetic sampling was to be performed in approximately 15 patients in each treatment arm in Cycles 1 and 2.

Number of patients:

Planned: 160

Randomized (intent-to-treat [ITT]) population: 163

Evaluable population: 152

Safety population : 162

Pharmacokinetics population : 69

Diagnosis and criteria for inclusion: Patients eligible for inclusion had to have histologically documented, measurable (RECIST, version 1.1) breast cancer (either at primary or metastatic site) that was estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative (<10% tumor staining by immunohistochemistry [IHC]), and human epidermal growth factor receptor 2 (HER2)-nonoverexpressing by IHC (0, 1+) or IHC 2+ and fluorescence in situ hybridization (FISH) negative. Prior treatment(s) could have included: a) no prior anticancer therapy for metastatic disease; OR b) having received 1 or 2 prior chemotherapy regimens in the metastatic setting. Prior neo-adjuvant/adjuvant systemic therapy was considered as a prior line of chemotherapy for metastatic disease if the first relapse occurred less than 1 year after the last treatment administration.

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 of administration: IV (over 60 minutes)

Dose regimen: 5.6 mg/kg on Days 1, 4, 8, and 11 every 3 weeks OR 11.2 mg/kg on Days 1 and 8 every 3 weeks

Batch numbers: [redacted]

Noninvestigational medicinal product(s):

Product: gemcitabine

Route of administration: IV (over 30 minutes)

Dose regimen: 1000 mg/m² on Days 1 and 8 every 3 weeks

Batch number: Not collected

Product: carboplatin

Route of administration: IV (over 60 minutes)

Dose regimen: AUC = 2 on Days 1 and 8 every 3 weeks

Batch number: Not collected

Duration of treatment: Treatment was to be administered every 3 weeks in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or end of study. Patients who continued benefiting from the study treatment at the time of the cut-off date were offered enrollment in a treatment extension protocol (LTS12674) after completion of parental trial primary objective.

Duration of observation: The duration of the study for an individual patient included a 3-week screening period, at least 1 cycle (3 weeks) of study treatment, and a minimum of 30 days of follow-up after the last study drug administration. In the case that a patient discontinued study treatment before disease progression, tumor assessments for evaluation of ORR and PFS were to be performed at 6-week intervals until disease progression, end of study, or death, whichever occurred first. After disease progression, patients were to be followed every 3 months for OS until the end of study.

The end of study was to be 12 months after the first dose of the last patient treated.

Criteria for evaluation:

Efficacy

The primary efficacy endpoint was ORR (based on IRRC adjudication), which was defined as the proportion of patients with confirmed CR or PR relative to the total number of patients in the analysis population. Patients without post-baseline tumor assessments or without a valid post-baseline tumor assessment (eg, assessment date was missing or the overall response was not evaluable) were to be considered nonresponders.

Progression-free survival, defined as the number of days from the date of randomization to the date of disease progression (ie, radiological progression based on IRRC assessment) or the date of death (from any cause), whichever was earlier, was evaluated as a secondary efficacy endpoint.

Clinical benefit rate (CR+PR+SD greater than 6 months; based on IRRC adjudication) and OS were also evaluated as secondary efficacy endpoints.

Safety

Safety was based on the incidence of AEs and changes in vital signs, physical examinations, laboratory tests (including chemistry, hematology, and coagulation parameters), ECG, and ECOG performance status. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 and with toxicity grade defined by the NCI-CTCAE v 4.0.

Pharmacokinetics, pharmacodynamics, and molecular-biological substudy

Molecular-biological, pharmacodynamic, and PK analyses were to be performed in voluntary patients who had signed a separate informed consent as outlined in the study protocol and laboratory study manual.

Molecular characterization of the tumor and effect of treatment on tumor were to be evaluated in this subgroup of patients. This analysis was not done as the number of samples collected (12) were below the target threshold (15) specified in the protocol.

PAR concentrations and other biomarkers of interest were to be evaluated in PBMC. Collection of PBMCs was discontinued by sponsor's decision and communicated to the sites on 14 September 2010. Therefore, data were not presented for this objective.

The PK parameters of iniparib, 4-iodo-aminobenzamide (IABM), and 4-iodo-3-amino-benzoic acid (IABA) metabolites to be determined for each patient included maximum concentration observed, first time to reach maximum observed concentration, AUC, AUC versus time curve from time 0 to the real time t_{last}, terminal half-life, volume of distribution at steady-state, and plasma clearance.

Statistical methods:

Sample size calculation

This study was based on a selection design ("pick the winner" design), which is typically used to maximize the probability of selecting the better of the 2 treatment regimens. The treatment with the highest response rate is selected as the best treatment. No statistically significant difference between the 2 treatment arms is required.

Based on the interim data (analysis cut-off date of 31 May 2010) from the randomized Phase 2 trial TCD11485/20070102 in patients with mTNBC treated with GC in combination with the twice-weekly schedule of iniparib, the ORR was assumed to be 48%. Based on this, with 80 patients per treatment arm (a total of 160 patients), the study provided 88% power to select the better treatment regimen if the expected difference between the arms was 10%. Therefore, a total of 160 patients (80 per arm) were to be randomized.

Analysis populations

The ITT population included all randomized patients (ie, the set of all patients who gave their informed consent and for whom there was confirmation of successful allocation of a randomization number through the IVRS). This population was used for efficacy analyses, which were based on the treatment arm assigned by IVRS.

The evaluable patient (EP) population included all treated patients with measurable disease at study entry with at least 1 baseline tumor assessment and 1 post baseline tumor assessment and also all treated patients with early disease progression (death from malignant disease or progressive disease before first planned tumor assessment [ie, 6 weeks after first infusion]). This population was used for supportive efficacy analyses.

The safety population included all randomized patients who received at least 1 (even incomplete) dose of the study treatments. This population was used for safety analyses, which were based on the treatment actually received.

The PK population included randomized and treated patients with available PK parameters. All analyses using the PK populations were based on the treatment received.

Analysis of the primary efficacy endpoint

The cut-off date for the primary efficacy analysis was 16 weeks after the first dose of the last patient treated in the study (time for 2 post-baseline evaluations and confirmation of response). The ORR results were updated at the time of the final analysis using the study cut-off date (ie, end of study) defined as 12 months after the first dose of the last patient treated. However, since the cutoff date at 16 weeks was primarily defined for early internal decision making, only results using all data collected through study completion are presented in the this report.

The ORR, as adjudicated by the IRRC, with associated 95% confidence intervals (CI) was calculated based on the ITT population. No formal statistical comparison of ORR was performed between the 2 schedules of administration.

The following supportive analyses were conducted:

- ORR, as adjudicated by the IRRC, with associated 95% CI was to be displayed based on the EP population
- ORR, as adjudicated by the IRRC, with associated 95% CI was to be displayed by randomized stratum (prior chemotherapies for metastatic disease: 0 versus 1 to 2, as reported in the IVRS) based on the ITT population
- ORR, as assessed by the investigator, with associated 95% CI was calculated on the ITT population

Analysis of secondary endpoints

The CBR, as adjudicated by the IRRC, with associated 95% CI was calculated on the ITT population. Similar supportive analyses as for ORR were conducted.

Progression-free survival, using disease progression as adjudicated by the IRRC, was analyzed using the Kaplan-Meier method, based on the ITT population. Median PFS and PFS rates at 3, 6, 9, 12, and 15 months were provided. Progression-free survival event types were summarized as documented disease progression or death without progression. Reasons for censoring were summarized (eg, no progression according to IRRC and no death at the cut-off date, new anticancer treatment started, death or progression after more than 1 missed tumor assessment). Kaplan-Meier curves were plotted. A similar analysis using investigator assessment was performed.

The analysis for OS was similar to that for PFS.

Analysis of safety

The number (%) of patients experiencing treatment emergent adverse events (TEAEs) summarized by MedDRA terms (eg, primary system organ class and preferred term) were summarized by CTCAE grade (all grades and Grade 3/4) for the safety population. A similar analysis was done for drug-related TEAEs, TEAEs leading to treatment discontinuation, and serious TEAEs. For patients with multiple occurrences of the same AE within the on treatment period, the worst grade was used.

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

Summary:

Patient disposition:

A total of 163 patients were randomized (ITT population) into the study. Of these 163 patients, 81 were in the GC+tw-iniparib arm and 82 were in the GC+w-iniparib arm. One patient in the GC+tw-iniparib arm was not treated and was excluded from the safety population, for a total of 162 in the safety population (80 and 82 patients in the GC+tw-iniparib and GC+w-Iniparib arms, respectively). Three patients from the safety population were excluded from the evaluable population in the GC+tw-iniparib arm, and 7 were excluded in the GC+w-iniparib arm (77 and 75 patients in the GC+tw-iniparib and GC+w-Iniparib arms, respectively). There were 34 patients in the PK population from the GC+tw-iniparib arm, and 35 from the GC+w-iniparib arm.

All patients discontinued treatment under this protocol at time of database lock. Two patients continued to clinically benefit from the treatment and were rolled over into the treatment extension protocol.

One hundred thirty-four (82.2%) patients discontinued treatment due to disease progression (radiological or clinical). Other reasons for treatment discontinuation included “Other” for 18 (11.0%) patients, and AEs for 9 (5.5%) patients. Of the 9 patients who discontinued treatment due to an AE, 4 (4.9%; n=81) were in the GC+tw-iniparib arm and 5 (6.1%; n=82) were in the GC+w-iniparib arm. In the GC+tw-iniparib arm, the events leading to permanent treatment discontinuation included decreased platelet count (1 patient), acute generalized exanthematous pustulosis (1 patient), tumor embolism (1 patient), and paraesthesia (1 patient). In the GC+w-iniparib arm, AEs leading to permanent treatment discontinuation included lung infection and anemia (1 patient), acute respiratory distress syndrome (1 patient), neutropenia (1 patient), asthenia (1 patient), and thrombocytopenia (1 patient).

Thirty-three patients (40.7%) in the GC+tw-iniparib arm and 35 (42.7%) in the GC+w-iniparib arm were randomized into the strata “no prior chemotherapy for metastatic disease.” Of note, the protocol specified that prior neo-adjuvant/adjuvant systemic therapy was considered as a prior chemotherapy for metastatic disease if the first relapse occurred less than 1 year after the last treatment administration. Based on this definition, 8 (9.9%) patients in the GC+tw-iniparib arm and 9 (11.0%) in the GC+w-iniparib arm were randomized into the wrong strata.

Demographics and baseline characteristics

Overall there were no major imbalances in demographic or baseline characteristics. The median age of the ITT population was 48.0 years (range, 32 to 78 years) in the GC+tw-iniparib arm, and 49.5 years (range 27 to 76 years) in the GC+w-iniparib arm. There was an 8% difference between the 2 arms in patients who had an ECOG performance status of 0 at baseline (GC+tw-iniparib: 63.0% vs GC+w-iniparib: 54.9%).

All patients had a confirmed diagnosis of TNBC accordingly to the protocol definition except for 3 patients. Of these 3 patients, 2 patients did not have TNBC confirmed at study entry, and 1 patient had no cancer diagnosis data initially entered into the CRF but was later diagnosed with a plasmocytoma. More than 80% of patients in both arms had ER and PgR ≤1% (entry criteria cut off <10%). Only 4% of patients in the GC+tw-iniparib and 10% of patients in the GC+w-iniparib arms were HER2 IHC 2+ and FISH negative. Overall, the predominant histological subtype was infiltrating ductal carcinoma (150 patients; 92% of the ITT population). Approximately 9% of the patients in the ITT population were *de novo* stage IV. All other patients had progressed following previous adjuvant/neoadjuvant treatment. Most (69.3%) patients had at least 2 organs involved at baseline, including the primary site. Lung metastases were 5% more frequent in patients in the GC+tw-iniparib than in the GC+w-iniparib arm (59.3% vs. 43.9%, respectively).

All but 9 (5.5%) patients received anticancer therapy prior to enrollment in this study. In the GC+tw-iniparib arm, 65% of the patients received adjuvant/neoadjuvant treatment only compared with 60% in the GC+w-iniparib arm. Approximately 30% of the patients in the GC+tw-iniparib arm and 40% of the patients in the the GC+w-iniparib arm had no prior chemotherapy for metastatic disease according to protocol definition (actual strata). Regarding prior chemotherapy treatment, 69 (85.2%) patients in the

GC+tw-iniparib arm and 71 (86.6%) in the GC+w-iniparib arm received docetaxel or paclitaxel. Epirubicin was given to 43 (53.1%) patients in the GC+tw-iniparib arm and to 42 (51.2%) patients in the GC+w-iniparib arm. Approximately 25% of the patients in each arm received prior bevacizumab. One hundred and fifty (92.0%) patients had prior breast surgery. The median time from last systemic therapy to randomization was comparable in the 2 arms; approximately 7 months.

Efficacy results:

IRRC-assessed best overall response

Table 1 summarizes the best overall response, overall response rate, and clinical benefit as assessed by the IRRC.
The best overall response as assessed by the IRRC was 29.6% in the GC+tw-iniparib arm (95% CI: 19.7% to 39.6%) and 34.1% (95% CI: 23.9% to 44.4%) in the GC+w-iniparib arm.

Table 1 – Best Overall response, Overall Response Rate and Clinical Benefit Rate by IRRC – ITT Population

	GC+tw-iniparib (N=81)	GC+w-iniparib (N=82)
Complete Response n(%)	2 (2.5%)	1 (1.2%)
Partial Response n(%)	22 (27.2%)	27 (32.9%)
Stable Disease n(%)	36 (44.4%)	38 (46.3%)
Overall response (CR or PR) n(%)	24 (29.6%)	28 (34.1%)
95% CI[a]	(19.7% to 39.6%)	(23.9% to 44.4%)
Clinical Benefit (CR or PR or SD for at least 24 weeks) n(%)	26 (32.1%)	34 (41.5%)
95% CI[a]	(21.9% to 42.3%)	(30.8% to 52.1%)
Progressive Disease n(%)	20 (24.7%)	13 (15.9%)
Not Evaluable/Missing Data n(%)	1 (1.2%)	3 (3.7%)

a Estimated by normal approximation. Records with missing values for factors or response were excluded from statistical analyses.

Best overall response by IRRC per randomization stratum was higher in the no previous chemotherapy compared with the 1 or 2 setting. Overall ORR was 41% in the former and 25% in the later. No difference is observed in response rate between the 2 arms in the second line setting while a 9% difference in favor of the weekly regimen is observed in first line patients.

When using the assessments provided by the investigator, more responses were reported in the GC+tw-iniparib arm (35.8%; 95% CI, 25.4% to 46.2%) than in the GC+tw-iniparib arm (30.5%; 95% CI, 20.5% to 40.5%). However, the CBR was higher with the weekly regimen that the twice-weekly (45.7% versus 53.7%).

Progression-free survival

Table 2 provides a summary of PFS as assessed by the IRRC. Overall, 70% of patients had a PFS event. Median PFS was 4.3 months (95% CI: 3.0 to 5.8 months) and 5.5 months (95% CI: 4.2 to 5.7 months), in the GC+tw-iniparib arm and the GC+w-iniparib arm, respectively.

Table 2 – Summary of analysis of progression-free survival by IRRC – ITT population

	GC+tw-iniparib (N=81)	GC+w-iniparib (N=82)
Number of patients with PFS events (%)	57 (70.4%)	57 (69.5%)
Documented disease progression	56 (69.1%)	55 (67.1%)

Death without progression	1 (1.2%)	2 (2.4%)
Number of patients censored (%)	24 (29.6%)	25 (30.5%)
No progression according to IRRC and not dead	8 (9.9%)	7 (8.5%)
New anti-cancer treatment started	14 (17.3%)	16 (19.5%)
Death or progression after more than one missed tumor assessment	2 (2.5%)	2 (2.4%)
Median progression-free survival in months (95% CI)	4.3 (3.0 - 5.8)	5.5 (4.2 - 5.7)
Probability of alive without progression at 3 months [a]	0.63 (0.51 - 0.73)	0.7 (0.59 - 0.79)
Probability of alive without progression at 6 months [a]	0.38 (0.26 - 0.49)	0.36 (0.25 - 0.48)
Probability of alive without progression at 9 months [a]	0.27 (0.17 - 0.39)	0.26 (0.16 - 0.37)
Probability of alive without progression at 12 months [a]	0.21 (0.12 - 0.32)	0.17 (0.08 - 0.28)
Probability of alive without progression at 15 months [a]	0.08 (0.02 - 0.2)	0.17 (0.08 - 0.28)

a Refer to Kaplan-Meier curve for the interpretation of the probability of PFS

When using investigator assessment of lesions, median PFS in the GC+tw-iniparib arm was 4.7 months (95% CI: 4.1 to 5.7 months) and 5.4 months (95% CI: 4.2 to 5.7 months) in the GC+w-iniparib arm.

Safety results:

Extent of exposure

The median number of cycles administered was 6 in both arms (range, 1 to 31 for GC+tw-iniparib; range 1 to 40 for GC+w-iniparib). There were no clinically meaningful differences in the relative dose intensity (RDI) of the 3 drugs between the 2 arms. For both arms, RDI for gemcitabine was >69%, for carboplatin >71%, and for iniparib >92%.

Adverse events

All patients in the safety population had at least 1 TEAE, and most had at least 1 event of Grade 3 or 4 (75 [93.8%] in the GC+tw-iniparib arm and 71 [86.6%] in the GC+w-iniparib arm). Thirty-two (40%) patients in the GC+tw-iniparib arm and 31 (37.8%) patients in the GC+w-iniparib arm experienced treatment-emergent SAEs. Twenty-nine (36.3%) patients in the GC+tw-iniparib arm and 28 (34.1%) patients in the GC+w-iniparib arm experienced a TEAE leading to study drug discontinuation of at least 1 drug. Nine patients (5 [6.3%] in the GC+tw-iniparib arm and 4 [4.9%] in the GC+w-iniparib arm) had TEAEs leading to death during the study.

Those TEAEs occurring in ≥20% of patients in at least 1 arm (all grades, by preferred term [PT]; GC+tw-iniparib vs GC+w-iniparib) included nausea (71.3% vs 53.7%), neutropenia (68.8% vs 62.2%), constipation (43.8% vs 37.8%), fatigue (43.8% vs 28.0%), asthenia (42.5% vs 47.6%), vomiting (37.5% vs 26.8%), leukopenia (32.5% vs 28.0%), anemia (32.5% vs 31.7%), thrombocytopenia (30.0% vs 28.0%), headache (30.0% vs 29.3%), white blood cell count decreased (28.8% vs 20.7%), decreased appetite (27.5% vs 13.4%), diarrhea (27.5% vs 22.0%), dyspnea (21.3% vs 18.3%), alopecia (21.3% vs 18.3%), myalgia (21.3% vs 7.3%), and pyrexia (20.0% vs 22.0%).

The incidence of TEAEs (all grades) of nausea, neutropenia, constipation, fatigue, vomiting, decreased white blood cell count, decreased appetite, diarrhea, myalgia, dizziness, urinary tract infection, pain in extremity, and dyspepsia was >5% higher in the GCI+tw-iniparib arm than in the GCI+w-iniparib arm. Whereas, asthenia and neck pain was >5% higher in the GCI+w-iniparib arm than in the GCI+tw-iniparib arm.

The most frequent Grade 3 or 4 TEAEs were neutropenia (67.5% in the GC+tw-iniparib arm; 61.0% in the GC+w-iniparib arm) and leukopenia (32.5% in the GC+tw-iniparib arm; 28.0% in the GC+w-iniparib arm).

Those drug-related TEAEs occurring in ≥20% of patients in the GC+tw-iniparib arm (all grades, by PT) included neutropenia (68.8%), nausea (66.3%), thrombocytopenia (30.0%), fatigue (38.8%), asthenia (35.0%), leukopenia (31.3%), anemia (30.0%), decreased white blood cell count (23.8%), vomiting (23.8%), alopecia (21.3%) and decreased appetite (20.0%). The most frequent Grade 3 or 4 drug-related TEAEs were neutropenia (67.5%), leukopenia (31.3%), and WBC decreased (22.5%).

Those drug-related TEAEs occurring in ≥20% of patients in the GC+w-iniparib arm (all grades, by PT) included neutropenia (61.0%), nausea (46.3%), asthenia (41.5%), anemia (28.0%), fatigue (26.8%), leukopenia (26.8%), thrombocytopenia (25.6%), vomiting (25.6%), and WBC decreased (20.7%). The most frequent Grade 3 or 4 drug-related TEAEs were neutropenia (59.8), leukopenia (26.8%) and WBC decreased (20.7%). The following mild events, Grade 1-2 occurred >10% in GC+tw-iniparib: decreased appetite, nausea and fatigue.

Sixty-three (38.9%) patients had at least 1 treatment-emergent SAE. The most frequently reported treatment-emergent SAEs in the GC+tw-iniparib arm were disease progression (3.8%), febrile neutropenia (2.5%), and dyspnea (2.5%). The most frequently reported treatment-emergent SAEs in the GC+w-iniparib arm were febrile neutropenia (4.9%) and pyrexia (4.9%). Serious AE incidence rates were similar between the 2 treatment arms and the difference between the 2 arms was <5% for all reported preferred terms in both treatment arms.

Fifty-seven (35.2%) patients had at least 1 TEAE leading to treatment discontinuation of at least 1 drug of the study regimen. More patients discontinued at least 1 drug in the GC+tw-iniparib arm compared with the GC+w-iniparib arm due to hematological toxicity. The most frequent TEAEs leading to discontinuation were neutropenia (16.3% and 9.8% in the GC+tw-iniparib and GC+w-iniparib arms, respectively) and thrombocytopenia (8.8% and 3.7% in the GC+tw-iniparib and GC+w-iniparib arms, respectively).

One-hundred and six (65.4%) patients died prior to the cut-off date. The cause of death in the majority of these patients (99; 61.1%) was disease progression. Four patients in each arm died while on treatment (8 patients total). Three of them (1.9%) died due to an AE; 1 patient (acute respiratory distress syndrome) in GC+w-iniparib, and 2 patients in GC+tw-iniparib (1 patient with hypoxia and 1 patient with tumor embolism). Four patients (2.5%) died due to other causes (all more than 30 days after last dose); 1 patient requested euthanasia, 1 patient died following a comma produced by a cardiac arrest, 1 patient died of a pulmonary embolism, and the cause of death was unknown for 1 patient . Only 1 patient had study drug related death (GC+w-iniparib arm), who died from acute respiratory distress syndrome.

Clinical laboratory evaluations

Grade 3 or 4 hematologic abnormalities during the treatment period included neutropenia (72.5% in GC+tw-iniparib arm; 71.6% in GC+w-iniparib arm), leukopenia (65.0% in GC+tw-iniparib arm; 53.1% in GC+w-iniparib arm), lymphopenia (37.5% in GC+tw-iniparib arm; 28.4% in GC+w-iniparib arm), thrombocytopenia (18.8% in GC+tw-iniparib arm; 18.5% in GC+w-iniparib arm), and anemia (12.5% in GC+tw-iniparib arm; 13.6% in GC+w-iniparib arm).

Grade 3 or 4 nonhematologic abnormalities during the treatment period included hyponatremia (2.5% in both arms), hyperkalemia (0.6% in the GC+w-iniparib arm only), hypercalcemia (1.3% in both arms), hypokalemia (1.3% in both arms), elevated alanine aminotransferase (20.5% in the GS+tw-iniparib arm, 12.8% in the GS+w-iniparib arm), elevated aspartate aminotransferase (10.8% in the GC+tw-iniparib arm, 8.9% in the GC+w-iniparib arm), elevated alkaline phosphatase (2.6% in the GS+tw-iniparib arm, 3.8% in the GC+w-iniparib arm), hyperbilirubinemia (1.3% in both arms), creatinine levels increased (0.6%, GC+w-iniparib arm only), and.hypoalbuminemia (2.7% in the GC+w-iniparib arm only).

Pharmakokinetic results:

Plasma concentrations of iniparib, IABM and IABA were measured used for determination of pharmacokinetic parameter estimations. These data are available upon request.

Conclusions:

[redacted]

Date of report: 24-Oct-2013