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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT01455532, UTN U1111-1118-6091 Study code: TED11746
Title of the study: A Phase 1/1b Dose Escalation Study Evaluating iniparib (BSI-201/SAR240550) as a Single Agent and in Combination with Chemotherapeutic Regimens in Patients with Solid Tumors	
Study center(s): 6 centers	
Study period: Date first patient enrolled: 11/Nov/2011 Date last patient completed: 15/Apr/2014	
Phase of development: Phase 1	

Objectives:

Primary Objective

Phase 1: To assess the safety and the maximum tolerated dose (MTD) of iniparib as a single agent in patients with advanced solid tumors that are refractory to standard therapy.

Phase 1b: To assess the safety and MTD of iniparib in combination with chemotherapeutic regimens in adult patients with advanced solid tumors.

Secondary Objectives (Phase 1 and Phase 1b):

- To assess the antitumor effect of iniparib (per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) in patients with measurable disease.
- To characterize iniparib (and its metabolites) pharmacokinetics (PK).

Exploratory objectives (Phase 1 and Phase 1b):

- To evaluate candidate biomarkers predictive of response to treatment with iniparib in archived tumor tissue, blood and/or serum.
- To assess any relationship between polymorphisms and drug metabolism and/or clinical activity.
- To evaluate pharmacodynamic (PD) biomarkers in blood.

Methodology: This was a multicenter, open-label and nonrandomized Phase 1 and 1b study of iniparib in patients with solid tumors. This study was conducted in 2 parts.

- During Phase 1, iniparib was administered in a dose-escalation fashion using the standard 3+3 design as a 1-hour intravenous (IV) infusion once weekly for 3 weeks in a 21-day cycle (Days 1, 8, and 15). The intended DLs were 15 mg, 20 mg, 26 mg, 32.5 mg, and 40 mg/kg respectively). After the appearance of dose limiting toxicities (DLT) (Grade 3 hypertension) at 26 mg/kg, protocol was amended to extend the iniparib infusion period to 2-hour IV infusion starting with the same DL and to add premedications for prevention of hypersensitivity reactions.

- During Phase 1b, iniparib was administered in a dose-escalation fashion using the standard 3+3 design as a 2-hour IV infusion once weekly for 5 planned dose-levels (15 mg, 20 mg, 26 mg, 32.5 mg, and 40 mg/kg, respectively) in combination with 2 different regimens of gemcitabine/carboplatin as described below under Study Treatments. Patients were assigned to 1 of 2 study cohorts in a nonrandomized manner dependent on the standard therapeutic regimen for their cancer. Premedication for prevention of hypersensitivity reactions was administered to all patients prior to iniparib administration (5HT3 antagonist, dexamethasone, and diphenhydramine 25 mg). The dose to be tested in Phase 1b was not to exceed the single-agent MTD.

Cycle 1 (Day 1 through Day 21) was defined as the DLT observation period.

A patient could participate in this study until he/she experienced drug intolerance, disease progression, or death. Safety, tolerability, and development of potential toxicity were assessed on an ongoing basis.

Efficacy: Evidence of antitumor activity in patients with measurable disease was assessed after every 2 cycles of treatment using RECIST Version 1.1. Computed tomography (CT), magnetic resonance imaging (MRI), or other appropriate imaging and/or clinical examination were used as defined in RECIST Version 1.1.

Number of patients:	Planned: Up to 100
	Randomized: Not applicable
	Treated: *59 (*Phase 1, 29; Phase 1b-GC2, 22; Phase 1b-GC5, 8)
Evaluated:	
	Efficacy: 59 (Phase 1, 29; Phase 1b-GC2, 22; Phase 1b-GC5, 8)
	Safety: 59 (Phase 1, 29; Phase 1b-GC2, 22; Phase 1b-GC5, 8)
	Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion: Patients eligible for inclusion were ≥18 years old with histological or cytological evidence of advanced cancer and/or metastatic disease refractory to standard therapies, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2, and adequate organ and bone marrow function. The disease was to be measurable or nonmeasurable as defined according to RECIST Version 1.1. Additionally, patients' blood pressure was to be within normal limit and well controlled as per amendment 1.

Study treatments

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

Formulation: 10 mg/mL; iniparib in 25% hydroxypropylbeta cyclodextrin/10 mM phosphate buffer, pH 7.3.

Route(s) of administration: IV

Dose regimen:

Phase 1: Initially iniparib was administered as a 1-hour IV infusion for Phase 1 monotherapy DLs 1 through 3 (15 mg, 20 mg, and 26 mg/kg weekly). After the appearance of Grade 3 hypertension meeting DLT criteria at 26 mg/kg, the protocol was amended to increase the duration of infusion to 2-hour for starting at dose-level 4 (26 mg/kg). Patients received iniparib infusions at the assigned dose-level on Day 1 of each week.

Phase 1b: Iniparib was administered on days 1 and 8 of each 21-day cycle as a 2-hour IV infusion at the assigned DL in combination with gemcitabine/carboplatin.

In both parts, the intended DLs were 15 mg, 20 mg, 26 mg, 32.5 mg, and 40 mg/kg.

Noninvestigational medicinal product(s): Gemcitabine and carboplatin were provided as marketed formulation via normal procedures at each site.

Formulation: Refer to package insert or summary of product characteristics for details.

Route(s) of administration: IV

Dose regimen:

Gemcitabine/carboplatin (GC2): Gemcitabine was administered at 1 000 mg/m² as a 0.5-hour IV infusion and carboplatin area under the curve (AUC) 2 mg/mL/min as a 1-hour IV infusion both on Days 1 and 8 in a 21-day cycle.

Gemcitabine/carboplatin (GC5): Gemcitabine was administered at 1 000 mg/m² as a 0.5-hour IV infusion on Days 1 and 8 and carboplatin AUC 5 mg/mL/min as a 1-hour IV infusion on Day 1 in a 21-day cycle.

Duration of treatment: The duration of the study for an individual patient included a screening period of up to 4 weeks, a treatment period of at least 1 cycle (3 weeks) of study treatment, and an end-of-treatment visit 30 days (± 5 days) following the last administration of investigational medicinal product). However, treatment could continue until precluded by toxicity, progression, or death.

Duration of observation: The end of study occurred when all patients had completed the end-of-treatment visit.

Criteria for evaluation: Because of the Sponsor's decision to discontinue clinical development of iniparib, this study is reported in a synoptic format and as such, only the safety results are being presented in full.

Efficacy: Efficacy was assessed by objective tumor assessments made according to the RECIST Version 1.1 of unidimensional evaluation, and treatment decisions by the Investigator were based on these assessments.

Safety: Safety, tolerability, and development of potential toxicity were assessed on an ongoing basis. Severity of adverse events (AEs) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Safety was based on the incidence of AEs and serious AEs (SAEs), concomitant medications, treatments, clinical examination (including vital signs, 12-lead electrocardiogram [ECG], and ECOG PS), and clinical laboratory tests (including complete blood count [CBC] with differential and platelets, chemistry panel).

Dose limiting toxicities were defined as any of the following events determined by the Investigator to be related to treatment with the investigational agents regardless of outcome:

- Grade 4 neutropenia (ie, absolute neutrophil count <0.5 x 109/L [<500/mm^3]) for 7 or more consecutive days, or Grade 3 febrile neutropenia (ie, a single temperature >38.3°C [101°F] or a sustained temperature of ≥38°C [100.4°F] for >1 hour with an ANC <1.0 x 109/L [<1 000/mm^3]).
- Grade 4 thrombocytopenia (ie, platelet count <25 x 109/L (<25 000/mm^3), or bleeding episode requiring platelet transfusion).
- Grade 4 hypertension; Grade 3 hypertension if duration >1 hour or associated with clinically significant symptoms in the opinion of the Investigator.
- Persistent (>24 hours) Grade 3 or greater nausea, vomiting, diarrhea, dehydration, or anorexia despite the use of adequate/maximal medical intervention.
- Any other clinically significant nonhematologic toxicity of Grade 3 or greater considered not related to underlying malignancy.
- Any toxic effect leading to a patient missing more than 1 dose of iniparib.
- Any toxic effect resulting in the delay of Cycle 2 by >14 days.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetics/Pharmacodynamics: Plasma and blood samples were collected on Days 1 and 15 following iniparib administration to assess the PK profile of iniparib and 2 metabolites, (IABM and IABA) and to evaluate any changes in gene expression profiles induced by Iniparib that could be correlated with clinical activity during Cycle 1. Analyses of the PK samples for iniparib, IABM and IABA concentrations were performed using validated LC-MS/MS methods.

Pharmacodynamics: Samples were samples were collected but not analyzed or reported.

Pharmacogenetics (PGx): At screening, a blood sample was collected to investigate allelic variants of drug metabolism enzymes or drug transporters as intrinsic factors associated with PK or PD variability of the development compound. The PGx samples were collected but not analyzed or reported. Pharmacodynamic samples were collected but not analyzed or reported.

Statistical methods:

Sample size calculation: The sample size was based primarily on clinical considerations and not on statistical power calculations.

Analysis populations:

The all treated/safety population included all patients who received at least 1 dose of iniparib single agent or in combination with chemotherapy regimen. Patients were classified in the cohort corresponding to the chemotherapy agents (if any) they actually received and were assigned to the DL corresponding to their actual starting dose of iniparib. This population was used for all safety analyses.

The evaluable for DLT population was the subset of patients from the safety population who completed the DLT observation period.

The PK population included all treated patients with available PK parameters.

General statistical approach Statistical analysis was performed separately for Phase 1 and Phase 1b. For Phase 1b, separate tables/listings were provided for each chemotherapy backbone. For each cohort (iniparib single-agent or chemotherapy backbones), tables and listings are presented overall and by DL. Descriptive statistics and listings are used to summarize patient characteristics, treatment administration, safety variables, and signs of antitumor activity.

Analysis of *pharmacokinetics:* Pharmacokinetic parameters were determined using compartmental or noncompartmental methods. Descriptive statistics were to be calculated for patients included in PK population. Plasma concentrations of iniparib and 2 metabolites are provided in a Bioanalytical report.

Summary:

Patient disposition: A total of 59 patients were enrolled and treated in this study (safety population). The single-agent iniparib Phase 1 included 29 patients, the Phase 1b-GC2 cohort 22 patients, and the Phase 1b-GC5 cohort 8 patients.

Note: One patient of the Phase 1b-GC2 cohort was treated by error with GC5 and iniparib at 20 mg/kg instead of GC2 + 20 mg/kg iniparib. This patient was dosed for 3 cycles and experienced dosing delays and dose reductions due to hematological toxicities (febrile neutropenia of Grade 4 for 1 day during Cycle 1 and thrombocytopenia of Grades 3 and 4 during Cycles 3 and 4 respectively). The patient continued with the treatment however, the dose was decreased to iniparib 15 mg/kg with only carboplatin during Cycle 4. The patient was treated for 2 additional cycles.

At time of database lock (DBL), all patients discontinued treatment and were followed for a minimum of 30 days after last dose of iniparib, gemcitabine or carboplatin. Four patients were transferred into a safety rollover protocol (LTS12674) or under a single-investigational new drug (IND) program to continue receiving treatment with iniparib.

The most common reason for treatment discontinuation in the single-agent iniparib Phase 1 was disease progression (20 [69.0%] patients). Nine (31.0%) patients were classified under “other” as reason for treatment discontinuation (including consent withdrawal, lack of efficacy and clinical progression).

In the Phase 1b-GC2 cohort, reasons for discontinuation were disease progression for 12 (54.5%) patients, “other” for 8 (36.4%) patients (including consent withdrawal, lack of clinical benefits, complete response and rolled over in LTS12674 study), and AE for 2 (9.1%) patients.

In the Phase 1b-GC5 cohort, reasons for discontinuation were disease progression for 7 (87.5%) patients and "other" for 1 (12.5%) patient (clinical progression).

No AEs leading to treatment discontinuation were reported in patients from the Phase 1 cohort or in the Phase 1b-GC5 cohort. In the Phase 1b-GC2 cohort, TEAEs leading to treatment discontinuation were reported in 2 (9.1%) patients.

Demographics and baseline characteristics: Phase 1 (single-agent): The median age of the safety population was 57.0 years (range: 35 to 79 years). Twenty-one (72.4%) patients were female. Most patients (26 [89.7%]) were white, and 3 (10.3%) African-American. Per protocol entry criteria, all patients had an ECOG PS of 0 to 2 at baseline (0: 8 [27.6%] patients, 1: 20 [69.0%] patients, or 2: 1 [3.4%] patient). At diagnosis, the most frequent primary locations were ovary for 8 [27.6%] patients and breast for 6 [20.7%] patients. All patients had metastatic disease at study entry.

Phase 1b-GC2 cohort: The median age of the safety population was 54.5 years (range: 28 to 80 years). Fourteen (63.6%) patients were female. Most patients (19 [86.4%]) were white, 2 (9.1%) patients were African-Americans, and 1 (4.5%) patient was Asian/oriental. Per protocol entry criteria, all patients had an ECOG PS of 0 to 2 at baseline (0: 9 [40.9%] patients, 1: 12 [54.5%] patients, or 2: 1 [4.5%] patient). At diagnosis, primary locations included: breast for 5 (22.7%) patients and ovary for 4 (18.2%) patients. All but 2 patients had metastatic disease at study entry.

Phase 1b-GC5 cohort: The median age of the safety population was 57.5 years (range: 31 to 69 years). Six (75.0%) patients were female. Most patients (7 [87.5%]) were white, and 1 (12.5%) patient was Native Hawaiian or other pacific islander. Per protocol entry criteria, all patients had an ECOG PS of 0 to 2 at baseline (0: 4 [50.0%] patients, 1: 4 [50.0%] patients, or 2: 0 patients). At diagnosis, primary locations included: breast for 3 [37.5%] patients and ovary for 1 (12.5%) patient. All patients had metastatic disease at study entry.

Efficacy results:

Phase 1: 0 complete response (CR), 1 (4.0%) partial response (PR), 8 (32.0%) stable disease (SD), 15 (60.0%) progressive disease, and 1 (4.0%) non-evaluable response.

Phase 1b-GC2: 1 (5.0%) CR, 4 (20.0%) PR, 14 (70.0%) SD, and 1 (5%) progressive disease.

Phase 1b-GC5: 0 CR; 2 (25.0%) PR, 5 (62.5%) SD, and 1 (12.5%) progressive disease.

Safety results:

Extent of exposure to iniparib:

Phase 1: The median number of cycles administered per patient was 2.0 (range: 1 to 24 cycles). Twenty-one (72.4%) patients received at least 2 cycles, 10 (34.5%) patients received at least 3 cycles, and 3 (10.3%) patients received at least 7 cycles. The median number of weeks on-treatment for the safety population was 6.0 weeks (range: 3 to 98 weeks).

Phase 1b-GC2: The median number of cycles administered per patient was 6.0 (range: 1 to 16 cycles). Twelve (54.5%) patients received at least 6 cycles, and 6 (27.3%) patients received at least 9 cycles. The median number of weeks on-treatment for the safety population was 22.4 weeks (range: 3 to 49 weeks).

Phase 1b-GC5: The median number of cycles administered per patient was 6.0 (range: 2 to 12 cycles). Five (62.5%) patients received at least 6 cycles, and 3 (37.5%) patients received at least 8 cycles. The median number of weeks on-treatment for the safety population was 23.4 weeks (range: 6 to 43 weeks).

Overview of adverse events:

The primary objective for this study was to assess the safety and the MTD of iniparib as a single-agent and in combination with chemotherapeutic regimens in adult patients with advanced solid tumors. Two DLTs were identified in this study: Grade 3 transient hypertension and Grade 4 thrombocytopenia (described in detail in the next section).

In the Phase 1 cohort, all 29 (100%) patients had at least 1 treatment-emergent adverse event (TEAE) and 22 (75.9%) patients had at least 1 Grade ≥3 TEAE. Treatment-related TEAEs were reported in 27 (93.1%) patients (Grade ≥3 for 18 [62.1%] patients). Treatment-emergent AEs leading to death were reported in 6 (20.7%) patients and serious TEAEs in 15 (51.7%) patients. No TEAEs leading to treatment discontinuation were reported in this group.

In the Phase 1b-GC2 cohort, all 22 (100%) patients had at least 1 TEAE and 21 (95.5%) patients had at least 1 Grade ≥3 TEAE. Treatment-related TEAE were reported in 21 (95.5%) patients (Grade ≥3 for 20 [90.9%] patients). Treatment-emergent AEs leading to death were reported in 1 (4.5%) patient and serious TEAEs in 7 (31.8%) patients. Two (9.1%) TEAEs leading to treatment discontinuation were reported in this group, both with Grade ≥3.

In the Phase 1b-GC5 cohort, all 8 (100%) patients had at least 1 TEAE and all patients had at least 1 Grade ≥3 TEAEs. Treatment-related TEAE were reported in all patients (Grade ≥3 for 7 [87.5%] patients). No TEAEs leading to death were reported and serious TEAEs were reported in 4 (50.0%) patients. No TEAEs leading to treatment discontinuation were reported in this group.

Dose Limiting Toxicities and Identification of Maximum Tolerated Dose

The protocol enrolled patients in 2 stages. In the first 1, patients were treated with iniparib single agent starting at 15 mg/kg on Days 1, 8, and 15 every 4 weeks. Grade 3 hypertension during the infusion of iniparib (see below) was defined as the DLT at 26 mg/kg. Protocol was amended to extend the infusion of iniparib to 2 hours and include premedication but Grade 3 hypertension recurred and 26m/kg was identified as the MAD. Once MTD was established as 20 mg/kg, dose-escalation was initiated with iniparib at 15 mg/kg in combination with either GC2 or GC5. In combination with GC2, iniparib was dosed up to 20 mg/kg (single agent MTD). GC5 plus iniparib 15 mg/kg was too toxic to continue the dose escalation (DLTs: Grade 4 thrombocytopenia and Grade 4 neutropenia).

Grade 3 transient hypertension 2 of 6 patients receiving single-agent iniparib at 26 mg/kg infused over 1 hour had Grade 3 transient hypertension that was considered a DLT (defined as any Grade 3 nonhematological toxicity considered related to the study drug and occurring during the first cycle of treatment). In some patients enrolled under the initial protocol, hypertension was also accompanied by symptoms suggesting drug hypersensitivity. These symptoms were chest tightness, flushing, watering eyes, oral dysesthesia, akathisia, wheezing, noncardiac right chest pain during infusion, and burning sensation. After these 2 DLTs were identified, enrollment was put on hold and the study protocol was amended (amendment 1, 09 June 2012) to extend the infusion of iniparib to 120 minutes, to add premedication and modify the DLT definition for hypertension was refined as any Grade 4 hypertension or Grade 3 hypertension of duration >1 hour or associated with clinically significant symptoms in the opinion of the investigator and related to the investigational agent. The infusion duration was also increased to 2 hours in Protocol Amendment 1. Under Protocol Amendment 1, 2 of the 4 patients dosed at 26 mg/kg iniparib over 2 hours with premedication experienced Grade 3 transient hypertension that met the criteria for DLT. Therefore, the 26 mg/kg was declared as the single-agent maximum administered dose (MAD).

According to the protocol, the MTD was defined as the highest DL at which at most 1 of 6 patients experiences a DLT. Thus, the 20 mg/kg weekly dose of single agent iniparib was declared the MTD.

After the implementation of intensive blood pressure monitoring in Protocol Amendment 1, other cases of Grade 3 hypertension not meeting DLT criteria were observed. Associated symptoms were significantly alleviated or disappeared with premedication. In most cases, when iniparib infusion was interrupted, it was also completed after symptoms recovered during the same infusion period (less than 30 minutes). None of the 10 patients discontinued the study because of hypertension. Grade 4 hypertension was not reported.

Overall, grade 3 hypertension has been reported in 14/29 patients in the Phase 1 cohort; 12/22 patients in the Phase 1b-GC2 cohort, and 2/8 patient in the Phase 1b-CG5 cohort. No case of higher than Grade 3 hypertension has been reported. Among the 28 patients with grade 3 hypertension, 12 had a history of hypertension. Three patients had hypertension events on nontreatment days. All episodes of hypertension resolved the same day following interruption of iniparib, administration of an antihypertensive medication, or spontaneously. Close monitoring of hypertension case reports was performed, including nonserious AEs and possible sequelae. At present, the mechanism of action of the drug provides no clear explanation for the transient hypertension during the infusion of iniparib.

Grade 4 thrombocytopenia and Grade 4 neutropenia were also identified as a DLT for Iniparib in combination GC5: 2 out of 6 patients treated with iniparib (15 mg/kg on Days 1 and 8), carboplatin (AUC 5 mg/mL/min on Day 1), and gemcitabine (1 000 mg/m^2 on Days 1 and 8) once weekly for 2 weeks presented with Grade 4 thrombocytopenia as a DLT. These 2 patients also presented with Grade 4 neutropenia of 7 or more consecutive days' duration (DLT as well). In addition, 1 patient in the expansion cohort treated with iniparib (20 mg/kg on Days 1 and 8), carboplatin (AUC 2 mg/mL/min on Days 1 and 8), and gemcitabine (1 000 mg/m² on Days 1 and 8) once weekly for 2 weeks presented with Grade 4 thrombocytopenia as a DLT.

Analysis of adverse events:

TEAEs reported in ≥20% of patients in the Phase 1 cohort (all grades by preferred term [PT]) were nausea (19 [65.5%] patients), vomiting (17 [58.6%] patients), fatigue (15 [51.7%] patients), hypertension (15 [51.7%] patients), constipation (10 34.5%] patients), abdominal pain (8 [27.6%] patients), diarrhea (8 [27.6%] patients), hot flush (8 [27.6%] patients), decreased appetite (6 [20.7%] patients), dyspnea (6 [20.7%] patients), flushing (6 [20.7%] patients), headache (6 [20.7%] patients), and stomatitis (6 [20.7%] patients). The 2Grade ≥3 TEAE reported in ≥10% of patients in this cohort (by PT) were hypertension (14 [48.3%] patients) and vomiting (3 [10.3%] patients).

TEAEs reported in ≥20% of patients in the Phase 1b-GC2 cohort (all grades by PT) were nausea (17 [77.3%] patients), fatigue (14 [63.6%] patients), hypertension (14 [63.6%] patients), neutropenia (10 [45.5%] patients), thrombocytopenia (10 [45.5%] patients), anemia (9 [40.9%] patients), constipation (8 [36.4%] patients), headache (8 [36.4%] patients), vomiting (7 [31.8%] patients), stomatitis (6 [27.3%] patients), chills (5 [22.7%] patients), flushing (5[22.7%] patients) and myalgia (5 [22.7%] patients). Grade ≥3 TEAE reported in ≥10% of patients (excluding single patients) in this cohort (by PT) were: hypertension (12 [54.5%] patients), neutropenia (9 [40.9%] patients), anemia (5 [22.7%] patients), and thrombocytopenia (6 [27.3%] patients).

Treatment-emergent AEs reported in ≥20% of patients in the Phase 1b-GC5 cohort (all grades by PT) were anemia (8 [100%] patients), neutropenia (7 [87.5%] patients), thrombocytopenia (7 [87.5%] patients), nausea (5 [62.5%] patients), diarrhea (4 [50.0%] patients), rash (4 [50.0%] patients, vomiting (4 [50.0%] patients), fatigue (3[37.5%] patients), headache (3 [37.5%] patients), hypertension (3 [37.5%] patients), white blood cell count decreased (3 [37.5%] patients), constipation (2 [25.0%] patients), decreased appetite (2 [25.0%] patients), neutrophil count decreased (2 [25.0%] patients), platelet count decreased (2 [25.0%] patients pruritus (2 [25.0%] patients), and pyrexia (2 [25.0%] patients). Grade ≥3 TEAE reported in ≥10% of patients (excluding single patients) in this cohort (by PT) were: thrombocytopenia (7 [87.5%] patients), neutropenia (5 [62.5%] patients), anemia (4 [50%] patients), hypertension (2 [25.0%] patients), nausea (2 [25.0%] patients), neutrophil count decreased (2 [25.0%] patients), vomiting (2 [25.0%] patients), and white blood cell count decreased (2 [25.0%] patients).

Treatment-related TEAEs

Treatment-related TEAEs reported in ≥20% of patients in the Phase 1 cohort (all grades by PT) were: hypertension (15 [51.7%] patients), nausea (15 [51.7%] patients), vomiting (14 [48.3%] patients), fatigue (8 [27.6%] patients), flushing (6 [20.7%) patients], and hot flush (6 [20.7%] patients). The only treatment-related TEAE of Grade ≥3 reported in ≥10% of patients (by PT) were hypertension (14 [48.3%] patients), and vomiting (3 [10.3%] patients).

Treatment-related TEAEs reported in ≥20% of patients (all grades by PT) in the Phase 1b-GC2 cohort were: nausea (15 [68.2%] patients), hypertension (14 [63.6%] patients), fatigue (13 [59.1%] patients), thrombocytopenia (9 [40.9%] patients), anemia(8 [36.4%] patients), headache (7 [31.8%] patients), neutropenia (6 [27.3%] patients), vomiting (6 [27.3%] patients), stomatitis (5 [22.7%] patients). The only treatment-related TEAE of Grade ≥3 reported in ≥10% of patients (by PT) were: hypertension (12 [54.5%] patients), thrombocytopenia (6 [27.3%] patients), neutropenia (5 [22.7%] patients), and anemia (4 [18.2%] patients).

Treatment-related TEAEs reported in ≥20% of patients (all grades by PT) in the Phase 1b-GC5 cohort were: thrombocytopenia (6 [75.0%] patients), neutropenia (5 [62.5%] patients), anemia (5 [62.5%] patients), nausea (3 [37.5%] patients), hypertension (3 [37.5%] patients), fatigue (3 [37.5%] patients), vomiting (3 [37.5%] patients), diarrhea (3 [37.5%] patients), rash (3 [37.5%] patients), decreased appetite (2 [25.0%] patients), pruritus (2 [25.0%] patients), neutrophil count decreased (2 [25.0%] patients), platelet count decreased (2 [25.0%] patients), and white blood cell count decreased (2 [25.0%] patients). The only treatment-related TEAE of Grade ≥3 reported in ≥10% of patients (by PT) were: thrombocytopenia (6 [75.0%] patients), anemia (4 [50.0%] patients), neutropenia (3 [37.5%] patients), hypertension (2 [25.0%] patients), nausea (1 [12.5%] patients), neutrophil count decreased (2 [25.0%] patients), white blood cell count decreased (2 [25.0%] patients), fatigue (1[12.5%] patients), platelet count decreased (1 [12.5%] patients), and vomiting (1 [12.5%] patients).

Deaths and adverse events with a fatal outcome:

In Phase 1, 5 patients died during the treatment period, and 2 died during the posttreatment period. In Phase 1b-CG2, 1 (4.5%) patient died during the on-treatment period. No deaths were reported in the Phase 1b-GC5 cohort. Cause of death was disease progression in all cases.

There were a total of 8 patients with TEAE that led to death, 7 in Phase 1 cohort, and 1 in the Phase 1b CG2 cohort. For 1 patient, the outcome of death of the TEAE Disease progression occurred more than 30 days after last dose. The reported PT was disease progression for 4 patients, general physical health deterioration for 2 patients, and dyspnea for 1 patient. All fatal TEAEs were considered to not be related to study treatment per investigator judgment. For 1 patient, no fatal AE was provided since death occurred more than 30 days after last dose.

Serious TEAEs:

In the Phase 1 cohort, at least 1 SAE (all grades) was reported in 15 (51.7%) patients; 14 (43.8%) patients had at least 1 Grade ≥3 SAE. The most frequently (≥2 patients) reported SAEs (by PT) were hypertension (all grades: 2 [6.9%] patients; Grade ≥3: 2 [6.9%] patients), disease progression (all grades: 3 [10.3%] patients; Grade ≥3: 2 [6.9%] patients), and general physical health deterioration (all grades: 2 [6.9%] patients; Grade ≥3: 2 [6.9%] patients).

In the Phase 1b-GC2 cohort at least 1 SAE (all grades) was reported in 7 (31.8%) patients; 6 (27.3%) patients had at least 1 Grade ≥3 SAE. The most frequently (≥2 patients) reported SAEs (by PT) were thrombocytopenia (all grades: 2 [9.1%] patients; Grade ≥3: 2 [9.1%] patients), and abdominal pain (all grades: 2 [9.1%] patients; Grade ≥3: 1 [4.5%] patients).

In the Phase 1b-GC5 cohort at least 1 SAE (all grades) was reported in 4 (50.0%) patients; 3 (37.5%) patients had at least 1 Grade ≥3 SAE. In this cohort, no SAE (by PT) was reported in 2 or more patients.

Serious treatment-related TEAEs:

In the Phase 1 cohort, at least 1 treatment-related SAE (all grades) was reported in 4 [13.8%] patients (hypertension [2], hypoxia, and vomiting) and 3 [10.3%] patients had at least 1 treatment-related SAE of Grade ≥3 (hypertension [2], and vomiting). Outcomes of related treatment-emergent SAEs are described in patient narratives.

In the Phase 1b-GC2 cohort, 2 (9.1%) serious treatment-related TEAE were reported (1 thrombocytopenia [Grade ≥3] and 1 pleuritic pain). No serious treatment-related TEAEs were reported in the Phase 1b-GC5 cohort.

Adverse events leading to discontinuation of study treatment:

No AEs leading to treatment discontinuation were reported in patients from the Phase 1 cohort or in the Phase 1b-GC5 cohort. In the Phase 1b-GC2 cohort, TEAEs leading to treatment discontinuation were reported in 2 (9.1%) patients. Two events of Grade ≥3 (thrombocytopenia and duodenal obstruction) were reported.

Analysis of laboratory results:

Hematologic laboratory parameters:

Hematologic laboratory abnormalities in the Phase 1 cohort during the on-treatment period included: anemia (all grades: 22 of 29 [75.9%] patients; Grade ≥3: none), leukopenia (all grades: 8 of 29 [27.6%] patients; Grade ≥3: none), lymphopenia (all grades: 20 of 29 [69.0%] patients; Grade ≥3: 10 of 29 [34.5%] patients), and thrombocytopenia (all grades: 5 of 29 [17.2%] patients; Grade ≥3: 1 of 29 [3.4%] patients).

In Phase 1b-GC2 and GC5 cohorts, hematologic laboratory abnormalities during the on-treatment period included: anemia (all grades: all patients; Grade ≥3: 6 of 22 [27.3%] and 5 of 8 [62.5%] patients respectively), leukopenia (all grades: all patients; Grade ≥3: 11 of 22 [50.0%] and 5 of 8 [62.5%] patients respectively), lymphopenia (all grades: 18 of 22 [81.8%] and 7 of 8 [87.5%] patients respectively; Grade ≥3: 8 of 22 [36.4%] and 3 of 8 [37.5%] patients respectively), neutropenia (all grades: 20 [90.9%] and all 8 of 8 [100.0%] patients respectively; Grade ≥3: 16 of 22 [72.7%] and 8 of 8 [100.0%] patients respectively), and thrombocytopenia (all grades: 20 of 22 [90.9%] and 8 of 8 [100.0%] patients respectively; Grade ≥3: 10 of 22 [45.5%] and 8 of 8 [100.0%] patients respectively).

Non hematologic laboratory parameters (liver and renal function):

Liver and renal function laboratory abnormalities in the Phase 1 cohort during the on-treatment period included: alkaline phosphatase (all grades: 13 of 25 [52.0%] patients; Grade ≥3: none), elevated alanine aminotransferase (all grades: 10 of 25 [40.0%] patients; Grade ≥3: 1 of 25 [4.0%] patients), elevated aspartate aminotransferase (all grades: 14 of 25 [56.0%] patients; Grade ≥3: 1 of 25[4.0%] patients), hyperbilirubinemia (all grades: 2 of 25 [8.0%] patients; Grade ≥3: none), and creatinine (all grades: 6 of 25 [24.%] patients; Grade ≥3: none).

In Phase 1b-GC2 and GC5 cohorts, liver and renal function laboratory abnormalities during the on-treatment period included: alkaline phosphatase (all grades: 12 of 20 [60.0%] and 4 of 8 [50.0%] patients respectively; Grade ≥3: 1 of 20 [5.0%] and 1 of 8 [12.5%] patient respectively), elevated alanine aminotransferase (all grades: 9 of 20 [45.0%] and 4 of 8 [50.0%] patients respectively; Grade ≥3: 1 of 20 [5.0%] and 1 of 8 [12.5%] patient respectively), elevated aspartate aminotransferase (all grades: 10 of 20 [50.0%] and 5 of 8 [62.5%] patients respectively; Grade ≥3: none), hyperbilirubinemia (all grades: 2 of 8 [25.0%] patients for the GC-5 cohort only; Grade ≥3: none), and creatinine (all grades: 8 of 20 [40.0%] and 1 of 8 [12.5%] patients respectively; Grade ≥3: 5 of 20 [25.0%] patients for the GC-2 cohort only).

Non hematologic laboratory parameters (electrolytes):

Electrolyte laboratory abnormalities in the Phase 1 cohort during the on-treatment period included: hypocalcemia (all grades: 11 of 25 [44.0%] patients; Grade ≥3: 1 of 25 [4.0%] patients), hyperkalemia (all grades: 1 of 25 [4.0%] patients; Grade ≥3: none), hypokalemia (all grades: 3 of 25 [12.0%] patients; Grade ≥3: none), hypernatremia (all grades: 2 of 25 [8.0%] patients; Grade ≥3: none), hyponatremia (all grades: 5 of 25 [20.0%] patients; Grade ≥3: 1 of 25 [4.0%] patients), and hypoalbuminemia (all grades: 15 of 25 [60.0%] patients; Grade ≥3: none).

In Phase 1b-GC2 and GC5 cohorts, electrolyte laboratory abnormalities during the on-treatment period included: hypocalcemia (all grades: 9 of 20 [45.0%] and 2 of 8 [25.0%] patients respectively; Grade ≥3: none), hypokalemia (all grades: 5 of 20 [25.0%] and 4 of 8 [50.0%] patients respectively; Grade ≥3: 2 of 8 [25.0%] patients for the GC-5 cohort only), hypernatremia (all grades: 2 of 20 [10.0%] patients and 2 of 8 [25.0%] patients respectively; Grade ≥3: none), hyponatremia (all grades: 2 of 20 [10.0%] patients and 2 of 8 [25.0%] patients respectively; Grade ≥3: none), and hypoalbuminemia (all grades: 7 of 20 [35.0%] patients and 4 of 8 [50.0%] patients respectively; Grade ≥3: none).

Analysis of vital signs:

Potentially clinically significant abnormality (PCSA) in systolic blood pressure (≥160 mmHg and increase from baseline ≥ 20 mmHg) occurred in all treatment groups and at all DLs during the treatment period; 15 of 29 (51.7%) patients in the Phase 1 cohort, 12 of 22 (54.5%) patients in the Phase 1b-GC2 cohort, and 6 of 8 (75.0%) patients in the Phase 1b-GC5 cohort. No other PCSA on vital sign occurred in more than 20% of the patients in the single-agent iniparib Phase 1 cohort and GC2 cohort. Heart rate PCSA (≥120 bpm and increase from baseline ≥20 bpm) was observed in 5 (17.2%) patients in GC5 cohort.

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