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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00422682 Study code: TCD11484
Title of the study: A Phase 1B, Open-label, Dose Escalation Study Evaluating the Safety of BSI-201 in Combination with Chemotherapeutic Regimens in Subjects with Advanced Solid Tumors (Dose Escalation Phase)	
Study center(s): 8 study centers in the United States	
Study period: Date first patient enrolled: 08/Jan/2007 Date last patient completed: 09/Jan/2009	
Phase of development: 1B	

Objectives of the dose escalation phase:

This report includes the results of the dose-escalation Phase of the study. The results of the concentration Phase of the study will be presented in a separate report.

Primary

- To assess the safety and establish the maximum tolerated dose of the combination of iniparib with standard chemotherapeutic regimens in adult patients with histologically-documented advanced solid tumors.

Secondary

- To evaluate the response in study patients with measurable disease (per Response Evaluation Criteria In Solid Tumors [RECIST] criteria).
- To assess safety profiles: significant laboratory changes and adverse events (AEs) not defined as a dose-limiting toxicity.

Exploratory

- To assess the extent and duration of poly (adenosine diphosphate [ADP]-ribose) polymerase 1 (PARP1) inhibition with combination therapy.
- To assess the relationship between breast cancer gene (BRCA) status and response in patients with breast and/or ovarian cancer.

Methodology: This was a Phase 1B, open-label, nonrandomized, multicenter sequential dose-escalation study designed to determine the safety and maximum tolerated dose of iniparib in combination with fixed doses of 4 chemotherapeutic regimens (topotecan, temozolomide, gemcitabine, or carboplatin/paclitaxel) in patients with advanced solid tumors. Patients may have started the chemotherapeutic regimen before study entry. Iniparib was to be administered intravenously twice weekly (Day 1 and Day 4 of each week) for the duration of the study. For this dose-escalation Phase of the study, Cycle 1 was defined as the safety portion of the treatment period, during which the maximum tolerated dose of the combination was to be determined. The remainder of the treatment period was termed the maintenance Phase. Patients could participate in this study until they experienced drug intolerance or progressive disease (PD). Safety assessments followed the guidelines provided in the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, dated December 2003. The first assessment of tumor response, for those patients with measurable disease, was performed after 2 cycles of treatment. Subsequent measures of tumor response were performed after every 2 cycles (every 6 or 8 weeks depending on study arm). RECIST version 1.0 was used to establish disease response or progression. For nonmeasurable disease, best medical practices were used to determine time of PD.
Number of patients: Planned: 72 Treated: 69 Evaluated: Efficacy: 69 Safety: 69
Diagnosis and criteria for inclusion: Adult patients with histologically- or cytologically-documented advanced solid tumor; an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of ≤1; an absolute neutrophil count ≥1.5 x 109/L (without granulocyte-colony stimulating factor [G-CSF] support within 2 weeks of study Day 1), platelet count ≥100.0 x 109/L (without transfusion within 2 weeks of study Day 1), and hemoglobin ≥9.0 g/dL (erythropoietic agents allowed); and any prior toxicity from prior chemotherapeutic treatment recovered to ≤ Grade 1.
Study treatments Investigational medicinal product(s): Iniparib (BSI-201, SAR240550) Route(s) of administration: Intravenous (IV) infusion over 2 hours, twice weekly Dose regimen: 2 mg/kg starting dose
Combination therapy: Topotecan Dose: The initial dose of 1.5 mg/m^2 was decreased to 1.1 mg/m^2 upon the decision of the safety monitoring committee after the occurrence of 2 dose-limiting toxicities of Grade 4 thrombocytopenia Administration: IV infusion over 30 minutes, once daily (OD) for 5 days every 21 days

Temozolomide

Dose: 75 mg/m^2

Administration: Orally OD for 21 days each 28-day cycle

Gemcitabine

Dose: 1000 mg/m^2

Administration: IV infusion over 30 minutes, once weekly for 7 weeks; 1 week treatment-free; subsequent treatment 3 consecutive weeks out of 4

Carboplatin/paclitaxel

Dose: Carboplatin AUC of 6.0 mg/mL*min; paclitaxel 200 mg/m^2

Administration: Carboplatin IV infusion over 1 hour on Day 1; paclitaxel IV infusion over 3 hours on Day 1;

repeat both drugs every 21 days

Duration of treatment: Until drug intolerance or PD

Duration of observation: 30 (±7) days after last dose of iniparib

Criteria for evaluation:

Efficacy: Measurable target lesions, measurable nontarget lesions, and nonmeasurable nontarget lesions were evaluated. Tumor response was evaluated according to modified RECIST version 1.0 criteria.

Safety: Safety was assessed by evaluating vital signs, clinical laboratory assessments, electrocardiogram (ECG), ECOG-PS, physical examination, recording of concomitant medications, and recording of AEs graded according to CTCAE Version 3.0 and coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0.

Dose-limiting toxicity was defined as any Grade 3 or 4 or severe hematological or nonhematological toxicity during the initial 28 days of study. However, for the events of fatigue, nausea, diarrhea, vomiting, neutropenia, febrile neutropenia, thrombocytopenia, anemia, hypertension, increased aspartate aminotransferase (AST), and increased alanine aminotransferase (ALT), dose-limiting toxicity was defined as follows:

- Grade 3 fatigue, persistent for more than 7 days;
- Grade 3 or 4 nausea, diarrhea, and/or vomiting despite maximum supportive care;
- Grade 3 or 4 neutropenia with fever greater than 38.5°C;
- Grade 4 neutropenia (absolute neutrophil count less than 0.5 x 109/L) for more than 7 days;
- Grade 4 thrombocytopenia (platelet count less than 25.0 x 109/L);
- Grade 4 anemia;
- Grade 4 hypertension despite antihypertensive medications;
- Grade change greater than 2 from baseline for AST or ALT;

Maximum tolerated dose was defined as the highest dose level with an observed incidence of a dose-limiting toxicity in less than 33% of the patients enrolled in the cohort.

Statistical methods:

Results from the dose-escalation Phase of the study were assessed as follows: All patients who received at least 1 dose of study drug were included in all the analyses.

Baseline demographics and patient disposition: Descriptive statistics were provided for demographics (age, sex, and race) and baseline disease characteristics. The number of patients who enrolled in the study, received study treatment, prematurely withdrew from the study (and reasons for the withdrawal), or died, are summarized by treatment arm and dose level.

Safety: Treatment-emergent adverse events (TEAEs) were defined as AEs occurring after the first dose of study drug until 30 days after the last dose of study drug or until another antitumor treatment was initiated, whichever occurred first.

The number and percent of patients reporting TEAEs (all, serious, and related) were tabulated by study arm, cohort, and overall. All AEs were listed by patient. All deaths, serious adverse events (SAEs), and AEs leading to study drug discontinuation were listed.

Efficacy: Best overall response was listed for each patient.

Summary:

Efficacy results: Results from the evaluation of best overall response during the dose-escalation Phase were as follows:

- Complete response in 1 patient in the carboplatin/paclitaxel arm (2 mg/kg iniparib);
- Partial response in 5 patients: 1 patient in the topotecan arm (4 mg/kg iniparib), 2 patients in the gemcitabine arm (4 mg/kg iniparib) and 2 patients in the carboplatin/paclitaxel arm (2 mg/kg iniparib);
- Stable disease (through Cycle 6) in 11 patients: 2 patients in the topotecan arm (2 mg/kg and 2.8 mg/kg iniparib), 1 patient in the temozolomide arm (8 mg/kg iniparib), 3 patients in the gemcitabine arm (2.8 mg/kg and 5.6 mg/kg iniparib), and 5 patients in the carboplatin/paclitaxel arm (2.8 mg/kg, 4 mg/kg, and 5.6 mg/kg iniparib);

Safety results: A total of 260 cycles of treatment were administered to 69 patients. The median number of cycles administered varied across study arms (topotecan: 2.0 [range: 1 to 7]; temozolomide: 2.0 [range: 1 to 6]; gemcitabine: 3.0 [range: 1 to 14]; carboplatin/paclitaxel: 5.5 [range: 1 to 13]).

Grade 4 thrombocytopenia was reported as the dose-limiting toxicity in the topotecan and gemcitabine arms. Grade 4 neutropenia was reported as the dose-limiting toxicity in the carboplatin/paclitaxel arm. There was no dose-limiting toxicity observed in the temozolomide arm.

All but 1 patient (98.6%) experienced at least 1 TEAE and most patients (68.1%) experienced a Grade 3 to 5 TEAE. In all arms, there was no apparent relationship between iniparib dose and the incidence of TEAEs.

- In the topotecan arm, the most common TEAEs were fatigue (71.4% all grade; 14.3% Grade 3 to 5), neutropenia (64.3% all grade; 42.9% Grade 3 to 5), diarrhea (64.3% all grade; 0% Grade 3 to 5), anemia (50.0% all grade; 21.4% Grade 3 to 5), nausea (42.9% all grade; 0% Grade 3 to 5), and vomiting (42.9% all grade; 0% Grade 3 to 5).
- In the temozolomide arm, the most common TEAEs were nausea (55.6% all grade; 0% Grade 3 to 5), vomiting (38.9% all grade; 0% Grade 3 to 5), fatigue (33.3% all grade; 0% Grade 3 to 5), dyspnea (22.2% all grade; 11.1% Grade 3 to 5), and anorexia (22.2% all grade; 0% Grade 3 to 5).
- In the gemcitabine arm, the most common TEAEs were nausea (56.5% all grade; 0% Grade 3 to 5), fatigue (47.8% all grade; 0% Grade 3 to 5), thrombocytopenia (43.5% all grade; 30.4% Grade 3 to 5), vomiting (34.8% all grade; 0% Grade 3 to 5), anemia (34.8% all grade; 13.0% Grade 3 to 5), and neutropenia (34.8% all grade; 26.1% Grade 3 to 5).
- In the carboplatin/paclitaxel arm, the most common TEAEs were neutropenia (92.9% all grade; 64.3% Grade 3 to 5), fatigue (78.6% all grade; 7.1% Grade 3 to 5), dysgeusia (64.3% all grade; 0% Grade 3 to 5), alopecia (64.3% all grade), and nausea (57.1% all grade; 0% Grade 3 to 5).

Fifty-six patients (81.2%) experienced a TEAE that was assessed by the Investigator as treatment-related.

Eleven patients died during the study (3, 4, 3, and 1 patient in the topotecan, temozolomide, gemcitabine, and carboplatin/paclitaxel groups, respectively); all deaths were considered either unlikely to be related or not related to study drug. One patient in the topotecan arm (dyspnea), 3 patients in the temozolomide arm (disease progression and metastasis), and 1 patient in the gemcitabine arm (disease progression) died within 30 days of the last dose, and all deaths were reported as a serious TEAE. Six additional deaths occurred more than 30 days after the last infusion of study drugs; all were from PD.

Serious TEAEs were reported in 27 patients, and were associated primarily with respiratory, thoracic and mediastinal disorders; neoplasms benign, malignant and unspecified; blood and lymphatic system disorders (eg, thrombocytopenia and neutropenia); gastrointestinal disorders; and infections and infestations. Five patients experienced 8 serious TEAEs that were deemed by the Investigator to be possibly related to study drug.

- In the topotecan arm, 8 patients experienced 11 serious TEAEs, including 1 deemed to be possibly related to study drug, 1 that resulted in study drug discontinuation, and 2 that resulted in a dose delay.
- In the temozolomide arm, 5 patients experienced 5 serious TEAEs. None were considered to be related to study drug; 1 event resulted in a dose delay.
- In the gemcitabine arm, 9 patients experienced 23 serious TEAEs, including 5 deemed to be possibly related to study drug. None of the serious TEAEs resulted in study drug discontinuation; 10 events resulted in dose delays for 6 patients.
- In the carboplatin/paclitaxel arm, 5 patients experienced 8 serious TEAEs, including 2 deemed to be possibly related to study drug. One resulted in study drug discontinuation, and 2 resulted in a dose delay.

Nine patients (3, 1, 1, and 4 patients in the topotecan, temozolomide, gemcitabine, and carboplatin/paclitaxel arms, respectively) experienced 9 TEAEs that resulted in discontinuation of study treatment.

Hematological abnormalities were common, as were Grade 3 to 4 hematological abnormalities (except in the temozolomide arm). There were no deaths from hematological complications. The incidence of Grade 3 to 4 biochemical abnormalities was low (less than 10% of patients in any treatment arm). Grade 3 to 4 hyperglycemia occurred in 2 patients (14.3%) in the carboplatin/paclitaxel arm, and Grade 3 to 4 elevated alkaline phosphatase (ALP) and elevated total bilirubin both occurred in 2 patients (14.3%) in the topotecan arm.

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Sponsor / Company: Sanofi Drug substance(s): SAR240550 (iniparib)	Study Identifiers: NCT00422682 Study code: TCD11484
Title of the study: A Phase 1B, Open-Label, Dose Escalation Study Evaluating the Safety of BSI-201 in Combination with Chemotherapeutic Regimens in Subjects with Advanced Solid Tumors (Concentration Phase)	
Study center(s): 8 study centers in the United States	
Study period: Date first patient enrolled: 17/Apr/2008 Study data cutoff date: 12/Sep/2011 (primary analysis); 01/Oct/2012 (last visit for last ongoing patient at time of primary analysis)	
Phase of development: Phase 1b, Part 2 (results of Part 1 [dose-escalation Phase] have been reported in separate study report)	

Objectives:

The primary study objective was as follows:

- To evaluate the response in study patients (per Response Evaluation Criteria in Solid Tumors [RECIST]) with measurable disease, dosed with a fixed-combination (iniparib plus chemotherapeutic agent regimen) dose level.

The secondary study objective was as follows:

- To assess safety profiles: significant laboratory changes and adverse events (AEs).

The exploratory study objectives were as follows:

- To assess the extent and duration of poly (ADP-ribose) polymerase (PARP) inhibition with combination therapy.
- To assess the relationship between breast cancer gene (BRCA) status and response in patients with pancreatic or ovarian cancer.

Methodology: The present report presents the cohort expansion (Part 2; concentration phase) of study 20060102 (TCD11484). The results of Part 1 (dose-escalation Phase) of the study have been presented in a separate study report.

The primary objective of this multicenter, open-label, nonrandomized, parallel group study was to evaluate the response rate in cancer patients with measurable disease. Based on the results of the dose-escalation in Part 1, a fixed-combination of iniparib plus a chemotherapeutic agent, as follows, was to be investigated in selected tumor types in Part 2 of the study:

- TOP + I: topotecan (intravenously [IV] every day for 5 days at 1.1 mg/m^2 in Cycle 1 [and then at 1.5 mg/m^2 in subsequent cycles if tolerated]) plus iniparib (IV twice weekly for 2 weeks [Days 1, 4, 8, and 11] at 5.6 mg/kg) in each 21-day cycle in patients with advanced ovarian cancer;
- TEM + I: temozolomide (orally [PO] every day for 21 days at 75 mg/m^2) plus iniparib (IV twice weekly for 3 weeks [Days 1, 4, 8, 11, 15, and 18] at 5.6 mg/kg) in each 28-day cycle in patients with sarcoma;
- G + I: gemcitabine (IV once weekly for 3 weeks at 1000 mg/m^2) plus iniparib (IV twice weekly for 3 weeks [Days 1, 4, 8, 11, 15, and 18] at 5.6 mg/kg) in each 28-day cycle in patients with BRCA-associated pancreatic cancer;
- C + P + I: carboplatin (IV on Day 1 at AUC = 6) plus paclitaxel (IV on Day 1 at 200 mg/m^2) plus iniparib (IV twice weekly for 2 weeks [Days 1, 4, 8, and 11] at 5.6 mg/kg) in each 21-day cycle in patients with non-small cell lung cancer (NSCLC);

Adverse events were collected and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE), Version 3.0, dated December 2003. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiograms (ECG), and laboratory safety tests (including chemistry, hematology, and coagulation parameters) were obtained prior to drug administration and at designated intervals throughout the study.

The first scheduled tumor response assessment for measurable disease was to be performed after 2 cycles of treatment and every 2 cycles (every 6 weeks or every 8 weeks depending on study arm) thereafter. RECIST, Version 1.0 (see Protocol Appendix D [Appendix 14.1.1]), was to be used to establish disease progression and to determine the overall response at each time point (the same technique used during screening was to be used for all subsequent tumor assessments). For nonmeasurable disease, best medical practices were to be used to determine disease progression.

Number of patients:	Planned: 80
	Treated: 68 (TOP + I: 19; TEM + I: 21; G + I: 10; C + P + I: 18)
Evaluated:	
	Efficacy: 66
	Safety: 68

Diagnosis and criteria for inclusion: Adult patients who had an ECOG score of ≤1; who had an absolute neutrophil count (ANC) ≥1.5 x 109/L (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks of study Day 1), platelet count ≥100.0 x 109/L (without transfusion within 2 weeks of study Day 1), and hemoglobin ≥9.0 g/dL (erythropoietic agents allowed); who had recovered to ≤Grade 1 from any prior toxicity from effects of recent surgery, radiotherapy, or other therapy; who had documented cancer of 1 of the following types: a) histologically confirmed advanced (stage III or IV), persistent, or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with documented disease progression [TOP + I cohort], b) advanced, metastatic, or recurrent sarcoma [TEM + I cohort], c) histologically or cytologically confirmed adenocarcinoma of the pancreas of any stage [G + I cohort], or d) histologically or cytologically confirmed stage IIIB (with pleural effusion) or stage IV NSCLC that was not amenable to curative therapy (either surgery or radiation therapy) [C + P + I cohort]; and who met all other inclusion criteria and fail 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) as follows (for all patients):

- with topotecan: IV twice weekly for 2 weeks (Days 1, 4, 8, and 11) in 21-day cycle;
- with temozolomide: IV twice weekly for 3 weeks (Days 1, 4, 8, 11, 15, and 18) in 28-day cycle;
- with gemcitabine: IV twice weekly for 3 weeks (Days 1, 4, 8, 11, 15, and 18) in 28-day cycle;
- with carboplatin/paclitaxel: IV twice weekly for 2 weeks (Days 1, 4, 8, and 11) in 21-day cycle.

Dose regimen: 5.6 mg/kg

Reference therapy:

Product: topotecan

Dose: 1.1 mg/m^2 in Cycle 1; 1.5 mg/m_2 in subsequent cycles if tolerated

Administration: IV (over 30 minutes) every day for 5 days in each 21-day cycle (in patients with advanced ovarian cancer only)

Product: temozolomide

Dose: 75 mg/m^2

Administration: PO every day for 21 days in each 28-day cycle (in patients with sarcoma only)

Product: gemcitabine

Dose: 1000 mg/m^2

Administration: IV (over 30-100 min) once weekly for 3 weeks in each 28-day cycle (in patients with BRCA-associated pancreatic cancer only)

Product: carboplatin

Dose: AUC = 6

Administration: IV (over 1 hour) on Day 1 of each 21-day cycle (in patients with NSCLC only)

Product: paclitaxel

Dose: 200 mg/m^2

Administration: IV (over 3 hours) on Day 1 of each 21-day cycle (in patients with NSCLC only)

Duration of treatment: Until drug intolerance or disease progression

Duration of observation: Approximately 24 weeks of treatment with study medication and 30 days of follow-up

Criteria for evaluation:

Efficacy: Tumor response was evaluated according to RECIST Version 1.0 criteria. Measurable target lesions, measurable nontarget lesions, and nonmeasurable nontarget lesions were evaluated at screening, every 2 cycles (every 6 or 8 weeks depending on study arm) thereafter, and at the end of study (EOS) visit only if not done within 30 days prior to the last dose of iniparib. 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 variable was best overall response recorded from the start of the treatment until progressive disease (PD)/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment depended on the achievement of both measurement and confirmation criteria.

Safety: Safety evaluations included vital signs, physical examinations, laboratory safety tests (including chemistry, hematology, and coagulation parameters), ECG, ECOG, and recording of concomitant medications. Adverse events were collected and graded according to NCI-CTCAE, Version 3.0, dated December 2003.

Biomarkers: The extent and duration of PARP inhibition and the relationship between BRCA status and response in patients with pancreatic or ovarian cancer with combination therapy (iniparib plus protocol-specified chemotherapeutic agent) were planned to be assessed as exploratory variables during the study. The PARP assay had never been validated as a pharmacodynamic tool to assess the activity of iniparib and subsequent studies indicated iniparib was not a potent inhibitor of PARP enzyme activity at pharmacologic concentrations. Thus, no biomarker data are presented in this report. BRCA status (if not already known) was to be obtained for patients with ovarian cancer (patients who refused to sign the separate informed consent for this testing were still allowed to participate in the study). BRCA status (if not already known) for patients with pancreatic cancer was required. For patients of Ashkenazi Jewish descent, the Ashkenazi Jewish mutation panel was to be tested; if negative, the full screening panel may then have been performed at the investigator's discretion. For all other patients, the full genes (BRCA1 and 2) were to be sequenced.

Statistical methods: All analyses were performed by cohort on the safety population, which consisted of all patients who received any study drug(s).

Demographics/baseline characteristics and patient disposition: Demographics (age, sex, and race) and other baseline disease characteristics were to be summarized using descriptive statistics. Medical history and BRCA mutations were presented in listings for each patient. History of current malignancy and anticancer treatment history were summarized and presented in by-patient listings. Prior and concomitant medications were coded using the World Health Organization Drug Dictionary (version 2009MAR) and were summarized by anatomic class and therapeutic class. The number of patients who were enrolled in the trial, received study drug, and reasons for treatment discontinuation were to be summarized by study arm.

Safety analyses: Treatment-emergent adverse events (TEAE) were defined as AEs occurring after the initial dose of the study drug until 30 days after the last dose of the study drug or until a nonstudy tumor treatment was initiated, whichever occurred first. Patient incidence rates of all TEAEs were tabulated by SOC and PT according to MedDRA, version 12.0, by maximum grade, as well as by relationship to either or both treatments. The number and percentage of patients reporting TEAEs (all, serious, and related) were tabulated by study arm. All AEs were listed by patient. All deaths, serious adverse events (SAE), and AEs leading to study drug discontinuation were listed. Hematology and chemistry results were graded according to the NCI-CTCAE, Version 3.0, when applicable. The number and percentage of patients with laboratory abnormalities using the worst grade during the ontreatment period were provided by treatment group. Laboratory abnormalities at baseline were also summarized by treatment arm. Physical examination findings, vital signs, ECG, and ECOG performance status were presented in listings for each patient.

Exploratory/biomarker analyses: The extent and duration of PARP inhibition with combination therapy (iniparib plus protocolspecified chemotherapeutic agent) was planned to be assessed as an exploratory variable during the study. The PARP assay had never been validated as a pharmacodynamic tool to assess the activity of iniparib and subsequent studies indicated iniparib was not a potent inhibitor of PARP enzyme activity at pharmacologic concentrations. Thus, no biomarker data are presented in this report. In the subgroup of patients with ovarian cancer, the response rates in patients with and without BRCA mutations was to be compared using the 2-sided Fisher exact test at the 5% level of significance. Due to sparse data, however, these analyses were not performed, and BRCA mutation data were only listed by patient.

Efficacy analyses: Best overall response was defined as the best response achieved during the study. The ordering of evaluations, from best to worst, is: CR, PR, SD, PD, and not evaluable. Evaluations were based on RECIST, Version 1.0. For each patient, the best overall response was presented in listings. Evaluations of measurable target lesions, measurable nontarget lesions, and nonmeasurable nontarget lesions were presented in the listings.

Summary: A total of 68 patients were treated in the 4 treatment cohorts: 19 in the TOP + I cohort, 21 in the TEM + I cohort, 10 in the G + I cohort, and 18 in the C + P + I cohort. One (5.3%) patient was receiving ongoing treatment with TOP + I at the time of the final data cutoff date. This patient was rolled over into the LTS12674 study on 01 October 2012 and all data collected for this patient, including after the primary data cutoff date for analysis to the end of treatment, are provided in a brief narrative and in a patient profile summary in this final report.

Efficacy results: Efficacy results are discussed by cohort in the body of this report and summarized briefly here. Five (7.6%) of the 66 patients who were evaluable for best overall response had PR: 2 in the TOP + I cohort and 3 in the C + P + I cohort. Thirty-seven (56.1%) of the 66 patients had SD: 13 in the TOP + I cohort, 8 in the TEM + I cohort, 4 in the G + I cohort, and 12 in the C + P + I cohort. Twenty-four (36.4%) of the 66 patients had PD: 4 in the TOP + I cohort, 11 in the TEM + I cohort, 6 in the G + I cohort, and 3 in the C + P + I cohort.

Safety results: Safety results are discussed by cohort in the body of this report and summarized briefly here. All 68 patients experienced at least 1 TEAE during the study, and the majority (69.1%) experienced a TEAE ≥Grade 3. Most (92.6%) patients experienced a TEAE that was considered related to study treatment. Across all study cohorts, 9 (13.2%) patients died during the study: none in the TOP + I cohort, 3 in the TEM + I cohort (all occurred within 30 days of the last dose of study drug), 2 in the G + I cohort (both occurred more than 30 days after the last dose of study drug), and 4 in the C + P + I cohort (2 occurred within 30 days of the last dose of study drug and 2 occurred more than 30 days after the last dose of study drug). All deaths were due to progressive disease and none was considered related to study treatment.

In all study cohorts, 25 of 68 (36.8%) patients experienced SAEs: 6 (31.6%) in the TOP + I cohort, 6 (28.6%) in the TEM + I cohort, 5 (50.0%) in the G + I cohort, and 8 (44.4%) in the C + P + I cohort. The majority of patients who experienced SAEs had SAEs that were ≥Grade 3. Within each cohort, the SAEs ≥Grade 3 that occurred were experienced by only 1 patient with the exception of malignant neoplasm progression in 3 (14.3%) patients (TEM + I cohort). The Grade 5 events across all cohorts included 2 instances of malignant neoplasm progression and 1 instance of failure to thrive (TEM + I cohort); and 1 instance each of malignant neoplasm progression and neutropenic sepsis (C + P + I cohort). The following SAEs were considered related to study drug: febrile neutropenia and pancytopenia in 1 patient, nausea in 1 patient, and large intestinal obstruction in 1 patient (TOP + I cohort; all were Grade 3); Grade 2 pyrexia in 1 patient (G + I cohort); and Grade 2 asthenia and Grade 3 neuralgia in 1 patient and Grade 4 anaphylactic reaction in 1 patient (C + P + I cohort).

Across all study cohorts, 12 (17.6%) patients experienced a TEAE leading to withdrawal of study treatment: 2 (10.5%) patients in the TOP + I cohort, 3 (14.3%) in the TEM + I cohort, 2 (20.0%) in the G + I cohort, and 5 (27.8%) in the C + P + I cohort. Of the TEAEs leading to withdrawal of study treatment experienced by these 12 patients, all were ≥Grade 3 except Grade 2 asthenia in 1 patient and Grade 2 peripheral neuropathy in 1 patient (both in the C + P + I cohort), and all were considered unrelated to study treatment except for Grade 3 intestinal dilatation and Grade 3 large intestinal obstruction in 1 patient and Grade 3 anemia and Grade 3 neutropenia in 1 patient (TOP + I cohort); Grade 3 fatigue in 1 patient (G + I cohort); and Grade 2 peripheral neuropathy in 1 patient and Grade 2 asthenia and Grade 3 neuralgia in 1 patient (C + P + I cohort).

Hematological abnormalities (all grades) were frequent (experienced by 14.3% to 100% of patients in all cohorts [42.1% to 100% of patients in TOP + I, 14.3% to 90.5% of patients in TEM + I, 40% to 100% of patients in G + I, and 47.1% to 100% in C + P + I]), as were Grade 3 to 4 hematological abnormalities (experienced by 0% to 68.% of all patients [21.1% to 68.4% in TOP + I, 9.5% to 52.4% in TEM + I, 0% to 40% in G + I, and 0% to 52.9% in C + P + I]), except in the temozolomide arm, in which Grade 3 to 4 hematological abnormalities were relatively less frequent (<15% of patients, except Grade 3 to 4 lymphopenia in 52.4% of patients). There were no deaths from hematological complications. The incidence of Grade 3 to 4 biochemical abnormalities was low, mostly occurring in only 1 patient (<10% of patients) in each cohort with the exception of creatinine abnormality in 2 (10.5%) patients, total bilirubin abnormality in 2 (10.5%) patients, and hyperglycemia in 2 (10.5%) patients (TOP + I cohort); hyponatremia in 3 (14.3%) patients (TEM + I cohort); and hyponatremia in 2 (11.8%) patients and hyperglycemia in 2 (11.8%) patients (C + P + I cohort).

Eight (11.8%) patients experienced AEs related to cardiac function. All of the AEs related to cardiac function were considered not related to study drug except for nonserious AEs of Grade 1 tachycardia (in 1 patient in TEM + I cohort and 1 patient in G + I cohort), and all were ≤Grade 2 except 2 SAEs of Grade 3 atrial fibrillation in 1 patient and an SAE of Grade 3 hypertensive heart disease and nonserious AE of Grade 3 electrocardiogram t-wave inversion in 1 patient (C + P + I cohort). One of the AEs related to cardiac function led to interruption of study medication: a nonserious AE of Grade 1 tachycardia in 1 patient (C+ P + I cohort). All of these AEs had an outcome of recovered except for 1 nonserious AE of palpitations in the TOP + I cohort, from which the patient did not recover.

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