HHS Public Access

Author manuscript

J Neurooncol. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

J Neurooncol. 2015 October ; 125(1): 123–131. doi:10.1007/s11060-015-1876-0.

Phase I study of iniparib concurrent with monthly or continuous temozolomide dosing schedules in patients with newly diagnosed malignant gliomas

Jaishri O. Blakeley, **Stuart A. Grossman**, **Tom Mikkelsen**, **Myrna R. Rosenfeld**, **David Peereboom**, **L. Burt Nabors**, **Andrew S. Chi**, **Gary Emmons**, **Ignacio Garcia Ribas**, **Jeffrey G. Supko**, **Serena Desideri**, and **Xiaobu Ye on behalf of the Adult Brain Tumor Consortium**

Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD (J.O.B., S.A.G., X.Y., S.D.); Henry Ford Hospital, Detroit, MI (T.M.); University of Pennsylvania, Philadelphia, PA (M.R.R.); Cleveland Clinic, Cleveland, OH (D.P.); Massachusetts General Hospital, Boston, MA (A.C. J.G.S.); University of Alabama at Birmingham, Birmingham, AL (L.B.N.); Sanofi (G.E., I.G.R.)

Abstract

Background—Iniparib is a prodrug that converts to highly reactive cytotoxic metabolites intracellularly with activity in preclinical glioma models. We investigated the maximum tolerated dose (MTD) of iniparib with monthly (m) and continuous (c) temozolomide (TMZ) dosing schedules in patients with malignant gliomas (MG).

Methods—Adults with newly diagnosed MG who had successfully completed ≥ 80% of radiation (RT) and TMZ without toxicity received mTMZ dosing (150-200 mg/m^2 days 1-5/28 days) or cTMZ dosing (75 mg/m^2/d × 6weeks) in conjunction with iniparib (i.v. 2 days/wk) in the adjuvant setting. Iniparib was dose escalated using a modified continual reassessment method (mCRM).

Results—43 patients (32 male; 34 GBM, 8 AA, 1 gliosarcoma; median age 54 yrs; median KPS 90) were enrolled across 4 dose levels. In the mTMZ group, 2/4 patients had dose limiting toxicities (DLT) at 19mg/kg/week (rash/hypersensitivity). At 17.2mg/kg/week, 1/9 patients had a DLT (grade 3 fatigue). Additional grade 3 toxicities were neutropenia, lymphopenia, and nausea. In the cTMZ group, one DLT (thromboembolic event) occurred at 10.2mg/kg/wk. Dose escalation stopped at 16mg/kg/week based on mCRM. The mean maximum plasma concentration of iniparib increased with dose. Concentration of the two major circulating metabolites, 4-iodo-3-aminobenzamide and 4-iodo-3-aminobenzoic acid, was ≤ 5% of the corresponding iniparib concentration.

Conclusions—Iniparib is well tolerated, at doses higher than previously investigated, in combination with TMZ after completion of RT + TMZ in patients with MG. Recommended phase 2 dosing of iniparib based on mCRM is 17.2mg/kg/wk with mTMZ and 16mg/kg/wk with cTMZ.

Corresponding Author: Jaishri O. Blakeley, MD, 1550 Orleans Street, Suite 1M-16, Baltimore, Maryland 21287, 410-955-8837, 410-614-9335, Jblakel3@jhmi.edu.

Conflict of Interest: None

An efficacy study of TMZ/RT + iniparib followed by TMZ + iniparib in newly diagnosed GBM using these doses has completed enrollment. Survival assessment is ongoing.

Keywords

malignant glioma; newly diagnosed; dose finding; cytotoxic; combination therapy

Introduction

The survival advantage demonstrated with the addition of temozolomide (TMZ) to radiation therapy (RT) for patients with newly diagnosed glioblastoma (GBM) changed the therapeutic landscape by demonstrating that survival can be enhanced with drug strategies and identifying the therapeutic target of the O6-methylguanine-DNA methyltransferase (MGMT) repair enzyme [1-3]. As a result, intense effort has gone into developing therapies that complement RT/TMZ without introducing additive systemic and central nervous system (CNS) toxicity.

Iniparib (4-iodo-3-nitrobenzamide) is a prodrug initially thought to be a poly (ADP-ribose) polymerase (PARP) 1 inhibitor [4, 5]. However, an unexpectedly favorable toxicity profile and variable activity in cells with mismatch repair defects raised questions about its mechanism of action [6, 7]. Ultimately, iniparib was shown to not directly inhibit PARP-1 at clinically relevant concentrations [6, 8]. Rather, it appears that it forms non-specific adducts with cysteine residues in many proteins, including PARP-1 [8, 9]. Specifically, iniparib is a prodrug with a nitro group that is converted to its active metabolite by components in the Nrf2-mediated antioxidant response pathway. The metabolite uncouples electron transport from oxidative phosphorylation, leading to the production of reactive oxygen species (ROS) at cytotoxic levels and to the binding to cysteine residues on enzymes critical for REDOX, including thioredoxin reductase (TrxR) [9, 10].

In glioma cell lines and human glioma xenografts, iniparib potentiates the cell cycle effects of both RT and TMZ resulting in complete tumor regression in 70% of animals [5]. Importantly, there is evidence that iniparib accesses the CNS based on human cerebrospinal fluid samples and brain tissue concentrations [5, 11]. This data paired with the observation that iniparib (alone or in combination with various cytotoxic drugs) is well tolerated in patients with other solid tumors raised interest in iniparib as a strategy to enhance the efficacy of RT/TMZ in patients with GBM.

The primary objectives of this study were to estimate the maximum tolerated dose (MTD) and describe the safety profile of iniparib given in combination with two dosing schedules of TMZ (monthly high dose versus continuous low dose) in order to simulate the dosages of TMZ that iniparib would be given with if advanced to an efficacy study in patients with newly diagnosed GBM [1]. In order to avoid potential confounding toxicity from RT in combination with iniparib and TMZ, the dose escalation of iniparib was assessed in the adjuvant setting in patients with newly diagnosed MG who had successfully completed RT/TMZ.

Patients and methods

This study was sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and conducted by the Adult Brain Tumor Consortium (ABTC). The protocol was approved by the institutional review board of each participating institution. All patients provided written informed consent as a condition for participating in the study. Patients eligible for enrollment met the following criteria: ≥18 years old, histologically proven newly diagnosed MG (AA, AO, GBM), completion of ≥80% of prescribed RT/TMZ without grade 3 or 4 toxicity. Additional enrollment requirements included: absolute neutrophil count ≥1,500/μL; platelet count ≥100,000/μL; serum creatinine≤1.7-mg/dL; total bilirubin ≤1.5-mg/dL; aspartate and alanine aminotransferase ≤4 times the upper limit of normal; stable dexamethasone dose for ≥5 days prior to enrollment; Karnofsky Performance Status (KPS) ≥ 60%; and a Mini Mental State Examination (MMSE) score ≥15. Exclusion criteria included: enzyme inducing antiepileptic medications; malignancy within 5 years; pregnant or nursing women; serious concurrent medical condition or other condition that would compromise safety or compliance. Agreement to practice adequate birth control methods was required.

Treatment Plan

This was an open-label, multi-center, study to estimate the MTD of iniparib administered in combination with two different dosing schedules of TMZ: monthly dose TMZ (mTMZ) and continuous TMZ (cTMZ) in patients with newly diagnosed MG. Both dosing schedules were started in the adjuvant setting after patients had completed standard concurrent RT/TMZ. Patients were assigned to cTMZ or mTMZ by sequential allocation. Patients in the mTMZ group were prescribed TMZ 150 mg/m^2 in cycle 1 and 200 mg/m^2 in cycles 2-6 on days 1-5 of each of six 4-week cycles. Patients in the cTMZ group were given oral TMZ 75 mg/m^2 daily for 6 weeks of each of three 10-week cycles. Iniparib plus TMZ was started 28-49 days after completion of RT/TMZ.

Iniparib was provided by Sanofi Pharmaceuticals, Inc. (Cambridge, MA) and administered intravenously (IV) on two consecutive days weekly (weeks 1-4 with mTMZ or weeks 1-6 with cTMZ) beginning with day 1 of TMZ. The starting dose was 5.1 mg/kg based upon prior solid tumor trials [12-14]. If a patient had to stop one drug for any reason, they stopped both. The use of antiemetics and pneumocystis jirovecii prophylaxis was at the discretion of the treating physician.

Evaluations

Baseline evaluations included brain magnetic resonance imaging (MRI), medical history and examination; MMSE; KPS; complete blood count (CBC); serum chemistry profile; and pregnancy test when appropriate. After initiating treatment, CBC and adverse event (AE) reports were obtained weekly; vital signs and serum chemistries were obtained before each cycle. Brain MRI, clinical examination, and KPS were repeated every other cycle.

For patients without tumor progression or toxicity, treatment with iniparib and TMZ were continued for a total of 6 cycles (mTMZ group) or 3 cycles (cTMZ group). Progression was

defined as: (1) greater than 25% increase in tumor on MRI with deteriorating neurologic status on a stable or increasing dose of steroids, (2) new lesion on MRI, (3) worsening neurologic function not explained by non-tumor causes (e.g. seizure, drugs, laboratory abnormalities, or confirmed treatment effect) [15]. Patients stopped treatment in the setting of progression, toxicity, noncompliance, or if the patient chose to discontinue treatment for any reason. Time to progression data was collected for the duration of treatment (6 months). All patients were followed for survival calculated from the date of diagnosis until death from any cause.

Dose Escalation

A modified continual reassessment method (mCRM) was used to estimate the MTD [16-18]. Five patients were treated at each dose level. Evaluation of toxicity for dose escalation was performed when 3/5 patients completed the observation window. Dose escalation proceeded until ≥33% DLT rate. The maximum increase in the dose was limited to 50% of the prior dose level. The MTD was defined when two recommended doses based on mCRM were within 10% of one another. An additional five patients in each group were entered at the putative MTD to confirm DLT rate.

AEs were recorded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DLTs were defined as grade 3-4 non-hematological toxicities (excluding nausea/vomiting without antiemetic prophylaxis; grade ≤ 3 radionecrosis; and ≤ 3 neurologic toxicity responding to steroids, anticonvulsants, or electrolyte correction) and hematologic toxicities including: (a) ANC ≤ 500/mm^3, (b) Platelets ≤ 25,000/mm^3; (c) WBC < 1000/mm^3. Any drug-associated toxicity that prevented administration of ≥ 80% of the planned TMZ and iniparib doses for the first cycle was also a DLT. Patients were taken off of treatment if they had a DLT that caused a delay in treatment of ≥ 21 days in the mTMZ group or ≥ 7 days in the cTMZ.

The AE observation window was two treatment cycles (56 days) for mTMZ patients and 10 weeks for the cTMZ group. All patients who had one dose of iniparib were evaluable for DLT. After completion of the observation window, all data was modeled with a logistic dose response function based on DLT to calculate the dose associated with a toxicity rate ≤33%.

Dose reductions were permitted for iniparib and mTMZ in the setting of a DLT. A total of two dose reductions of iniparib were permitted before off-treatment. For patients in the mTMZ group, TMZ dose reductions to a minimum of 100mg/m^2 were permitted for > grade 2 non-hematological toxicity or platelets < 50,000/μL (50.0 × 10^9/L), ANC < 1000/μL (1.0 × 10^9/L) or WBC < 2000/μL (2.0 × 10^9/L) related to TMZ in the prior cycle. No dose reductions were allowed in the cTMZ group. DLTs were assigned as possibly, probably or definitely related to iniparib and/or TMZ.

Pharmacokinetic Studies

Maximum concentration (C_{max}) of iniparib and its two major circulating metabolites, 4-iodo-3-aminobenzamide (IABM) and 4-iodo-3-aminobenzoic acid (IABA) were assessed in plasma samples obtained before dosing and within 5 min of infusion end for the first two and last doses of cycle 1 and the first and last dose of cycle 2. This timing was selected as

prior human pharmacokinetic studies revealed that iniparib is cleared from plasma rapidly with a biological half-life of roughly 10-20 min (unpublished observations courtesy of Sanofi). Hence, pharmacokinetic sampling was designed to assess the C_{max} of iniparib and its major markers of circulating metabolites (IABM and IABA) at the end of the infusion to indirectly assess prodrug activation.

At each sample time, peripheral venous blood (7 mL) was collected in potassium EDTA tubes and promptly chilled in wet ice until centrifuged (within 30 min). The plasma was removed and stored at -70°C until analyzed by high performance liquid chromatography with tandem mass spectrometry by Intertek Analytical Services (El Dorado Hills, CA). The lower limit of quantitation of the analytical method was 1.0 ng/mL for iniparib and 0.40 ng/mL for IABM and IABA. Acceptability criteria for study samples were: (1) the i.v. infusion of iniparib was completed within 60 ± 5 min; and (2) samples were collected within ± 5 min of infusion end. Geometric means were calculated from all peak concentrations of the three analytes that satisfied the acceptability criteria at each dose level, with the SD estimated by the jackknife technique.

Statistical Considerations

The primary objective of this study was to define the MTD of iniparib given concurrently with two dosing regimens of TMZ (cTMZ and mTMZ) in patients with newly diagnosed MG who had completed RT + TMZ. Dose escalation was determined based on the mCRM [17]. The mCRM is a model base approach for dose finding with a pre-specified logistic dose-toxicity relationship and a pre-defined probability of DLT. The MTD was estimated at a target DLT rate of 33%. The study also was designed to assess the overall safety of the treatment, to describe the pharmacokinetics of iniparib in combination with TMZ, and to estimate overall survival. Descriptive statistics were used to summarize patient characteristics, toxicity data, and the pharmacokinetic outcomes. Survival probability was estimated using the Kaplan-Meier method [19]. The confidence interval of median survival time was constructed by the method of Brookmeyer-Crowley [20]. All analyses were conducted using the SAS software (version 9.2, SAS Institute).

Results

Patient Characteristics

Forty-three patients were enrolled between 7/2008 and 11/2010 across 12 centers. All patients had undergone surgery and completed RT/TMZ per the EORTC protocol with >80% of the prescribed doses completed as per enrollment criteria and full recovery from any hematologic toxicity [1]. The median age was 54 years (range 20-74) and the median KPS 90 (range 70-100). A total of 23 patients were enrolled into the mTMZ group and 20 patients into the cTMZ group. The patient characteristics were similar between groups (Table 1).

Toxicity

Overall rates of AE were low with the most common AE across all patients being fatigue and low blood counts (Table 2). In the mTMZ group (Table 3), there were no grade 4 toxicities, but 2 of 4 patients (50%) treated at 9.5mg/kg (19mg/kg weekly dose) developed

DLTs including grade 3 rash and grade 3 hypersensitivity. At 8.6mg/kg (17.2mg/kg weekly) 1/9 patients (11%) had a DLT (grade 3 fatigue) confirming 17.2mg/kg weekly as the MTD for iniparib given concurrently with mTMZ. Other toxicities attributed as at least possibly related to iniparib across all dose levels in the mTMZ group included grade 3 elevation of alanine aminotransferase (1), hyperkalemia (1), neutropenia (1), leukopenia (1) and thrombocytopenia (1) (Table 3). Three patients (13%) came off of treatment and 5 (22%) required treatment delay due to toxicity in the mTMZ group.

In the cTMZ group, there was one thromboembolic event that met DLT criteria at 10.2mg/kg/wk reported as possibly related to iniparib. There were otherwise only 2 grade 3 events related as ≥ possible to iniparib: lymphopenia at 12.2 mg/kg weekly and nausea at 16 mg/kg weekly (Table 4). One patient had grade 4 leukopenia at the 16 mg/kg/wk, unlikely related to iniparib. Interestingly, like the patients in the mTMZ group, there were two patients with rash at the 16 mg/kg weekly dose, but only at grade 2 severity. Although only one patient came off drug for toxicity in the cTMZ group across all iniparib dose levels, 10 patients (50%) required treatment delays due to toxicity. Based on the mCRM results, the final recommended efficacy doses were iniparib 17.2mg/kg/week when given in combination with mTMZ and 16mg/kg/week when given in combination with cTMZ.

Five of the 43 patients (12%) underwent surgery within 30 days of protocol treatment for a question of psuedoprogression. Of these, 2 patients had active malignant glioma, 2 had mixed treatment effect and glioma and 1 had pure treatment effect. No patients resumed treatment after surgery.

Pharmacokinetics

With very few exceptions, iniparib and the two assayed metabolites were undetectable in plasma samples collected shortly before starting the infusions subsequent to the initial dose. The extent of data from samples satisfying the acceptability criteria did not permit meaningful statistical comparisons of mean C_{max} values between different infusions in patients receiving the same dose or the cTMZ and mTMZ groups. However, visual data inspection revealed no obvious indications of a trend in the C_{max} of iniparib or the two metabolites for the series of infusions given within each dose level or between groups. Overall mean values of the C_{max} of iniparib and the two metabolites in plasma at each dose level are presented in Table 5. The mean (±SD) C_{max} of iniparib achieved in patients was 1,517 ± 987 ng/mL. The relative concentrations of the two metabolites in plasma were independent of the iniparib dose and their combined concentrations were less than 5% of the corresponding concentration of the parent compound.

Clinical Outcome

Seven patients (30%) in the mTMZ group and 8 patients (40%) in the cTMZ had tumor progression on treatment. In these patients, the median time to progression (TTP) for the mTMZ group was 3 months (range 2-5 months) from protocol start and 7 months (range 5-11 months) from diagnosis. The median TTP for the cTMZ group was similarly 3 months (range 2-4 months) from protocol start and 6 months (range 5-8 months) from diagnosis. Eleven of 23 patients (48%) in the mTMZ group completed all 6 cycles without progression.

Eight of 20 (40%) patients in the cTMZ group completed treatment without progression. Five patients withdrew consent after enrollment.

Seven of the 43 patients enrolled (16%) are alive an average of 60 months from the start of protocol treatment and 65 months from diagnosis. The estimated median OS calculated from date of diagnosis across all 43 patients enrolled is 18.9 months (95% CI: 16.2-23.4 months, Figure 1).

Discussion

Iniparib had a favorable tolerability and safety profile when combined with both mTMZ and cTMZ dosing schedules given in the adjuvant setting in patients with newly diagnosed MG who had completed standard RT/TMZ. These two dosing regimens were assessed as they comprise the standard TMZ “backbone” for patients with newly diagnosed GBM, with cTMZ being given concurrently with RT and mTMZ given in the adjuvant setting. Notably, the mCRM resulted in higher recommended doses (17.2mg/kg and 16mg/kg per week) than tested in prior solid tumor trials (8-11.2mg/kg/wk) [12-14]. Further, the pharmacokinetic data indicate that at the doses identified in this study, the peak plasma Cmax (5.2 μM/L for 17.2mg/kg/wk and 12.0 μM/L for 16mg/kg/wk) are within the range of IC_{50} for iniparib across a variety of cell lines (3.5-114μM), including the glioma U251 line [5]. Unfortunately, we could not assess intratumoral concentrations of iniparib as it is adhesive to microdialysis tubing making recovery unreliable and is not well suited for clinical brain tissue sampling based on its known pharmacokinetic profile. However, the results of this dose finding study indicate that iniparib is well tolerated at doses that have a reasonable likelihood of efficacy based on pharmacokinetics and in combination with full dose TMZ.

A concern at study initiation had been the risk of exaggerated hematologic toxicity or brain injury in patients with glioma status-post RT/TMZ when iniparib was given in conjunction with adjuvant TMZ given iniparib's mechanism of action. Although 53% of patients had a hematologic toxicity of any grade or relationship to iniparib, only four patients (9%) had a grade 3 hematologic toxicity. The majority of hematologic toxicities were ≤grade 2 and related to TMZ, with the mTMZ group having slightly more hematologic events (67) than the cTMZ group (44). These rates are similar to other studies in which either mTMZ or cTMZ were given as monotherapy in patients with MG [1, 21-23]. Hence, iniparib did not appear to influence the tolerability of either mTMZ or cTMZ with overall similar safety and tolerability seen across these dosing regimens. Regarding the concern about brain injury hypothesized to occur due to enhanced effects of alkylating therapy with iniparib and TMZ, only 5 (12%) patients had surgery within 30 days of study drug and of these only 1 patient had pure treatment effect. There was no pathological evidence of radionecrosis and no AE reported consistent with brain injury. Hence, there was no evidence of a high frequency of treatment related brain injury related to iniparib and TMZ.

Finally, although this study was not designed to assess efficacy endpoints based on the study population consisting of newly diagnosed patients with a variety of histologies, treated at two different dosing schedules of TMZ and various doses of iniparib in this dose finding study, the survival data is provocative with a median OS of 19 months (95% CI: 16.2-23.4

months) across all patients. In addition, although we did not include response rate as an endpoint, the 6 month PFS was 48% for mTMZ and 40% for cTMZ. In addition, as of March 2015, the target number of deaths to trigger analysis for the phase 2 efficacy study (opened December 2012) has not occurred, suggesting a possible survival benefit. This data must be interpreted with caution as several prognostic factors are not known (e.g. MGMT, IDH1/2 status and subsequent therapies) for the patients in this study. Moreover, the median KPS across all patients was 90 and the study design selected for patients that were clinically well enough to meet enrollment criteria after completion of standard RT/TMZ. Both of these factors may result in a prognostic advantage. However, the tolerability and hints of efficacy are encouraging. The phase 2 study for patients with newly diagnosed GBM using iniparib 16mg/kg/week added to RT and TMZ and iniparib 17.2mg/kg/week added to adjuvant mTMZ for 6 months with a primary endpoint of OS has completed enrollment and the results are expected in the near future.

Acknowledgments

The authors thank Susan Passwaters for assistance with administrative management of the manuscript; Joy Fisher for assistance with data collection oversight on behalf of the Adult Brain Tumor Consortium and the team at Cancer Therapy Evaluation Program for their oversight and collaboration through the Adult Brain Tumor Consortium.

Funding: National Institutes of Health **(U01 CA-62475 to S.G., U01 CA-137443 to S.G.);** Sanofi Pharmaceuticals, Inc.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005; 352:987–996.10.1056/NEJMoa043330 [PubMed: 15758009]
2. Hegi ME, Liu L, Herman JG, Stupp R, Wick W, Weller M, Mehta MP, Gilbert MR. Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. J Clin Oncol. 2008; 26:4189–4199.10.1200/JCO.2007.11.5964 [PubMed: 18757334]
3. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005; 352:997–1003.10.1056/NEJMoa043331 [PubMed: 15758010]
4. Ossovskaya V, Lim C, Schools G, Kalurupalle S, Roninson I, Broude E. The chemosensitizing properties of iniparib in combination with DNA-damaging agents in the MDA-MB -468(–) triple-negative breast cancer (TNBC) cell line. AACR Annual Meeting. 2011 Abstract LB-401.
5. BiPar Sciences personal communication. BSI-201 Investigator's Brochure. 2011
6. Patel AG, De Lorenzo SB, Flatten KS, Poirier GG, Kaufmann SH. Failure of iniparib to inhibit poly(ADP-Ribose) polymerase in vitro. Clin Cancer Res. 2012; 18:1655–1662.10.1158/1078-0432.CCR-11-2890 [PubMed: 22291137]
7. Mahany JJ, Lewis N, Heath EI, LoRusso PM, Mita MM, Rodon J, Tolcher AW, Sherman BM, Bradley CR, Papadopoulos KP. A phase IB study evaluating BSI-201 in combination with chemotherapy in subjects with advanced solid tumors. J Clin Oncol. 2008; 26
8. Liu X, Shi Y, Maag DX, Palma JP, Patterson MJ, Ellis PA, Surber BW, Ready DB, Soni NB, Ladror US, et al. Iniparib nonselectively modifies cysteine-containing proteins in tumor cells and is not a bona fide PARP inhibitor. Clin Cancer Res. 2012; 18:510–523.10.1158/1078-0432.CCR-11-1973 [PubMed: 22128301]
9. Mendeleyev J, Kirsten E, Hakam A, Buki KG, Kun E. Potential chemotherapeutic activity of 4-iodo-3-nitrobenzamide. Metabolic reduction to the 3-nitroso derivative and induction of cell death in tumor cells in culture. Biochem Pharmacol. 1995; 50:705–714. [PubMed: 7669074]

10. Licht, S.; Cao, H.; Li, Z.; Zhang, J.; Liu, F.; Brittain, S.; Shen, J.; Zhang, B.; Hopke, J.; Newcombe, R., et al. Mechanism of action of iniparib: Stimulation of reactive oxygen species (ROS) production in an iniparib-sensitive breast cancer cell line. American Association for Cancer Research; San Francisco, CA: 2011. nrA226
11. Castro M, Li L, Stallings TE. Pharmacokinetics of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in cerebrospinal fluid (CSF) of a patient with breast cancer with carcinomatous meningitis. 2010. Journal of Clinical Oncology. 2010; 15_suppl(May 20 Supplement):e13559.
12. O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, Koo IC, Sherman BM, Bradley C. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med. 2011; 364:205–214.10.1056/NEJMoa1011418 [PubMed: 21208101]
13. Novello S, Besse B, Felip E, Barlesi F, Mazieres J, Zalcman G, von Pawel J, Reck M, Cappuzzo F, Ferry D, et al. A phase II randomized study evaluating the addition of iniparib to gemcitabine plus cisplatin as first-line therapy for metastatic non-small-cell lung cancer. Ann Oncol. 2014; 25:2156–2162. doi:0.1093/annonc/mdu384[doi]. [PubMed: 25139550]
14. Aghajanian C, Sill MW, Secord AA, Powell MA, Steinhoff M. Iniparib plus paclitaxel and carboplatin as initial treatment of advanced or recurrent uterine carcinosarcoma: a Gynecologic Oncology Group Study. Gynecol Oncol. 2012; 126:424–427.10.1016/j.ygyno.2012.05.024[doi] [PubMed: 22634397]
15. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010; 28:1963–1972.10.1200/JCO.2009.26.3541 [PubMed: 20231676]
16. Grossman SA, Carson KA, Phuphanich S, Batchelor T, Peereboom D, Nabors LB, Lesser G, Hausheer F, Supko JG. New Approaches to Brain Tumor Therapy CNS Consortium. Phase I and pharmacokinetic study of karenitecin in patients with recurrent malignant gliomas. Neuro Oncol. 2008; 10:608–616.10.1215/15228517-2008-030;10.1215/15228517-2008-030 [PubMed: 18577560]
17. Piantadosi S, Fisher JD, Grossman S. Practical implementation of a modified continual reassessment method for dose-finding trials. Cancer Chemother Pharmacol. 1998; 41:429–436. [PubMed: 9554585]
18. Piantadosi, S. Clinical Trials: A Methodologic Perspective. Second. John Wiley & Sons, Inc; New York: 2005.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Amer Statist Assn. 1958; 53:457–481.
20. Brookmeyer R, Crowley JA. Confidence Interval for the Median Survival Time. Biometrics. 1982; 38(1):29–41.
21. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, Armstrong TS, Wefel JS, Won M, Blumenthal DT, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013; 31:4085–4091.10.1200/JCO.2013.49.6968[doi] [PubMed: 24101040]
22. Brada M, Hoang-Xuan K, Rampling R, Dietrich PY, Dirix LY, Macdonald D, Heimans JJ, Zonnenberg BA, Bravo-Marques JM, Henriksson R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol. 2001; 12:259–266. [PubMed: 11300335]
23. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, Brada M, Spence A, Hohl RJ, Shapiro W, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer. 2000; 83:588–593.10.1054/bjoc.2000.1316[doi] [PubMed: 10944597]

Table 1

Patient characteristics

	mTMZ 1-4 weeks ***N=23***	**cTMZ 1-6 weeks** ***N=20***	**Total** ***N=43***
Age – year			
Median	55	50	54
Range	40--73	19--72	19—73
Gender – no. (%)			
Male	18 (78)	14 (70)	32 (74)
Female	5 (22)	6 (30)	11 (26)
Karnofsky Performance Status			
Median	90	90	90
Range	70-100	70-100	70-100
Mini Mental Score			
Median	29	29	29
Range	16-30	20-30	16-30
Anticonvulsant - no. (%)			
Yes	18 (79)	14 (70)	32 (74)
No	5 (21)	6 (30)	11 (26)
Diagnosis - no. (%)			
GBM (IV)	18 (78)	16 (80)	34 (79)
AA (III)	5 (22)	3 (15)	8 (19)
Gliosarcoma (IV)		1 (5)	1 (2)

Table 2

All adverse events with relationship of possible, or probable, or definite to iniparib (No. of pts had the type of AE >=5)

Adverse Event	mTMZ N=23 No. (% of pts)	cTMZ N=20 No. (% of pts)	Total N=43 No. (% of pts)
ALT		6 (30)	6 (14)
Anemia	13 (57)	11 (55)	24 (56)
Constipation	9 (39)	7 (35)	16 (37)
Dizziness	5 (22)		5 (12)
Fatigue	15 (65)	13 (65)	28 (65)
Nausea	9 (39)	9 (45)	18 (42)
Rash maculo-papular	5 (22)		5 (12)
Platelet decreased	15 (65)	6 (30)	21 (49)
White blood cell count decreased	11 (48)	17 (85)	28 (65)

Table 3

All adverse events for patients receiving monthly temozolomide (mTMZ) dosing and iniparib

Adverse Event	Grade 1 No. (% of pts)	Grade 2 No. (% of pts)	Grade 3 No. (% of pts)	Grade 4 No. (% of pts)	Total No. (% of pts)
ALT	2 (9)		1 (4)		3 (13)
Alkaline phosphatase	1 (4)				1 (4)
Allergic reaction			**1 (4)**		1 (4)
Anemia	12 (52)	1 (4)			13 (57)
Anorexia	2 (9)				2 (9)
Arthralgia	1 (4)				1 (4)
AST	3 (13)				3 (13)
Blood bilirubin increased	1 (4)				1 (4)
Chills	1 (4)				1 (4)
Confusion	1 (4)				1 (4)
Constipation	8 (35)	1 (4)			9 (39)
Elevated serum creatinine	1 (4)				1 (4)
Depression	1 (4)				1 (4)
Diarrhea	1 (4)				1 (4)
Dizziness	5 (22)				5 (22)
Dry skin	1 (4)				1 (4)
Fatigue	10 (43)	4 (17)	**1 (4)**		15 (65)
Headache	2 (9)				2 (9)
Hyperglycemia	4 (17)				4 (17)
Hyperkalemia			1 (4)		1 (4)
Hypertension	1 (4)				1 (4)
Hypoalbuminemia		2 (9)			2 (9)
Hypocalcemia	3 (13)				3 (13)
Hypokalemia	1 (4)				1 (4)
Injection site reaction	1 (4)	2 (9)			3 (13)
Nausea	9 (39)				9 (39)

Adverse Event	Grade 1 No. (% of pts)	Grade 2 No. (% of pts)	Grade 3 No. (% of pts)	Grade 4 No. (% of pts)	Total No. (% of pts)
Neutrophil count decreased			1 (4)		1 (4)
Pain	1 (4)	1 (0.8)			2 (9)
Platelet decreased	11 (48)	3 (13)	1 (4)		15 (65)
Pruritus	1 (4)				1 (4)
Purpura	1 (4)				1 (4)
Rash maculo-papular	2 (9)	3 (13)	**1 (4)**		6 (26)
Urticaria			**1 (4)**		1 (4)
Venous injury	1 (4)				1 (4)
Vomiting	4 (17)				4 (17)
White blood cell count decreased	8 (35)	3 (13)	2 (8)		13 (56)

(Bold indicates met criteria for DLT)

Table 4

All adverse events for patients receiving continuous temozolomide (cTMZ) dosing and iniparib

Adverse Event	Grade 1 No. (% of pts)	Grade 2 No. (% of pts)	Grade 3 No. (% of pts)	Grade 4	Total No. (% of pts)
ALT	6 (30)				6(30)
Alkaline phosphatase	1 (5)				1 (5)
Anemia	9 (45)	1 (5)	1 (5)		11 (55)
Anorexia	2 (10)	1 (5)			3 (15)
AST	2 (10)				2 (10)
Blurred vision	1 (5)				1 (5)
Constipation	5 (25)	2 (10)			7 (35)
Elevated serum creatinine	1 (5)				1 (5)
Cushingoid		1 (5)			1 (5)
Dehydration	1 (5)				1 (5)
Diarrhea	1 (5)				1 (5)
Dry skin		1 (5)			1 (5)
Dysgeusia	1 (5)				1 (5)
Edema limbs		1 (5)			1 (5)
Erythema multiforme		1 (5)			1 (5)
Fatigue	6 (30)	9 (45)			15 (75)
Flatulence	1 (5)				1 (5)
Flushing	2 (10)				2 (10)
GI complaints	1 (5)				1 (5)
Hypoalbuminemia	1 (5)				1 (5)
Injection site reaction	1 (5)				1 (5)
Insomnia	3 (15)				3 (15)
Intracranial haemorrhage		1 (5)			1 (5)
motion decreased	1 (5)				1 (5)
Mucositis oral	1 (5)				1 (5)
Nausea	7 (35)	1 (5)	1 (5)		9 (45)

J Neurooncol. Author manuscript; available in PMC 2016 October 01.

Adverse Event	Grade 1 No. (% of pts)	Grade 2 No. (% of pts)	Grade 3 No. (% of pts)	Grade 4	Total No. (% of pts)
Nervous system		1 (5)			1 (5)
Pain	1 (5)				1 (5)
Pruritus	1 (5)	2 (10)			3 (15)
Rash maculo-papular	1 (5)	1 (5)			2 (10)
Urinary frequency	1 (5)				1 (5)
Vomiting	2 (10)				2 (10)
Weight loss	1 (5)				1 (5)
Thromboembolic event				**1 (5)**	1 (5)
Platelet decreased	5 (25)	1 (5)			6 (30)
White blood cell decreased	7 (35)	7 (35)	4 (20)	1 (5)	19 (95)

(Bold indicates met criteria for DLT)

Table 5

Peak concentrations of iniparib and its two major metabolites in plasma[a]

Dose (mg/kg)	No. of Patients	No. of samples	C_{max} (ng/mL)			Metabolite/iniparib	
			Iniparib	IABM	IABA	IABM	IABA
5.1	8	20	642 ± 315	5.7 ± 4.1	16.6 ± 5.2	1.1 ± 0.6	3.0 ± 2.0
6.1	5	11	928 ± 397	7.2 ± 1.8	14.9 ± 8.3	0.9 ± 0.6	2.0 ± 1.5
6.8	7	18	1,019 ± 463	8.4 ± 3.7	19.9 ± 6.6	1.1 ± 0.9	2.4 ± 1.4
8.0	4	5	3,687 ± 1,464	10.3 ± 2.9	14.5 ± 15.0	0.3 ± 0.1	0.7 ± 0.7
8.6	5	18	1,517 ± 987	9.7 ± 2.4	31.5 ± 10.4	0.8 ± 0.6	2.5 ± 1.4
9.5	4	7	2,139 ± 2,133	13.6 ± 5.3	19.8 ± 14.0	0.8 ± 0.6	2.0 ± 2.0

[a]Data are presented as the geometric mean ± SD for peak plasma concentrations (C_{max}) and the arithmetic average ± SD for the metabolite/iniparib concentration ratio as expressed as a percentage.