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A Phase Ib multicenter, dose-escalation study of the polyamine analogue PG-11047 in combination with gemcitabine, docetaxel, bevacizumab, erlotinib, cisplatin, 5-fluorouracil, or sunitinib in patients with advanced solid tumors or lymphoma.

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Conflicts of Interest

During the development of PG-11047, in vitro and in vivo preclinical studies of PG-11047 and related analogues were funded in part by a gift to the laboratory of RAC by Cellgate, Inc., the previous owner of PG-11047.

Ethics approval and consent to participate

All participants provided written informed consent that was approved by the Institutional Review Boards (IRBs) associated with the study site prior to study initiation. The trial was conducted in accordance with the IRB-approved protocol and amendments, Good Clinical Practice guidelines, and the Declaration of Helsinki.

Availability of data and material

Data collected during the study are available on www.clinicaltrials.gov, #NCT00705874

Code availability

Not applicable

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Abstract

Purpose: Polyamines are absolutely essential for maintaining tumor cell proliferation. PG-11047, a polyamine analogue, is a nonfunctional competitor of the natural polyamine spermine that has demonstrated anticancer activity in cells and animal models of multiple cancer types. Preclinical investigations into the effects of common chemotherapeutic agents have revealed overlap with components of the polyamine metabolic pathway also affected by PG-11047. This report describes a Phase Ib clinical trial investigating PG-11047 in combination with cytotoxic and anti-angiogenic chemotherapeutic agents in patients with advanced refractory metastatic solid tumors or lymphoma.

Methods: A total of 172 patients were assigned to treatment arms based on cancer type to receive the appropriate standard-of-care therapy (gemcitabine, docetaxel, bevacizumab, erlotinib, cisplatin, 5-fluorouracil (5-FU), or sunitinib as directed) along with intravenous infusions of PG-11047 on days 1, 8, and 15 of a 28-day cycle. PG-11047 dose escalation ranged from 50 mg to 590 mg.

Results: The maximum tolerated dose (MTD) of PG-11047 in combination with bevacizumab, erlotinib, cisplatin, and 5-FU was 590 mg. Dose-limiting toxicities (DLTs) in these groups were rare (5 of 148 patients). Overall partial responses (PR) were observed in 12% of patients treated with PG-11047 and bevacizumab, with stable disease documented in an additional 40%. Stable disease occurred in 71.4% of patients in the 5-FU arm, 54.1% in the cisplatin arm, and 33.3% in the erlotinib arm. Four of the patients receiving cisplatin + PG-11047 (20%) had unconfirmed PRs. MTDs for gemcitabine, docetaxel, and sunitinib could not be determined due to DLTs at low doses of PG-11047 and small sample size.

Conclusions: Results of this Phase Ib trial indicate that PG-11047 can be safely administered to patients in combination with bevacizumab, erlotinib, cisplatin, and 5-FU on the once weekly dosing schedule described and may provide therapeutic benefit. The manageable toxicity profile and high MTD determination provide a safety profile for further clinical studies.

Keywords

Bis-alkyl polyamine analogue PG-11047; Cancer; Clinical trial; Bevacizumab; Cisplatin; Chemotherapy; 5-fluorouracil; Erlotinib; Docetaxel; Sunitinib

Introduction

Putrescine, spermidine, and spermine constitute the mammalian polyamines, small aliphatic molecules with essential roles in sustaining cell growth and viability. The individual intracellular concentrations of these polyamines are tightly regulated through a complex regulatory network, comprised of biosynthesis, catabolism, uptake, and excretion, that

ensures the strict maintenance of normal polyamine homeostasis. Disruptions in this balance can lead to pathologies, including cancer, where increased polyamine requirements have been demonstrated in nearly every solid tumor type. Multiple members of the polyamine biosynthetic pathway are under the control of oncogenic regulators, including *MYC,* and increases in intracellular polyamine concentrations fuel the increased proliferation and biomass required of tumor cells [1]. Conversely, inhibition of polyamine synthesis inhibits tumor cell proliferation [2]. However, compensatory uptake of polyamines from the extracellular environment limits the utility of biosynthesis inhibitors as a chemotherapeutic strategy *in vivo*, though polyamine biosynthesis inhibition is a promising chemopreventive strategy for certain at-risk patient populations [3,4]. In particular, difluoromethylornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase (ODC), the first rate-limiting enzyme in polyamine biosynthesis, has shown clinical benefit to patients predisposed to colorectal carcinoma [5,6], children with relapsed/refractory neuroblastoma [7–9], men at risk for invasive prostate cancer [10], and patients with certain types of gliomas [11].

An alternative approach to limiting polyamine pools in cancer cells uses polyamine analogues that both down-regulate natural polyamine biosynthesis and enhance their catabolism [2,12]. The most widely studied of these analogues incorporate alkyl groups onto the primary amines of spermine [13]. These compounds, known as bis(ethyl) polyamine analogues, compete with the natural polyamines for uptake into the cell where they accumulate and induce the catabolism of the higher polyamines (spermine and spermidine). Biosynthesis is subsequently reduced via feedback mechanisms, ultimately depleting the natural polyamines and inhibiting growth, as the bis(ethyl) polyamine analogues are unable to substitute for the natural polyamines in growth-supporting functions. In this regard, bis-ethylated analogues of spermine have been more effective in preclinical models than their spermidine counterparts [14–16]. Additionally, in sensitive tumor cell types, bis-alkylated spermine compounds highly induce polyamine catabolism through both spermidine/spermine N^1-acetyltransferase (SSAT) and spermine oxidase (SMOX) activities [15,17]. Spermine oxidation results in the production of reactive oxygen species (ROS) as well as 3-aminopropanal, a highly reactive and toxic aldehyde, resulting in analogue-associated apoptosis and cytotoxicity that is exacerbated by the depletion of intracellular spermine, which is an important free radical scavenger [18,19].

PG-11047 (N^1,N^{12}-bisethyl-*cis*-6,7-dehydrospermine) is a second-generation, conformationally restricted bis(ethyl) polyamine analogue [20]. The insertion of a central *cis* double bond increases the spatial rigidity of the analogue with the intention of reducing nonspecific binding and clinical toxicities observed with the structurally related compound bis(ethyl)norspermine (BENSpm) [21,22]. Multiple preclinical studies have demonstrated the growth inhibitory effects of PG-11047 through the modulation of polyamine catabolism in cancer cell lines of lung, colon, breast, and prostate origin both *in vitro* and in human tumor xenograft mouse models [23,24,20,25–29].

We previously reported a Phase I study of PG-11047 (NCT# 00705653) administered weekly as a monotherapy via intravenous infusion (IV) to patients with advanced refractory solid tumors [30]. This study determined a maximum tolerated dose (MTD) of 610 mg PG-11047 when given on days 1, 8 and 15 of 28-day cycles. The drug was generally well

tolerated; the most common adverse events (AEs) were anorexia and fatigue. Of the treated patients, 30% demonstrated stable disease as indicated by controlled tumor growth. In preclinical studies, adding PG-11047 to various standard-of-care oncolytic drugs enhances the efficacy of these agents without incompatibilities or interference [24], suggesting the utility of PG-11047 in combination studies.

Therefore, an open-label, multicenter, Phase I, dose-escalation trial was designed to determine the safety, tolerability and maximum tolerated dose (MTD) of intravenous PG-11047 when used in individual combinations with gemcitabine, docetaxel, bevacizumab, erlotinib, cisplatin, 5-flurouracil or sunitinib in patients with advanced solid tumors or lymphoma. Additional goals of the study were to determine dose-limiting toxicities (DLT) and evidence for anti-tumor activity of PG-11047 when administered in each of the combinations.

Patients and Methods

Patient populations

Patients at least 18 years of age who had a histologically or cytologically confirmed non-hematological advanced solid tumor malignancy or lymphoma for which no curative therapy exists and for which monotherapy with the oncolytic drugs of the treatment arms would be warranted were eligible for enrollment. Other study entrance criteria included measurable disease (by radiographic evaluation or elevated tumor markers), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, life expectancy greater than 3 months, ability to understand and willingness to provide written informed consent, and acceptable organ and marrow function during the screening period (absolute neutrophil count ≥ 1500 cells/mm^3; hemoglobin ≥ 9 g/dL; platelets ≥ 100,000 cells/mm^3; total bilirubin < 1.5X upper limit of normal; AST (SGOT) < 2.5X institutional upper limit of normal (ULN) or ≤ 5X ULN for patients with liver metastasis; ALT (SGPT) < 2.5X ULN or ≤ 5X ULN for patients with liver metastasis; creatinine within normal limits or creatinine clearance ≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal limits. Exclusion criteria included patients who had received chemotherapy within 21 days (or 6 weeks for nitrosoureas or mitomycin C) prior to day 1 of cycle 1 or had not recovered from AEs) from agents administered more than 21 days prior, and those who had received radiotherapy or an investigational agent within 4 weeks prior to Day 1. Also excluded were patients with known active brain metastases or leptomeningeal carcinomatosis; peripheral neuropathy ≥ grade 2 (NCI CTC version 3 AE scale); a history of allergic reactions to compounds of similar chemical or biological composition to PG-11047; or uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, ventricular arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Immune deficiency or HIV-positive patients receiving combination antiretroviral therapy were excluded, as were those with a history of myocardial infarction or hospitalization for decompensated congestive heart failure within the 6 months prior to cycle 1, day 1, or who are actively being treatment for uncontrolled cardiac arrhythmias on the basis of pretreatment ECG monitoring. Also excluded were patients with clinically significant

gastrointestinal tract hemorrhage that had required transfusion therapy within the 3 months prior to study commencement and women who were pregnant, breast-feeding, or of childbearing age and unwilling to use approved, effective means of contraception.

Patients enrolled in the study could continue treatment and assessment until one of the following occurred: disease progression, illness that prevented further treatment administration, unacceptable AE(s), decision by the patient to withdraw from the study, changes in the patient's condition rendering the patient unacceptable for further treatment as determined by the investigator, protocol non-compliance by the patient, or termination of the study. If discontinuation was due to toxicity, the patient was monitored to document toxicity duration, patient response, and time to progression to the point at which the toxicity was resolved or stabilized or new systemic therapy was initiated.

PG-11047 formulation and administration

PG-11047 was formulated in water for injection at a concentration of 100 mg/mL. The resulting "PG-11047 for Injection 10%" was diluted in 0.9% Sodium Chloride for Injection, USP and used within 8 hours of final dilution. Drug was prepared by the pharmacy and contained the desired dose in a total volume of either 100 or 200 mL, which was administered via infusion over a 60- or 90-minute period, respectively, depending on the date of patient enrollment. A single batch of PG-11047 drug (Progen Pharmaceuticals, Inc.) was used at all sites throughout the course of the study.

Clinical trial design

This was an open-label Phase I, multi-center trial using a classic dose escalation design to assess the dose-limiting toxicities (DLTs), the maximum tolerated dose (MTD), and safety of intravenous (IV) PG-11047 when used in combination with 1 of 7 treatment arms that included gemcitabine, docetaxel, bevacizumab, erlotinib, cisplatin, 5-flurouracil, or sunitinib in adult patients with histologically or cytologically confirmed advanced solid tumors or lymphoma. Patients were assigned to treatment arms based on their cancer type and the appropriate standard-of-care therapy determined by the investigator. All participants provided written informed consent that was approved by the Institutional Review Boards (IRBs) associated with the study site prior to study initiation. The trial was conducted in accordance with the IRB-approved protocol and amendments, Good Clinical Practice guidelines, and the Declaration of Helsinki.

The dose of PG-11047 was escalated in cohorts of 3 patients, and dose escalation could proceed in each treatment group independently of dose escalation in the other treatment groups. Eight dose levels of PG-11047 were evaluated, with dosage escalated from 100 mg to 590 mg. An additional Dose Level −1 of 50 mg was used in the event of excessive toxicity at Dose Level 1 (100 mg). Frequency of PG-11047 administration depended on treatment arm and was based on regimens of PG-11047 dosing from a previous study [30]. The doses of gemcitabine, docetaxel, bevacizumab, erlotinib, cisplatin, 5-flurouracil or sunitinib remained fixed according to their respective product labeling. The treatment regimen, dose, schedule and cycle length of these drugs are presented in Table 1. The treatment period was intended to be at least two cycles of PG-11047 (8 weeks), with patients who tolerated

treatment eligible to receive additional cycles. The primary endpoints were the determination of the MTD and DLTs of PG-11047 when used in combination. Secondary endpoints included obtaining evidence of anti-tumor activity.

Determination of safety parameters

MTD was defined as the dose below that at which one-third of at least six patients experienced a dose-limiting toxicity (DLT). Only patients who completed the first scheduled cycle of therapy were evaluable for dose escalation and determination of DLTs. A cohort of up to six additional patients was entered at the MTD level to better describe the safety profile. These DLTs had to occur during the first treatment cycle and be considered related to PG-11047 administration. DLTs included any one of the following conditions: (i) any nonhematologic toxicity ≥ grade 3 and lasting longer than 3 days in spite of supportive care; (ii) grade 4 thrombocytopenia (< 25,000 cells/mm^3); (iii) grade 4 anemia (Hgb < 6.5 g/dL) on the following scheduled dosing day; (iv) grade 4 neutropenia (ANC < 500 cells/mm^3) lasting longer than 5 days; (v) any febrile neutropenia (temperature > 101°F with an absolute neutrophil count < 1000 cells/μL (grade 3 or 4)); or (vi) inability to receive all standard doses of PG-11047 during the first dosing cycle due to any unexpected toxicity thought to be related to the combination therapy. Toxicities were graded according to the NCI Common Toxicity Criteria, Version 3.0.

Safety was assessed on all patients who received treatment and was based on treatment emergent AEs as defined according to the International Conference on Harmonization (ICH) guidelines.

Evaluation of anti-tumor effects

Analysis of efficacy was based on best overall response and was performed for all PG-11047 dose levels combined. Patients with measurable disease were included in the efficacy evaluation. Anti-tumor response was evaluated after every 2 cycles of PG-11047 administration based on standard criteria according to cancer type. Response and progression were analyzed according to the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST) Committee and included complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD) of target lesions as well as evaluation of non-target lesions [31]. To be assigned a status of PR or CR, changes in tumor measurements were confirmed by repeated assessments performed 3–4 weeks subsequent to when the criteria for response were first met.

Results

Patients

A total of 172 individuals enrolled into the study were treated with PG-11047 in combination with gemcitabine (n = 12), docetaxel (n = 9), bevacizumab (n = 34), erlotinib (n = 34), cisplatin (n = 48), 5-FU (n = 32), or sunitinib (n = 3). Patient baseline and demographic data including cancer history are available as Online Resource 1. The majority of patients enrolled were Caucasian, and patients among the 7 combination treatment groups ranged between 26 and 81 years, averaging 56.3–63.2 years of age in each of the individual

treatment arms. Most patients had metastatic cancer and had received multiple prior anticancer therapies, including surgery, radiotherapy, chemotherapy, and/or hormonal therapy. With the exception of the 5-FU/Leucovorin group, most patients had not previously received treatment with the combination agent of their assigned treatment arm (gemcitabine: 1 of 12 patients; docetaxel: 0 of 9; bevacizumab: 4 of 34; cisplatin: 9 of 48; erlotinib: 0 of 34; and sunitinib: 0 of 3). However, 25 of the 32 patients in the 5-FU/Leucovorin treatment arm had been previously administered 5-FU in the course of their disease. Baseline ECOG performance status grades among the treatment arms were “0” in 8.3–37.5% of patients and “1” in 58.8 – 83.3% of patients. Approximately 50% of patients discontinued the study due to disease progression.

Safety

A total of 133 patients (77.3% of total treated) completed at least two cycles of treatment with PG-11047 (Table 2). Of these, 57 patients (40.3% of total treated) completed at least 3 cycles of PG-11047 treatment. Although the majority of treated patients experienced at least one AE, they generally ranged from grade 1 to grade 3 in severity. The most commonly experienced AEs (of all grades) were in the following System Organ Classes (SOCs): Gastrointestinal disorders and General disorders and administration site conditions. Seventy patients experienced serious treatment-emergent adverse events (TESAEs) during the study. Among the seven combination treatment groups, 29.4% to 53.1% of patients experienced at least one TESAE. The majority of the TESAEs were grade 3 (severe) in severity. Twenty-nine patients discontinued the study due to an AE, 4 of which were attributed to DLT (1 each in the bevacizumab and erlotinib groups and 2 patients in the cisplatin group). Fifty-five deaths occurred during the study, of these, the primary cause of death in 48 patients was tumor progression. Of the seven remaining deaths, four were considered unlikely to be treatment related (cardiac arrest, cardiopulmonary arrest, respiratory failure, and hypoxia). Three deaths were likely related to treatment: (1) cardiopulmonary arrest due to COPD exacerbation in the bevacizumab group; (2) renal failure in the erlotinib group; and (3) CNS hemorrhage in the sunitinib group. As intracranial bleed has been reported in up to 7% of patients receiving sunitinib, this death could have been due to either the sunitinib or the combination. However, since an extensive literature search as well as the latest bevacizumab package insert gave no indication of bevacizumab specifically causing exacerbation of COPD, we must conclude that this exacerbation was due to its combination with PG-11047. Similarly, kidney dysfunction in response to erlotinib has been reported only as a rare case report, suggesting that the one renal failure in our study was most likely due to the combination of erlotinib and PG-11047 [32]. Weight loss across the groups ranged from 37.5% (docetaxel group) to 69.2% (erlotinib group) of patients at the end of cycle 1, with the majority of patients losing ≤ 5% from baseline measurements. Very few patients showed ECG changes from baseline at the end of cycle 1: 15 patients changed from normal at baseline to abnormal and 17 showed improvement from abnormal at baseline to normal. Of the patients with abnormal ECG changes, none were of sufficient concern to require additional monitoring. An increase in hypersensitivity reactions related to PG-11047 occurred at the 590 mg dose level. Consequently, patients treated at or above this dose, or those experiencing hypersensitivity reactions below this dose, were pre-medicated with the following prior to subsequent infusions: dexamethasone (20 mg PO administered 6 and 12

hours prior to PG-11047), diphenhydramine or equivalent (50 mg IV 30– 60 minutes before PG-11047), and cimetidine (300 mg) or ranitidine (50 mg) IV 30– 60 minutes prior to PG-11047).

Overall, 11 patients experienced DLTs and either completed the first cycle of treatment or dropped out due to the DLT (Table 3). There was a very low incidence of DLT (0–6.5% of patients) reported in five of the seven combination therapies (PG-11047 individual combinations with bevacizumab, erlotinib, cisplatin, 5-flurouracil/leucovorin, and sunitinib). MTD, determined as the highest dose at which less than one-third of at least six patients experienced a DLT during the infusion period of Cycle 1, was determined to be 590 mg in the bevacizumab, erlotinib, cisplatin, and 5-FU treatment arms (Table 3). The MTDs of PG-11047 in combination with gemcitabine, docetaxel, or sunitinib were undetermined due to DLTs at the lowest dosing levels and small sample size.

There were very few patients with a change in ECOG scores from 0–1 at baseline (normal activity to symptoms but ambulatory) to 2–4 (in bed <50% of time to 100% bedridden) during the study. The majority of patients showed no change from baseline ECOG score (0–1) at the end of Cycle 1 or Cycle 2.

Antitumor activity

The most common overall response evaluated was Stable Disease (SD) (Table 4). Of the 21 patients receiving PG-11047 in combination with 5-FU/leucovorin, 71.4% had SD. Patients receiving PG-11047 combined with gemcitabine, docetaxel, or cisplatin had rates of SD ranging from 50– 60%. Unconfirmed PRs were reported for 4 of the 20 SD patients in the cisplatin group (10.8% of total patients in this group), although the overall response for these patients was considered SD. Of these patients, two were treated with 250 mg of PG-11047 and one each with 100 and 150 mg of PG-11047. Their cancer histories included lung carcinoma, transitional cell carcinoma of the ureter, and prostate cancer (Table 5). In the PG-11047 + bevacizumab or erlotinib groups, 40% and 33.3% of patients had SD, respectively. Notably, 3 (12%) additional patients in the PG-11047 + bevacizumab treatment group were evaluated as having PRs in this study; one patient was treated with 200 mg and two patients received 375 mg of PG-11047. Primary cancers of these patients were breast (invasive ductal carcinoma), squamous cell carcinoma of the piriform sinuses, and adenocarcinoma of unknown origin. The rate of controlled tumor growth (CR+PR+SD) for each treatment group was the same percentage as the number of patients with stable disease except for the PG-11047 + bevacizumab treatment group, in which 52% of patients had tumor growth controlled. There were no differences observed in PG-11047 dosing (50 to 590 mg) for patients who had SD or PRs. The median duration of SD is shown in Table 4 for the individual combination treatment groups, and the median duration of overall survival varied from 1 to 267 days. Due to the small sample size of the PG-11047 + sunitinib group (n = 3), the duration of overall survival could not be determined.

Additional details of the reported partial responses, including patient cancer history, are provided in Table 5. All patients had metastatic disease with a variety of primary cancer diagnoses.

Discussion and Conclusion:

In the current study, intravenous PG-11047 was administered as a combination therapy with 1) gemcitabine, 2) docetaxel, 3) bevacizumab, 4) erlotinib, 5) cisplatin, 6) 5-flurouracil, or 7) sunitinib in 172 patients with advanced solid tumors or lymphoma. As in our previous Phase I single-agent study in patients with advanced refractory solid tumors (NCT#00705653)[30], PG-11047 was generally well tolerated in the individual combinations, with safety results demonstrating the occurrence of AEs that are common and expected in cancer patients, ranging from grades 1–3 in severity.

The MTD for PG-11047 as a single agent was previously determined to be 610 mg, administered once weekly, with SD reported in 9 (30%) of 30 patients. Similarly, a very low incidence of dose-limiting toxicity (0–6.5% of patients) was reported for PG-11047 when administered in combination with bevacizumab, erlotinib, cisplatin, 5-flurouracil/leucovorin or sunitinib, in the current study. The MTD for PG-11047 was determined to be 590 mg when in combination with bevacizumab, erlotinib, cisplatin and 5-flurouracil/leucovorin. These results provide a promising safety profile for further clinical studies with these combination regimens.

The MTDs for PG-11047 in combination with gemcitabine, docetaxel and sunitinib, however, could not be determined. DLTs at the initial PG-11047 dosing level (100 mg) of the gemcitabine and docetaxel treatment arms necessitated a reduction of PG-11047 to dose level −1 (50 mg), which also resulted in DLTs in both combinations. The paucity of data from the PG-11047 + sunitinib arm was the result of low patient enrollment (n = 3), probably due to the infrequent use of sunitinib in practice. Dose modifications and a larger sample sizes may be required for future safety studies of these combinations.

As noted in Tables 4 and 5, there were 4 unconfirmed partial responses in the PG-11047 + cisplatin group that included patients with poorly differentiated lung cancer, a transitional cell carcinoma of the ureter, a poorly differentiated adenocarcinoma of unknown origin, and a patient with prostate cancer. Given the unusual histology types of these cancers, there is no historical percent response rate to single-agent cisplatin for comparison except for prostate cancer, where a response rate of up to 23% of patients has been observed [33]. Therefore, it might not be unusual in the above types of cancer to see a histological response to single-agent cisplatin in these patients.

In addition to the four partial responses to PG-11047 and cisplatin, three patients (12%) treated with the combination therapy of PG-11047 + bevacizumab achieved partial responses per SAP definition. These seven patients all had at least a 30% decrease in the sum of the longest diameter (LD) of their baseline target lesions, and all had advanced metastatic disease originating from primary cancers of various tissue origins. Of the three patients with documented PRs who received PG-11047 + bevacizumab (one patient with adenocarcinoma of unknown origin, one with invasive ductal carcinoma of the breast, and one with poorly differentiated squamous carcinoma of the piriform sinuses), the only tumor type common enough for a historical response rate is the ductal carcinoma of the breast, with a single-agent bevacizumab response rate of 9.3% (n = 75 patients) [34]. Thus, while the patient with

breast cancer could have responded to the bevacizumab alone (although not likely), there is no reported single-agent experience with bevacizumab alone in the other two tumor types. This makes it uncertain whether or not it was single-agent bevacizumab alone or in combination that gave these salutary responses in these two patients (unknown primary and piriform sinuses). In summary, given the rarity of some of the tumors in these particular patient treatments, the single agent activity of the conventional agents (cisplatin or bevacizumab) cannot not discounted.

Based on historical data given above, we conclude that PG-11047 is likely adding activity to the bevacizumab treatment. Further conclusions are not possible, particularly in the combination of PG-11047 + cisplatin. Bevacizumab is a monoclonal antibody that targets the pro-angiogenic factor vascular endothelial growth factor (VEGF), which is upregulated in response to hypoxic tumor conditions. Coincidentally, hypoxia has also been shown to increase polyamine transport into the cell as well as polyamine biosynthesis, and depleting intracellular polyamines during hypoxia increases tumor cell apoptosis [35]. These data imply an essential role for polyamines in tumor cell adaptation to hypoxic stress and suggest an underlying mechanism of action responsible for the partial responses in the PG-11047 + bevacizumab treatment group. Preclinical studies using cytotoxic drugs including cisplatin and 5-FU have been shown to upregulate polyamine catabolism through SSAT activity, which is also upregulated by PG-11047, providing mechanistic data in support of these combinations as a clinical strategy [36,37].

Overall, the anti-tumor activity of PG-11047 in six of the seven combination therapies thus was reported as “Stable Disease”. Lesion growth was controlled in 71.4% of patients treated with PG-11047 + 5-flurouracil/leucovorin, 50 – 60% of those treated with PG-11047 + gemcitabine, docetaxel, bevacizumab or cisplatin, and 33.3% of those receiving PG-11047 + erlotinib combination therapy. In spite of the DLTs observed with gemcitabine and docetaxel, stable disease was reported in 57.1% and 50% of the treated patients, respectively.

In conclusion, the results of this study indicate that PG-11047 can be safely administered in combination with the common anticancer agents bevacizumab, erlotinib, cisplatin, and 5-FU/Leucovorin. Our data also provide preliminary evidence of antitumor efficacy, in particular when PG-11047 is combined with bevacizumab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Dosing schedules

Combination treatment	Dose	Administration route	Administration days (cycle duration)	PG-11047 infusion days (cycle duration)
gemcitabine	1000 mg/m^2	30’ IV	1,8,15 (28)	1,15 (28)
docetaxel	75 mg/m^2	60’ IV	1 (21)	1 (21)
bevacizumab	5 mg/kg	IV	1,15 (28)	1,8,15 (28)
erlotinib	150 mg	oral	daily (28)	1,8,15 (28)
cisplatin	80 mg/m^2	60’ IV	1 (28)	1,8,15 (28)
(leucovorin) + 5-FU	(500 mg/m^2) 500 mg/m^2	(120’ IV) IV bolus 1 h post leucovorin start	1,8,15,22,29,36 (56)	1,8,15 (28)
sumitinib	50 mg	oral	daily for 28 d (42)	1,8 (21)

On days when both agents were administered, PG-11047 was administered first via 60- or 90-minute IV infusions.

Table 2.

Safety of PG-11047 administered in combination

	Total treated	*PG-11047 cycles completed*				
Combination	***n***	**1**	**≥2**	**% of patients with TEAEs**	**% of patients with TESAEs**	**most common TEAEs (occurring in > 5% of patients)**
gemcitabine	12	33.3%	66.7%	41.7%	41.7%	neutropenia, fatigue (16.7%)
docetaxel	9	11.1%	88.9%	88.9%	44.1%	neutropenia (55.6%); anemia, thrombocytopenia, fatigue, candidiasis, alopecia (22.2%)
bevacizumab	34	23.5%	76.5%	58.8%	29.4%	thrombocytopenia, nausea, facial hypoaesthesia (8.8%); fatigue (5.9%)
erlotinib	34	17.6%	82.4%	67.6%	35.5%	anemia (17.6%); anorexia (14.7%); nausea, dermatitis acneiform (11.8%): diarrhea, vomiting, fatigue, hypokalaemia, angioedema, drug eruption, hypotension (8.8%); constipation, dysgeusia, paraesthesia, facial hypoaesthesia (5.9%)
cisplatin	48	27.1%	72.9%	77.1%	43.8%	nausea (16.7%); fatigue (14.6%); thrombocytopenia (12.5%); vomiting (10.4%); increased lipase (8.3%); neutropenia, anorexia, dehydration, dysgeusia (6.3%)
(leucovorin) 5-FU	32	15.6%	84.4%	68.8%	53.1%	increased lipase (18.8%); fatigue (15.6%); anorexia (12.5%); mucosal inflammation, increased blood amylase (9.4%); anemia, neutropenia, thrombocytopenia, diarrhea, nausea, infusion-related reaction, pyrexia, paraesthesia, facial swelling (6.3%)
sunitinib	3	66.7%	33.3%	100.0%	33.3%	fatigue (66.7%)

TEAE, treatment-emergent adverse event

Table 3.

DLT and MTD of PG-11047 combination treatments

Combination	patients with DLT s (% of evaluable pts)	PG-11047 DLT dose	PG-11047 MTD
gemcitabine	3 (50%)	50 mg 100 mg (2)	ND
docetaxel	3 (33.3%)	50 mg (2) 100 mg	ND
bevacizumab	1 (3.4%)	375 mg	590 mg
erlotinib	2 (6.5%)	470 mg 590 mg	590 mg
cisplatin	2 (5.9%)	250 mg 300 mg	590 mg
(leucovorin) 5-FU	0	n/a	590 mg
sunitinib	0	n/a	ND

Table 4.

Overall responses to PG-11047 combination therapies.

	SD	PR	median duration of SD (range) (d)
gemcitabine	57.1% (4/7)	0	ND (52 – 195)
docetaxel	50.0% (4/8)	0	93 (29 – 110)
bevacizumab	40.0%(10/25)	12.0% (3/25)	145 (42 – 239)
erlotinib	33.3% (8/24)	0	116 (57 – 173)
cisplatin	54.1% (20/37) *	0	141(40 – 200)
(leucovorin) 5-FU	71.4 (15/21)	0	119 (53 – 132)
sunitinib	0%	0	ND

* 4 of these 20 patients had unconfirmed PRs; ND, not determinable due to sample size; SD, Stable Disease; PR, Partial Response

Table 5.

Details of patients with responses to PG-11047 combination therapies.

Combination	Cancer history	Target lesion response	Non-target lesion response	Off-study responses
bevacizumab	adenocarcinoma – unknown primary	PR after cycle 2	SD after cycle 2	ND
bevacizumab	breast - invasive ductal carcinoma	SD	PR	PR
bevacizumab	Poorly/moderately differentiated squamous cell carcinoma of the piriform sinuses	PR after cycle 2	NA	PR
cisplatin	poorly differentiated lung carcinoma with mixed SCLC/NSCLC features	PR after cycle 2	SD after cycle 2	PD non-target (multiple new brain lesions)
cisplatin	transitional cell carcinoma of the ureter	PR after cycles 2 and 4	SD after cycles 2 and 4	PD target SD non-target
cisplatin	poorly differentiated adenocarcinoma, unknown primary	PR after cycle 2	SD after cycle 2	PD target SD non-target
cisplatin	prostate cancer	PR after cycle 4, PD after cycle 6	PD after cycle 4, SD after cycle 6	PD target SD non-target

PR, partial response; SD, stable disease; PD, progressive disease; ND, not determined; NA not applicable