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# Phase II study of PX-866 in recurrent glioblastoma

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See the editorial by Nichol and Mellinghoff, on pages 1183–1184.

***Background.*** Glioblastoma (GBM) is the most aggressive malignancy of the central nervous system in adults. Increased activity of the phosphatidylinositol-3-OH kinase (PI3K) signal transduction pathway is common. We performed a phase II study using PX-866, an oral PI3K inhibitor, in participants with recurrent GBM.

***Methods.*** Patients with histologically confirmed GBM at first recurrence were given oral PX-866 at a dose of 8 mg daily. An MRI and clinical exam were done every 8 weeks. Tissue was analyzed for potential predictive markers.

***Results.*** Thirty-three participants (12 female) were enrolled. Median age was 56 years (range 35–78y). Eastern Cooperative Oncology Group performance status was 0–1 in 29 participants and 2 in the remainder. Median number of cycles was 1 (range 1–8). All participants have discontinued therapy: 27 for disease progression and 6 for toxicity (5 liver enzymes and 1 allergic reaction). Four participants had treatment-related serious adverse events (1 liver enzyme, 1 diarrhea, 2 venous thromboembolism). Other adverse effects included fatigue, diarrhea, nausea, vomiting, and lymphopenia. Twenty-four participants had a response of progression (73%), 1 had partial response (3%, and 8 (24%) had stable disease (median, 6.3 months; range, 3.1–16.8 months). Median 6-month progression-free survival was 17%. None of the associations between stable disease and PTEN, PIK3CA, PIK3R1, or EGFRvIII status were statistically significant.

***Conclusions.*** PX-866 was relatively well tolerated. Overall response rate was low, and the study did not meet its primary endpoint; however, 21% of participants obtained durable stable disease. This study also failed to identify a statistically significant association between clinical outcome and relevant biomarkers in patients with available tissue.

**Keywords:** clinical trial, glioblastoma, PI3K.

Glioblastoma (GBM) is the most common malignant tumor of the adult central nervous system, and it carries a poor prognosis.[1] Even with the standard first-line treatment of radiation and temozolomide following maximal surgical resection, nearly all patients will suffer disease progression.[2] At progression, no agents have demonstrated a predictable advantage in overall survival (OS), and consequently no standard of care exists. A variety of agents have demonstrated modest improvements in progression-free survival (PFS) and are used in clinical practice. Commonly used agents include bevacizumab, temozolomide, nitrosoureas, platinum analogs, etoposide, procarbazine, cis-retinoic acid, and high dose tamoxifen given alone or in various combinations.[3–7] With these agents, 6-month PFS (PFS-6) has usually been usually <20%, although 50% PFS-6 has recently been reported for regimens incorporating bevacizumab. Therapies targeting specific molecular aberrations, believed to be important in GBM, have been tried but with little success.[8]

PX-866 is a biologically stable pan-isoform inhibitor of the PI3K pathway.[9] Signal transduction by PI3K is critical for many of the cellular processes that are dysregulated in cancer,

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including cell motility, proliferation, survival, and angiogenesis.[10–14] Many common molecular aberrations in GBM activate the PI3K pathway, including changes in the epidermal growth factor receptor (EGFR) and the phosphatase and tensin homologue (PTEN) tumor suppressor.[15–17] EGFRvIII strongly and persistently activates the PI3K pathway.[18–20] The normal function of PTEN is to inhibit the PI3K pathway, and loss of PTEN activity is a poor prognostic factor in GBM.[21–23] Somatic mutations within the catalytic and regulatory subunits (PIK3CA and PIK3R1, respectively) of the PI3K complex are also common in GBM and allow for constitutive activation of the PI3K pathway.[23–25] Inhibition of the PI3K pathway with PX-866 leads to inhibition of cell growth and decreased activation of downstream targets in GBM, both in vitro and in vivo, using U87–tumor-bearing mice, including Akt, S6, and mTOR.[9,12,26]

PX-866 was well tolerated in phase I clinical trials, with common side effects being diarrhea, nausea, vomiting, and elevated liver enzymes.[27,28] We performed a nonrandomized, nonblinded, 2-stage, multicenter phase II clinical trial to examine the safety, tolerability, and efficacy of PX-866 in patients with progressive GBM.

## Patients and Methods

### *Patients*

This multicenter, open-label, single arm, phase II study was conducted in patients ≥18 years of age with histologically confirmed GBM at first progression during or following primary treatment. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2, tissue available for translational studies, and at least one contrast-enhancing lesion measuring a minimum of $1 \times 1$ cm on CT or MRI within the 14 days prior to registration. Laboratory requirements for enrollment included neutrophils $\geq 1.5 \times 10^9$/L, platelets ≥100 $1.5 \times 10^9$/L, creatinine ≤1.5× upper limit of normal (ULN), total bilirubin ≤1.5× ULN, AST and ALT ≤1.5× ULN, and glucose ≤ 8.9 mmol/L. Women must have been postmenopausal or on reliable contraception with a negative pregnancy test. Patients with other active malignancies, HIV, or uncontrolled diabetes mellitus were not eligible. All patients were required to provide informed consent. Accrual occurred between March 2011 and September 2012. The Clinical Trials registration number was NCT01259869. Ethics approval to run this study was received in every center.

Patients may have received radiation with concurrent temozolomide, followed by adjuvant temozolomide, but not within 28 days of registration. Targeted therapy was permitted (except for PI3K inhibition) as part of primary treatment but not within 28 days of registration or 56 days for antiangiogenic agents. No prior therapy for recurrent or progressive disease was permitted. Patients receiving corticosteroids were required to be on a stable or decreasing dose for at least 2 weeks prior to registration.

### *Treatment*

Eligible patients were given 8 mg of PX-866 by mouth daily, starting within 2 days of registration. Each cycle was 8 weeks long. Doses were held if neutrophils were $<1.0 \times 10^9$/L or platelets were $<50 \times 10^9$/L, until >1.5 and >75, respectively, and were reduced by 2 mg to a minimum of 4 mg daily. Modifications were made for hepatotoxicity, nausea, vomiting, and diarrhea, with doses held for grade 3 toxicity (according to NCI CTCAE v.4.0) until recovery and reduced by 2 mg to a minimum of 4 mg daily. Patients discontinued therapy for grade 3 AST/ALT with grade 2 bilirubin. For diarrhea, patients were treated with loperamide to a maximum of 16 mg per day; with dyphenoxylate and atropine being added if necessary. PX-866 was stopped for any grade 4 toxicity.

### *Evaluation*

Baseline evaluations of history and physical examination, complete blood count, chemistry, and urinalysis were done within 7 days of registration; MRI was performed within 14 days. Blood counts and chemistry were done weekly for 4 weeks, every 2 weeks to complete cycles 2 and 2, then every 4 weeks thereafter. MRI, clinical exam, and urinalysis were done at every 8-week cycle.

Tumor tissue from diagnostic samples was collected for analysis of potential markers of PI3K inhibitory activity. PTEN expression was determined by fluorescent in situ hybridization and sequencing. Next-generation sequencing was performed on the Illumina MiSeq following target enrichment using the Agilent HaloPlex Cancer Panel with additional coverage of PTEN exon regions. *EGFRvIII, PIK3CA,* and *PIK3R1* mutations were determined by sequencing and Oncocarta Sequenom mutational analysis.

### *Statistical Design and Analysis*

The primary endpoints were objective response and early progression (within 8 weeks on the study) as defined by Macdonald.[29] A multinomial design, which tests the null hypothesis of a response rate of ≤5% and an early progression rate of ≥60% against an alternate hypothesis of ≥20% response rate and early progression rate of ≤30, was used for this trial.[30] Stage 1 would enroll 15 participants, and observation of ≥1 responses or <10 early progressions was required to continue to the second stage, which would enroll an additional 15 participants. If ≥4 responses *or* if ≤13 early progressions were observed from a total of 30 participants, the drug would be considered to be worthy of further study. The actual type 1 error rate and the power of this design were 0.1 and 0.93, respectively.

The asymptotic method was used to calculate confidence interval (CI) for response, progression, or stable disease rate, and the Fisher' exact test was used for the correlation between stable disease and biomarker status. The Kaplan-Meier method was used to estimate the PFS-6 rate and associated CI.

## Results

Stage 1 enrolled 17 participants, and enrollment proceeded to stage 2 on the basis of <10 of the first 15 evaluable participants having early progression. A total of 33 participants were enrolled from the 2 stages of the trial. All were eligible and evaluable (Table 1). The median age was 56 years, and 29 participants were performance status (PS) 0-1. Median

**Table 1.** Demographics

| Parameter | *n* | % |
|---|---|---|
| Number of participants | 33 | |
| Age in years | | |
| Median | 56 | |
| Range | 35–78 | |
| Female | 12 | 36.4 |
| ECOG performance status | | |
| 0 | 13 | 39.4 |
| 1 | 16 | 48.5 |
| 2 | 4 | 12.1 |
| Prior therapy | | |
| Concurrent/adjuvant TMZ | 32 | 97.0 |
| Radiotherapy | 33 | 100 |
| Days from diagnosis | | |
| Median | 308 | |
| Range | 141–1256 | |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TMZ, temozolomide.

**Table 2.** Treatment details

| | | |
|---|---|---|
| **Cycles given** | | |
| Median | 1 | |
| Range | 1–8 | |
| **Dose intensity (mg/week)** | | |
| Median | 55 | |
| Range | 8.5–56.0 | |
| **Treatment modifications** | ***n*** | |
| None | 14 | |
| ≥1 dose not taken | 19 | |
| | 9 | AST/ALT |
| | 4 | Other |
| | 4 | Progression |
| | 3 | Diarrhea |
| | 3 | Patient forgot |
| | 2 | Nausea |
| | 2 | Vomiting |
| | 1 | Other AE |
| | 1 | Patient request |
| ≥1 dose reduction | 7 | |
| | 3 | AST/ALT |
| | 2 | Diarrhea |
| | 1 | Nausea |
| | 1 | Other |

Abbreviations: AE, adverse event; ALT, alanine amino transferase; AST, aspartate aminotransferase.

time from initial diagnosis to enrollment was 308 days (range, 141–1256 d), and from end of radiation to enrollment was 239 days (range, 76–1191 d). Twenty-six participants completed one 8-week cycle of PX-866, while 3 participants completed 2 cycles. One participant completed 3, 4, 5, and 8 cycles each (Table 2). All 33 participants discontinued therapy, 27 due to disease progression and 6 due to toxicity (5 liver enzyme elevation and 1 allergic reaction).

**Table 3.** Treatment-related adverse effects

| | Any | | Grade III | | Grade IV | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| **Hematological** | | | | | | |
| Anemia | 12 | 36 | | | | |
| Leukopenia | 10 | 30 | | | | |
| Lymphopenia | 29 | 88 | 6 | 18 | 1 | 3 |
| Neutropenia | 3 | 9 | | | | |
| Thrombocytopenia | 10 | 30 | | | | |
| **Nonhematological** | | | | | | |
| Creatinine | 1 | 3 | | | | |
| Alanine transaminase | 28 | 85 | 4 | 12 | 4 | 12 |
| Aspartate aminotransferase | 27 | 82 | 6 | 18 | 1 | 3 |
| Total bilirubin | 2 | 6 | | | | |
| Fasting hyperglycemia | 15 | 46 | | | | |
| Hypocalcemia | 12 | 36 | | | | |
| Hypokalemia | 4 | 12 | | | | |
| Hyponatremia | 7 | 21 | 1 | 3 | | |
| **Patient reported**[a] | | | | | | |
| Diarrhea | 11 | 33 | 5[b] | 15 | | |
| Nausea | 19 | 58 | 1 | 3 | | |
| Vomiting | 11 | 33 | 1 | 3 | | |
| Fatigue | 15 | 45 | 2 | 6 | | |
| Muscle weakness | 3 | 9 | 1 | 3 | | |
| Thromboembolic event | 2[b] | 6 | 1[b] | 3 | | |

[a]Only patient-reported events of grade III or IV were included.
[b]One or more events reported as a serious adverse event.

Common adverse events included fatigue, diarrhea, nausea, vomiting, and lymphopenia (Table 3). Four participants had related serious adverse events, which were considered by the local investigator to be possibly, probably, or definitely related to PX-866 (1 liver enzyme abnormality, 1 diarrhea, and 2 venous thromboembolism).

All participants were evaluable for response (Table 4). The response was progression of disease in 24 participants (73%; 95% CI, 57%–88%). One participant had a partial response for an overall response rate of 3% (95% CI, 0%–9%); however, this occurred in the participant who registered within 90 days of radiotherapy, which raised the possibility that this represented pseudoprogression. Eight participants (24%; 95% CI, 10%–39%) had stable disease while on PX-866 and maintained disease stability for a median of 6.3 months (range, 3.1–16.8 months). The waterfall plot for percentage change in tumor size is presented in Fig. 1. The PFS-6 was 17% (95% CI, 5%–32%).

Among those participants with adequate tissue for evaluation, no statistically significant association was found between stable disease and PTEN status, *EGFRvIII* mutation, *PIK3CA* mutation status or *PIK3R1* mutation status (Table 5).

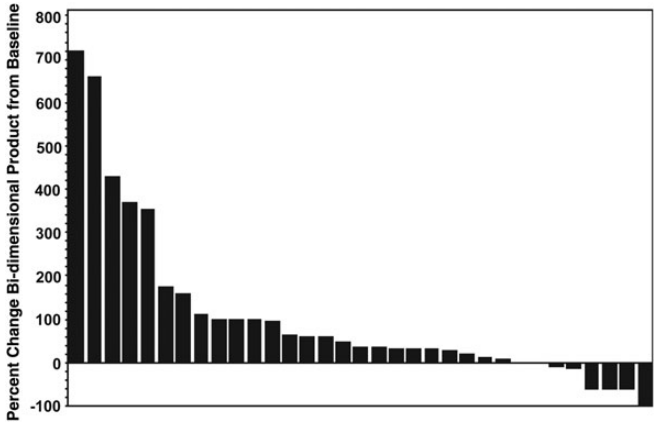


**Fig. 1.** Waterfall plot of radiological response to treatment.

**Table 4.** Efficacy outcomes

| Best Response | *n* (%) | Duration in Months | |
|---|---|---|---|
| | | Median | Range |
| Complete response | 0 (0) | | |
| Partial response | 1 (3) | 3.6 | 3.6–3.6 |
| Stable disease | 8 (24) | 6.3 | 3.1–16.8 |
| Progressive disease | 24 (73) | | |

**Table 5.** Correlative studies

| | Detected | Not Detected | Not Available | *P* value* |
|---|---|---|---|---|
| PTEN deletion | | | | |
| Status | 10 | 6 | 17 | .30 |
| PR/SD/PD | 0/2/8 | 0/3/3 | 1/3/13 | |
| *EGFRvIII* | | | | |
| Status | 6 | 9 | 18 | >.99 |
| PR/SD/PD | 0/2/4 | 0/4/5 | 1/2/15 | |
| *PIK3CA* | | | | |
| Status | 1 | 14 | 18 | >.99 |
| PR/SD/PD | 0/0/1 | 0/3/11 | 1/5/12 | |
| *PIK3R1* | | | | |
| Status | 3 | 12 | 18 | .52 |
| PR/SD/PD | 0/1/2 | 0/2/10 | 1/5/12 | |

Abbreviations: PR/SD/PD, partial response/stable disease/progressive disease; PTEN, phosphatase and tensin homolog.
*P value from Fisher's Exact Test for the correlation between stable disease and biomarker status.

## Discussion

We have evaluated the efficacy and safety of PX-866 for the treatment of GBM at first recurrence after standard radiotherapy and temozolomide chemotherapy. This is the first reported efficacy study of a pan-isoform PI3K inhibitor in GBM. The use of single agent PX-866 did not meet the primary endpoint of this study with an overall response rate of only 3%, possibly representing pseudoprogression, and progression rate of 73%. Notably, 24% of participants had stable disease, lasting a median of 6.3 months and up to 16.8 months in one patient. This observation is not trivial, given that recurrent GBM has an expected median PFS of <2 months.[3] We were not able to identify common molecular characteristics of the participants with response or stable disease in our preplanned correlative studies. While the overall response rate and PFS-6 suggest that PX-866 is not effective as a single agent in GBM, it remains possible that it could be effective in an as yet unidentified molecular subgroup or as part of a rational combination.

PI3K is a central regulator of cellular functions that are believed to be critical for glioblastoma growth, including proliferation, motility, survival, and angiogenesis.[10–14] It is possible that the portion of participants with stable disease in this study had tumors whose growth depended highly on a functional PI3K pathway. Our correlative studies were focused on identifying tumors that may rely on signaling through PI3K for their growth advantage. We looked for mutant *EGFRvIII*, which is common in GBM,[23] in tissue samples, as evidence of a reliance on PI3K for those tumors and a potential sensitivity to PI3K inhibition. We examined the tissue for PTEN mutations or loss, as have been reported to occur in 36% of GBMs.[23] PTEN is a negative regulator of PI3K, such that loss of function may induce overactive signaling through PI3K. Finally, we looked for intrinsic activating mutations in the regulatory subunits of PIK3CA, which render the PI3K complex constitutively active.[23] We were unable to correlate these molecular features with improved patient outcome in this study, although the power to detect this difference was limited by the low frequency of these derangements, the availability and adequacy of tissue samples, and the small study sample size. It is possible that PX-866 may not have effectively blocked signaling in these participants or that alternate pathways or mechanisms prevented growth arrest from being observed in a clinically meaningful way. A study design that enriched for these molecular factors may have increased the power of detecting an effect of PX-866. The results of this study underscore the importance of study design for investigational drugs in neuro-oncology. The multinomial 2-stage design we used allowed us to stop accrual if specific criteria were met. As a single arm study, we were unable to compare this agent directly with others currently in use or under evaluation. The efficacy of targeted agents in GBM relies on a number of assumptions that may have influenced the outcome of this study. In particular, these drugs must reach the target tissue and suppress the pathways of interest, those pathways must be dominant or integral to a critical function of the cell, there must be no compensatory pathways ready to take their place, and the pathways must be integral across the range of intratumoral heterogeneity of a GBM.[31]

The adverse effects of this drug were modest, and overall tolerability was high in this population. One-third of the participants in our study developed diarrhea, which was severe in 15% of them. We noted a high rate of significantly elevated liver enzymes, which was not previously reported in clinical studies of PX-866. In our study, 5 (15%) patients discontinued PX-866 because of liver enzyme abnormalities. No association was seen with elevated liver enzymes and concomitant medications, and the reason for the higher rate in our study is not clear.

We studied the PI3K inhibitor PX-866 in this single arm phase II study in recurrent GBM. This agent was reasonably well tolerated but did not meet the predefined efficacy endpoints. Despite this, a notable portion of the participants had prolonged stable disease while on PX-866, but there was no unifying molecular profile that defined these individuals.

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*Conflict of interest statement*. D.F.H. is employed by and owns stock in Oncothyreon.

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