A First-in-Human Phase I Study to Evaluate the Brain-Penetrant PI3K/mTOR Inhibitor GDC-0084 in Patients with Progressive or Recurrent High-Grade Glioma

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BACKGROUND

- Glioblastoma is the most common primary malignant brain tumor in adults. With the current standard of care, few patients survive beyond 5 years,[1] highlighting the need for new therapeutic strategies.
- The phosphoinositide 3-kinase (PI3K) pathway is activated in ≥80% of glioblastoma multiforme (GBM) tumors, making it a compelling target for the treatment of GBM[2]
- GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of phosphoinositide PI3K and mammalian target of rapamycin (mTOR) kinase that was specifically designed for treatment of brain cancer
- In mouse xenograft models, GDC-0084 demonstrated dose-dependent tumor-growth inhibition (TGI), with 60% and 90% TGI observed at exposures equivalent to those achieved in the clinic[3,4]

OBJECTIVES

- Assess the safety, tolerability, and pharmacokinetics of GDC-0084 in patients with progressive or recurrent high-grade gliomas (WHO Grade III–IV)
- Determine the MTD of GDC-0084 and to characterize the dose-limiting toxicities (DLTs)
- Characterize pharmacodynamic (PD) effects of GDC-0084 treatment in patients with progressive or recurrent high-grade gliomas (WHO Grade III–IV) through assessment of change in glucose metabolism by means of ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) scans.
- Make a preliminary assessment of anti-tumor activity of single-agent GDC-0084

METHODS

- Open-label, multicenter, Phase I, dose-escalation study using a standard 3+3 design
- GDC-0084 was administered orally once daily in cycles of 28 days, on a continuous dosing schedule at doses of 2–65 mg
- Dose escalation continued in accordance with the dose-escalation rules until the MTD was exceeded, excessive pill burden was declared, or analysis of available PK data indicated that exposure was unlikely to increase with further increases in the dose of GDC-0084

Safety Evaluation

- All adverse events (AEs) occurring on or after treatment on Day 1 of Cycle 1 were summarized by mapped term, appropriate thesaurus levels, and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 toxicity grade
- Cycle 1 was the DLT assessment window

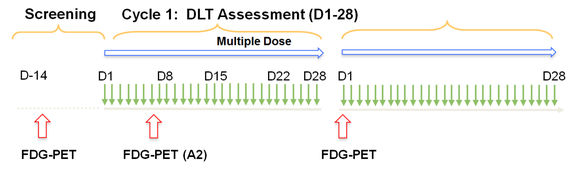
Pharmacokinetic Evaluation

- Plasma samples for PK analysis were collected on Days 1 and 8, or Day 15 of Cycle 1

Clinical Evaluations

- Objective response rate was estimated only for patients with disease that was measurable by Response Assessment in Neuro-Oncology Criteria (RANO) guidelines[5]
- FDG-PET was performed at baseline and on-treatment

Figure 1. Study Design.



The timing of the on-treatment FDG-PET scan was changed from Cycle 2, Day 1 to Cycle 1, Day 8 as part of a protocol amendment in November 2011 (A2).

RESULTS

Patient Characteristics

- 47 pts enrolled in 8 successive dose escalation cohorts (2–65 mg)

Table 1. Patient Demographics and Disease Characteristics.

	2 mg (n=7)	4 mg (n=4)	8 mg (n=5)	15 mg (n=6)	20 mg (n=4)	30 mg (n=7)	45 mg (n=8)	65 mg (n=6)	All Patients (N=47)
Age in years, median (range)	58 (32–63)	61 (30–64)	44 (38–59)	57 (38–62)	38 (30–50)	56 (44–73)	49 (31-62)	42 (29–59)	50 (29–73)
Sex (male)	5 (71%)	3 (75%)	5 (100%)	6 (67%)	2 (50%)	3 (43%)	6 (75%)	6 (100%)	34 (72%)
Time from primary diagnosis (mo.), median (range)	56 (13–182)	37 (22–47)	53 (22–67)	43 (14–87	24 (18–132)	20 (11–45)	97 (23–190)	35 (12–100)	41 (11–190)
WHO Grade									
III	3 (43%)	1 (25%)	1 (20%)	1 (17%)	1 (25%)	-	5 (63%)	2 (33%)	14 (30%)
IV	4 (57%)	3 (75%)	4 (80%)	5 (83%)	3 (75%)	7 (100%)	3 (38%)	4 (67%)	33 (70%)
Baseline KPS score									
70	1 (14%)	-	1 (20%)	-	1 (25%)	2 (29%)	3 (38%)	1 (17%)	9 (19%)
80	4 (57%)	1 (25%)	1 (20%)	1 (17%)	1 (25%)	3 (43%)	-	2 (33%)	13 (28%)
90	2 (29%)	3 (75%)	3 (60%)	5 (83%)	2 (50%)	2 (29%)	4 (50%)	3 (50%)	24 (51%)
100	-	-	-	-	-	-	1 (13%)	-	1 (2%)

WHO=World Health Organization; KPS=Karnofski Performance Status. The median number of prior systemic treatments across all dose levels was 3 (range 1-5).

Safety

- The most frequent AEs attributed to GDC-0084 were fatigue, hyperglycemia, nausea, rash, hypertriglyceridemia, mucositis, hypophosphatemia, decreased appetite, and diarrhea
- The most common Grade 3 AEs related to GDC-0084 were hyperglycemia (4 patients [8.5%]) and mucositis (3 patients [6.4%])
- DLTs were 1 case of Grade 2 bradycardia and Grade 3 myocardial ischemia (15 mg), Grade 3 stomatitis (45 mg), and 2 cases of Grade 3 mucosal inflammation (65 mg)
- The MTD was determined to be 45 mg GDC-0084 given orally once daily in 28 day cycles
- Overall, the AE profile was consistent with PI3K/mTOR class effects; AEs at the MTD were amenable to monitoring, manageable, and reversible upon dose hold or discontinuation

Table 2. Adverse Events Related to GDC-0084 Occurring in ≥ 3 Patients.

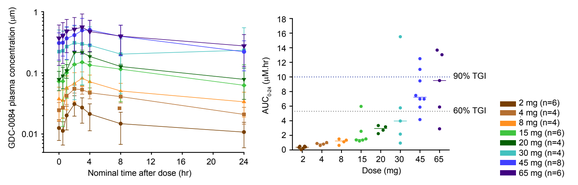
	2 mg (n=7)		4 mg (n=4)		8 mg (n=5)		15 mg (n=6)		20 mg (n=4)		30 mg (n=7)		45 mg (n=8)		65 mg (n=6)		All Patients (N=47)	
	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All	Gr 3	All
Any adverse events	0	1 (14%)	0	3 (75%)	0	3 (60%)	1 (17%)	4 (67%)	0	4 (100%)	2 (29%)	6 (86%)	2 (25%)	7 (88%)	4 (67%)	5 (83%)	9 (19%)	33 (70%)
Fatigue [a]	0	0	0	0	0	1 (20%)	0	2 (33%)	0	1 (25%)	1 (14%)	2 (29%)	0	5 (62%)	0	3 (50%)	1 (2%)	14 (30%)
Hyperglycemia	0	0	0	1 (25%)	0	1 (20%)	1 (17%)	3 (50%)	0	0	1 (14%)	3 (43%)	0	2 (25%)	2 (33%)	3 (50%)	4 (9%)	13 (28%)
Nausea	0	0	0	2 (50%)	0	1 (20%)	0	0	0	3 (75%)	0	1 (14%)	0	2 (25%)	0	2 (33%)	0	11 (23%)
Rash [b]	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (38%)	0	5 (83%)	0	8 (17%)
Hypertriglyceridemia	0	0	0	1 (25%)	0	0	0	1 (17%)	0	0	0	2 (29%)	0	2 (25%)	0	1 (17%)	0	7 (15%)
Mucositis [c]	0	0	0	0	0	0	0	0	0	0	0	0	1 (12%)	4 (50%)	2 (33%)	3 (50%)	3 (6%)	7 (15%)
Hypophosphatemia	0	0	0	1 (25%)	0	2 (40%)	0	0	0	0	0	0	0	2 (25%)	1 (17%)	1 (17%)	1 (2%)	6 (13%)
Decreased appetite	0	0	0	0	0	0	0	0	0	1 (25%)	0	0	0	4 (50%)	0	0	0	5 (11%)
Diarrhea	0	0	0	1 (25%)	0	0	0	0	0	0	0	1 (14%)	0	1 (12%)	0	2 (33%)	0	5 (11%)
Vomiting	0	0	0	0	0	0	0	0	0	2 (50%)	0	0	0	1 (12%)	0	1 (17%)	0	4 (9%)
Cholesterol increased	0	0	0	0	0	0	0	0	0	0	0	2 (29%)	0	1 (12%)	0	0	0	3 (6%)
Hypercholesterolemia	0	0	0	1 (25%)	0	0	0	1 (17%)	0	0	0	0	0	0	0	1 (17%)	0	3 (6%)
Platelet count decr.	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (25%)	0	1 (17%)	0	3 (6%)

No Grade 4 or 5 drug-related AEs were reported. [a] Fatigue includes fatigue and asthenia. [b] Rash includes rash and rash maculo-paular. [c] Mucositis includes mucosal inflammation and stomatitis.

Pharmacokinetics

- GDC-0084 displayed an approximately linear and dose proportional increase in C_{max} and $AUC_{0\text{-}24}$ following single and multiple doses across all cohorts (2–65 mg once daily)
- GDC-0084 was rapidly absorbed with a median T_{max} of ~2 hours following a single dose
- GDC-0084 had a mean half-life of approximately 18.7 hours
- In 2 specimens, GDC-0084 was detected at similar levels in brain tumor and brain tissue, with a brain tissue/tumor to plasma ratio of > 1 and > 0.5 for total and free drug, respectively

Figure 2. GDC-0084 Pharmacokinetics. (A) Concentration-Time Plot and (B) Steady-State AUC in Individual Patients.



Concentration-time plot shown as multiple dose, mean ± S.E. Horizontal lines indicate exposures that correlate to 60% or 90% tumor growth inhibition (TGI) in the u87 model.

Pharmacodynamic Effects and Clinical Activity

- Of the patients who underwent FDG-PET imaging, 7 of 27 (26%) patients had metabolic partial response
- At doses of ≥ 45 mg QD, a trend towards decreased median SUV in normal brain was observed, suggesting CNS penetration of study drug
- Overall, as assessed by RANO criteria, 26 patients (55%) had a best overall response of progressive disease, 19 patients (40%) had stable disease, 1 patient was not evaluable, and the data for 1 patient was missing

Figure 3. FDG-PET: (A) Change in Mean Standard Update Value (SUV_{max}) in Tumor, and (B) Median SUV in Normal Brain.

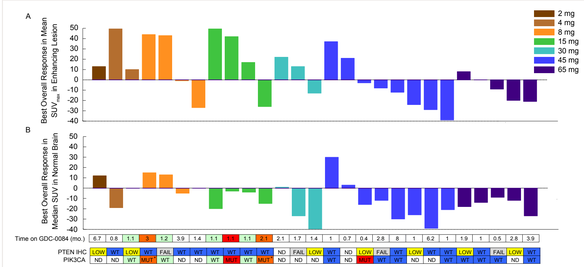
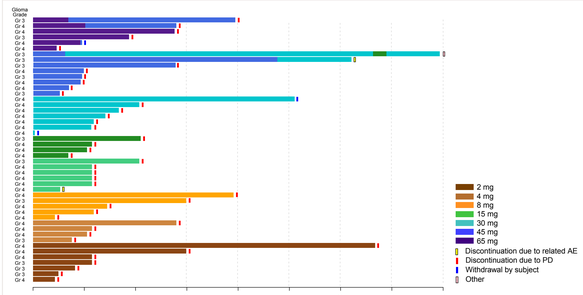
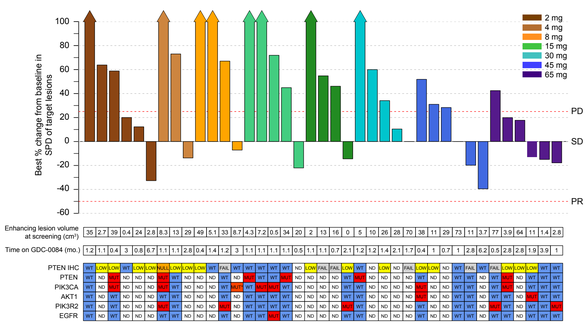


Figure 4. GDC-0084 Time on Study.



Patients are grouped by dose levels. WHO glioma grade (3 or 4) is noted for each patient.

Figure 5. Objective Response Estimated for Patients with Disease Measurable by Response Assessment in Neuro-Oncology Criteria (RANO) Guidelines.



SPD=sum of products of diameters; PD=progressive disease; SD=stable disease; PR=partial response; IHC=immunohistochemistry; WT=wild type; MUT=mutant; ND=not detected; MUT* = local assessment. Best change in sum of product of diameters of target lesions is displayed by dose level.

SUMMARY

- The safety profile demonstrated classic Pi3K/mTOR-inhibitor related AEs and acceptable tolerability at the recommended dose of 45 mg daily
- GDC-0084 is rapidly absorbed and demonstrates linear- and dose-proportional increases in exposure, with a half-life supportive of once daily dosing; 7/8 patients dosed at the MTD of 45 mg had drug exposures consistent with anti-tumor activity in pre-clinical models.
- FDG-PET scans of tumor brain tissue and normal brain tissue suggest that GDC-0084 crosses the blood brain barrier, with a uniform distribution throughout the brain
- Single-agent anti-tumor activity is minimal, with 55% of patients demonstrating a best response of progressive disease, and 40% of patients demonstrating stable disease
- These data support further development of GDC-0084 as a combination therapy

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