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Clinical Pharmacokinetics and Brain Penetration of GDC-0084, an Oral PI3K/mTOR Inhibitor, in Patients with High-Grade Glioma

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INTRODUCTION

- 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.
- GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of PI3K and mammalian target of rapamycin (mTOR) kinase.
- In preclinical models, GDC-0084 was shown to readily distribute into the brain, with brain-to-plasma ratios ≥1, and brain concentrations leading to marked suppression of the PI3K pathway[1] **(Table 1, Figure 1)**.
- In mouse xenograft models, GDC-0084 demonstrated dose-dependent tumor-growth inhibition (TGI), with 60% and 90% TGI observed at a human equivalent AUC values of 4.9 and 9.5 uM.hr, respectively[1] **(Figure 2)**.

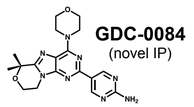


Table 1. Brain and CSF distribution of GDC-0084 in preclinical models

Species	Brain-to-Plasma Ratio	Free Brain-to-Free Plasma Ratio	CSF-to-Free Plasma Ratio
Mouse	1.3	0.40	N/A
Rat	2.4	0.68	1.5
Dog	2.2	0.45	1.03

Figure 1. Inhibition of p-AKT by GDC-0084 in mouse brain

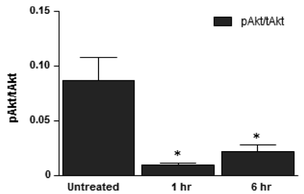
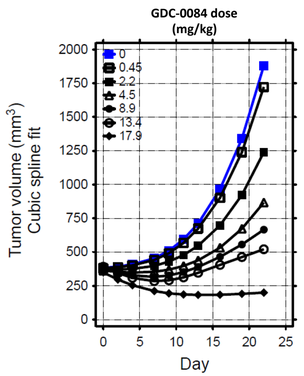


Figure 2. In vivo efficacy of GDC-0084 against U87 mouse xenograft tumors



- A first-in-human, phase 1 dose escalation study was conducted in patients with high-grade glioma using a 3+3 study design. The pharmacokinetic (PK) objective of this study was to evaluate the PK of GDC-0084 after single and multiple once daily dosing.

MATERIALS AND METHODS

- GDC-0084 was administered orally, once daily on a continuous dosing schedule. Plasma samples for PK analysis were collected on Day 1 and Day 8 or 15 of Cycle 1.
- The PK parameters of GDC-0084 at dose levels ranging from 2 – 65 mg (n = 47) were determined by non-compartmental analysis.
- Brain-to-plasma ratios were calculated by measuring GDC-0084 concentrations in a post-dose surgical brain tissue sample and a post-mortem brain tissue specimen.

RESULTS

- GDC-0084 is rapidly absorbed (T_{max} ~2 hr) and demonstrates linear and dose proportional increases in exposure, with a half-life supportive of once daily dosing ($t_{1/2}$ ~19 hr) **(Figures 3 and 4, Table 2)**.
- Exposure of GDC-0084 observed at 45 mg QD exceeds the pre-clinically predicted exposure associated with efficacy (60%TGI) in 7 of 8 patients **(Figure 5)**.

Figure 3. Mean ± SD Plasma Concentration vs. Time Profiles of GDC-0084 Following a Single Dose

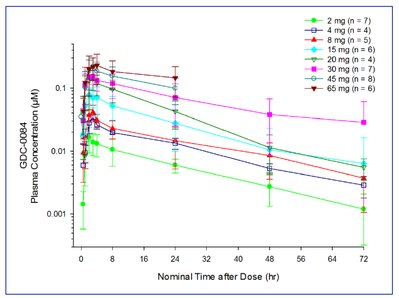


Figure 4. Dose Proportionality of GDC-0084

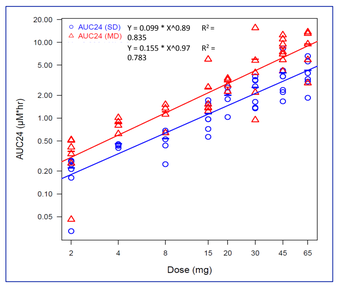
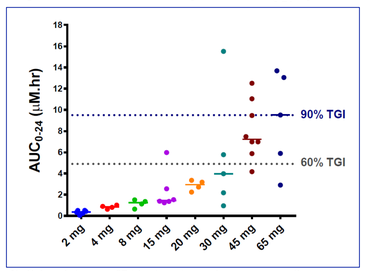


Table 2. Single Dose Mean PK Parameters

Dose (mg)	Half-life (hr)	T_{max} (hr)	C_{max} (μM)	AUC_{0_24} (μM*hr)	n
2	16.9	2.0	0.02	0.21	7
4	21.8	3.0	0.04	0.44	4
8	18.2	3.0	0.05	0.51	5
15	18.1	2.0	0.09	1.09	6
20	14.8	2.0	0.16	1.90	4
30	22.0	2.0	0.17	2.42	7
45	ND	3.0	0.23	3.12	8
65	ND	2.5	0.26	4.06	6

Figure 5. Observed Steady-state AUC_{0-24} by dose



%TGI targets from a U87 (PTEN null) subcutaneous xenograft model

- GDC-0084 was detected at similar levels in brain tissue and brain tumor in two patient specimens, with a favorable brain-to-plasma ratio:
  - Surgical brain specimen **(Table 3)**:
    - Brain tumor/plasma: >1.43 (total), >0.48 (free)
    - Brain tissue/plasma: >1.54 (total), >0.51 (free)
  - Post-mortem brain specimen **(Table 4)**:
    - Brain tumor/plasma: ~1.10 (total), ~0.38 (free)
    - Brain tissue/plasma: ~0.60 (total), ~0.21 (free)
    - CSF/free plasma: ~0.45

Table 3. GDC-0084 Concentration in a Surgical Brain Specimen[a]

Sample	Total GDC-0084	Free GDC-0084
Plasma	0.56 uM	0.11 uM
Brain Tissue	0.86 uM	0.058 uM
Brain Tumor	0.80 uM	0.054 uM[a]

[a] Resection of brain tissue and tumor from a patient dosed at 45 mg QD; samples obtained 5.5 hr (plasma) and 7 hr (brain) post-dose
[b] Assumes same binding as brain (fu 0.067)

Table 4. GDC-0084 Concentration in a Post-Mortem Brain Specimen and CSF[a]

Sample	Total GDC-0084 (post-mortem)	Free GDC-0084 (post-mortem)	*Estimated* Total GDC-0084[c] (at steady-state)	*Estimated* Free GDC-0084[c] (at steady-state)
Estimated Plasma[b]	1.64 nM	0.33 nM	0.42 uM	0.08 uM
CSF		0.14 nM		0.036 uM
Brain Tissue	0.972 nM	0.065 nM	0.25 uM	0.02 uM
Brain Tumor	1.79 nM	0.12 nM[b]	0.46 uM	0.03 uM[d]

[a] Post-mortem samples from a 45 mg subject who discontinued treatment due to disease progression; samples were obtained 11 days after last dose
[b] Estimated from observed data at earlier time points
[c] Estimated from observed $C_{max,ss}$ data in this patient; assumes the same rate of elimination in all matricies
[d] Assumes same binding as brain (fu 0.067)

REFERENCE

1. Heffron et al, ACS, Med. Chem. Lett., 2016

CONCLUSIONS

1. GDC-0084 is rapidly absorbed and demonstrates linear and dose proportional increases in exposure, with a half-life supportive of once daily dosing.
2. At a dose of 45 mg, steady-state exposures were consistent with exposures associated with antitumor activity in mouse xenograft models.
3. Concentration data from a brain tumor resection and a post-mortem brain specimen suggest that GDC-0084 crosses the blood brain barrier, with a uniform distribution throughout the brain.
   - Brain-to-plasma ratios observed in human brain specimens are consistent with preclinical observations
   - Results from preclinical studies and post-mortem samples suggest that GDC-0084 CSF concentrations may be representative of free brain concentrations