Phase 2 study to evaluate the safety, pharmacokinetics, and clinical activity of the PI3K / mTOR inhibitor GDC-0084 given to glioblastoma (GBM) patients with unmethylated 06-methyglycine-methyltransferase (MGMT) promoter status

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BACKGROUND

- Glioblastoma (GBM) is the most common and aggressive form of primary brain cancer, with survival rates of 12-15 months with standard therapy.
- Standard of care therapy (the “Stupp Regimen”), i.e. debulking surgery + chemoradiation therapy with temozolomide (XTM/TMZ), show a ~65% failure rate, with unmethylated MGMT promoter status being the main driver of resistance.
- GDC-0084 is a potent, oral, selective, brain-penetrant, small molecule inhibitor of class I phosphoinositide-3-kinase and mammalian target of rapamycin (PI3K/mTOR).1
- The PI3K pathway is upregulated in ~90% of GBM cases per the Cancer Genome Atlas1, and GDC-0084 has shown efficacy in a range of preclinical models.
- Phase I study (NCT01547546) investigated GDC-0084 given once-daily as an oral (PO) dose in 47 patients with recurrent high-grade gliomas.
- Maximum tolerated dose (MTD) was 45 mg once daily.
- GDC-0084 was rapidly absorbed and demonstrated linear and dose-proportional increases in exposure in 7/8 patients receiving the 45 mg dose had drug exposure consistent with anti-tumor activity in preclinical models.
- Adverse events (AEs) were consistent with established Class I PI3K/mTOR inhibitor class-effects (Table 1).
- 19/40 (48%) of patients in the study demonstrated a best observed response of Stable Disease (SD) per RANO criteria, consistent with a primarily cytostatic mode of action; at the 45 mg dose, 3/6 patients (50%) achieved SD (Figure 1).
- Fluorodeoxyglucose-potassium emission tomography (FDG-PET) scans suggested that GDC-0084 crossed the BBB with a uniform distribution throughout the brain.
- Of the patients who underwent FDG-PET imaging, 7/27 (26%) had metabolic partial response.

STUDY ENDPOINTS

Primary Safety Endpoint
- Dose limiting toxicities (DLTs)

Key Secondary Safety Endpoints
- Treatment-emergent adverse events (TEAEs), Grade 3-5 TEAEs, serious adverse events (SAEs), fatal AEs, TEAEs leading to drug discontinuation or study withdrawal.
- Treatment-emergent Grade 3/4 clinical laboratory abnormalities.
- Change/shift in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters.
- Change in carcinoid use.
- Change in left ventricular ejection fraction (LVEF).
- Change in Karnovsky Performance Status (KPS).

Secondary Clinical Benefit Endpoints
- Progression free survival (PFS) from first dose (Stage 1) or (randomization) Stage 2) to death.
- Time to progression (TTP) from first dose (Stage 1) or (randomization) Stage 2) to death.

Exploratory endpoints will include PK parameters, FDG-PET uptake in tumor and normal brain tissue, and disease control rate.

CURRENT STATUS

Stage 1 is complete, as of May 2019, and has determined an MTD of 60 mg. It is envisaged that this dose will be adopted for future studies in the newly-diagnosed population.

Stage 2 is currently recruiting and full recruitment is expected by end of calendar 2019.

SUMMARY

Discussion
- Despite the importance of the PI3K pathway in GBM, there have been few brain-penetrant agents developed specifically for this population.
- A previous study has shown GDC-0084 to be generally well-tolerated, and has provided signals of activity in a recurrent population.
- The newly-diagnosed population may respond differently to treatment, as a result of higher performance status, lower tumour burden, and potentially a lesser degree of tumour heterogeneity.
- The present study is designed to assess the tolerability and activity of GDC-0084 in a newly-diagnosed, unmethylated population, and it is anticipated that this will be the lead indication for future development.

Future Directions
- A randomised phase II/III study is planned to commence in 2020 to establish definitive efficacy.
- Investigator-initiated studies are underway in DIPG (NCT03569335), breast metastases (NCT03994796), breast cancer brain metastases (with trastuzumab) (NCT07376583), and breast metastases (with radiotherapy) (NCT TBD).

METHODS

This open-label, multicentre, 2 year study recruiting patients with newly diagnosed GBM from 6-8 sites in the US has 2 phases: Stage 1 (dose escalation) and Stage 2 (expansion cohort) (Figure 2).

- Patients are screened and treated with GDC-0084 in 2 stages as follows:
  - Stage 1: dose escalation
  - Stage 2: expansion cohort

Subject Eligibility
- Male and female patients ≥ 18 years
- Histologically confirmed diagnosis of GBM with unmethylated MGMT promoter status
- Undergone surgical debulking of tumor(s) and initial treatment with XTM/(TMZ) or XRT only if indicated

Treatment
- Following screening, patients are treated with GDC-0084 with escalating doses (Stage 1) or at the MTD (Stage 2) (Figure 3).
- Patients who discontinue treatment are followed every 6 weeks until determination of disease progression.
- Subsequent anti-cancer therapy and survival follow-up (FU) collected every 12 weeks until death.

STUDY DESIGN FOR STAGE 1 & 2

Primary Safety Endpoint
- Dose limiting toxicities (DLTs)

Subject Eligibility
- Male and female patients ≥ 18 years
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- Patients who discontinue treatment are followed every 6 weeks until determination of disease progression.
- Subsequent anti-cancer therapy and survival follow-up (FU) collected every 12 weeks until death.

Stage 1: dose escalation
- Standard “3+3” design: allowance of 3 newly-diagnosed patients further to define safety, tolerability and PK of GDC-0084.
- Patients receive GDC-0084 13 patients (range: 6-24) patients
- Patients who discontinue treatment are followed every 6 weeks until determination of disease progression.

Stage 2: expansion cohort
- Two-arm, open-label design: chemoradiation safety, tolerability and PK of GDC-0084.
- patients receive GDC-0084 20 patients (parallel groups of 10).

Objectives
- Investigating the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK), and clinical activity of GDC-0084 in newly-diagnosed patients with GBM with unmethylated 06-methylglycine-methyltransferase (MGMT) promoter status as adjuvant therapy following surgical resection and initial chemoradiation with TMZ.

Table 1: Key Adverse Events at 45mg Dose (n=8)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>2 (25%)</td>
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<td></td>
<td></td>
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<tr>
<td>Stomatitis / mucositis</td>
<td>4 (50%)</td>
<td>1 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (38%)</td>
<td>1 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (25%)</td>
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<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (63%)</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>5 (63%)</td>
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Figure 1: Response of patients by dose cohort and exposure to GDC-0084 shows a trend towards disease stabilization at the 45 mg dose.

Figure 2: Study Design for Stage 1 & Stage 2

Stage 1: Dose Escalation
- Standard “3+3” design: allowance of 3 newly-diagnosed patients further to define safety, tolerability and PK of GDC-0084.
- Patients receive GDC-0084 13 patients (range: 6-24) patients
- Patients who discontinue treatment are followed every 6 weeks until determination of disease progression.

Stage 2: Expansion Cohort
- Two-arm, open-label design: chemoradiation safety, tolerability and PK of GDC-0084.
- patients receive GDC-0084 20 patients (parallel groups of 10).

Dose-Escalation Rules for Stage 1
- If no patients in a Cohort experience a dose limiting toxicity (DLT) after 6 patients, Cohort is expanded (Stage 2).
- If 2 patients experience a DLT at dose level 1 to MTD declared to be 45 mg (per phase 1 study).

Key Study Assessments
- Overall survival (OS) from first dose (in Stage 1) or (randomization) Stage 2 to death.
- Time to progression (TTP) from first dose (Stage 1) or (randomization) Stage 2 to death.
- Overall survival (OS) from first dose (in Stage 1) or from randomization (Stage 2) to death.

DISCLOSURES

The authors wish to thank the patients and their families for participating in this study.

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REFERENCES
5. American Society for Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2016, Chicago, IL.

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(Original abstract))