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 O6-methylguanine-methyltransferase (MGMT) promotor status

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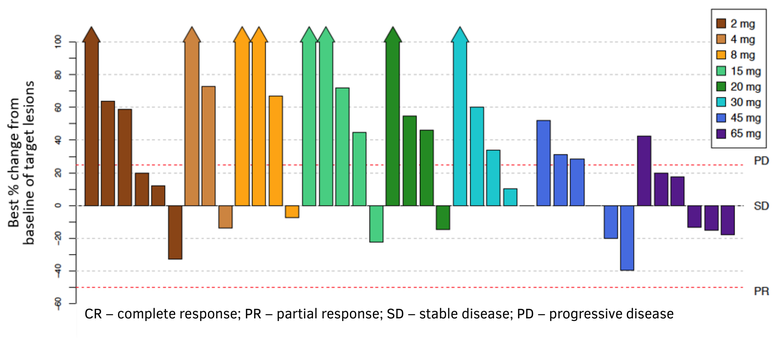
BACKGROUND

- **Glioblastoma (GBM)** is the most common and aggressive form of primary brain cancer, with survival rates of 12-15 months with best available care
- Standard of care therapy (the 'Stupp Regimen'), i.e. debulking surgery + chemoradiation therapy with temozolomide (XRT/TMZ), show a ~65% failure rate[1], with **unmethylated MGMT promotor status** being the main driver of primary 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)[2,3]
- The **PI3K pathway** is upregulated in ~85% of GBM cases per the Cancer Genome Atlas[4], 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 and 7/8 patients receiving the 45mg dose had drug exposure consistent with anti-tumor activity in pre-clinical models
  - Adverse events (AE) were consistent with established Class I PI3K/mTOR inhibitor class-effects (Table 1)
  - 19/45 (40%) 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 45mg dose, 3/6 patients (50%) achieved SD (Figure 1)
  - Fluorodeoxyglucose-positron 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[5]

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

Preferred Term	All	≥ Grade 3
Hyperglycemia	2 (25%)	-
Stomatitits / Mucositis	4 (50%)	1 (12%)
Diarrhea	1 (12%)	-
Nausea / Vomiting	2 (25%)	-
Rash	5 (63%)	-
Fatigue	5 (63%)	-

Figure 1: Response of patients by dose cohort and exposure to GDC-0084 shows a trend towards disease stabilization at the 45 mg dose



CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease

OBJECTIVES

The current **phase IIa study** (NCT03522298) is investigating the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK), and clinical activity of GDC-0084 in patients with newly-diagnosed GBM with unmethylated O^6-methylguanine-methyltransferase (MGMT) promoter status as adjuvant therapy following surgical resection and initial chemoradiation with TMZ

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METHODS

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

Figure 2: Study Design for Stage 1 & Stage 2

Stage 1: Dose Escalation	Stage 2: Expansion Cohort
Standard "3+3" design: • determine the MTD in newly-diagnosed patients • further define safety, tolerability and PK of GDC-0084 ~12 patients (range: 6-24)	Two-arm, open-label design: • characterize safety, tolerability and PK of GDC-0084 • assess single agent activity of GDC-0084 • explore effect of fed vs. fasting state on PK of GDC-0084 ~20 patients (2 parallel groups of 10)

Subject Eligibility

- Male and female patients ≥ 18 years
- Histologically confirmed diagnosis of GBM with unmethylated MGMT promoter status
- Undergone surgical resection of tumor(s) and initial treatment with XRT/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

Figure 3: Treatment Algorithm

	Screening	Stage 1	Stage 2
Treatment	**Debulking surgery → XRT** 2 Gy/d (5 d/wk for 6 wks; total 60 Gy) + **Concomitant TMZ** 75 mg/m²/d PO from first to last day of radiotherapy	**Cohort 1:** GDC-0084 60 mg PO QD (4x15 mg caps) in 28-day cycles **Cohort 2-x:** dose increases at 15 mg increments Patients treated until disease progression or unacceptable toxicity)	GDC-0084 PO QD at RP2D from Stage 1, dosing in 28-day cycles until disease progression or unacceptable toxicity
Sample		*n*=3 per cohort *Recovery from side effects before entering Stage 1*	Randomized: • n=10 - fed • *n*=10 - fasted

Dose-Escalation Rules for Stage 1

- If no patients in a Cohort experience a dose limiting toxicity (DLT) (defined *a priori* in protocol) within assessment period (d 1-28), escalation will proceed to the next higher dose in 3 newly-recruited patients
- If 1 patient experiences DLT, Cohort expanded (max. 6); if a second patient experiences a DLT → MTD 1 dose level below; if no further DLTs, continue dose escalation
- If ≥2 patients experience a DLT at dose level 0 → MTD declared to be 45 mg (per phase I study)

Key Study Assessments

	SCR (-28 d)	CYC. 1 Wk 1 D 1	CYC. 2 D 1	CYC. 3 onwards Every 4 Wks	Every 8 Wks	Every 8 Wks	EOT/ FU start	Post-EoT FU
KPS	X	X	X	X			X	
MRI		X			X		X	
FDG-PET scan		X						
ECG	X	X	X	X			X	
LVEF	X					X		
aPTT / PT / INR	X	X	X	X			X	
Pregnancy Test	X	X	X	X			X	
PK Sampling		X	X					
Hematol/Chemistry	X	X	X	X			X	
AEs	X	X	X	X			X	X
Disease status								X

SCR: screening; EOT: end of treatment

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 corticosteroid 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 (in Stage 1) or randomization (Stage 2) to disease progression (RANO criteria) or death.
- Overall survival (OS) from first dose (in Stage 1) or from randomization (Stage 2) to death.
- Time to progression (TTP) from first dose (Stage 1) or randomization (Stage 2) to disease progression.

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 60mg. 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 disease
- 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 (NCT03696355), brain metastases (NCT03994796), breast cancer brain metastases (with trastuzumab) (NCT03765983), and brain metastases (with radiotherapy) (NCT TBD)

DISCLOSURES

WEN: Agios, Astra Zeneca, Beigene, Eli Lilly, Genentech, Roche, Karyopharm, Kazia Therapeutics, MediciNova, Merck, Novartis, Oncoceutics, Sanofi-Aventis, VBI Vaccines, Prime Oncology, Abbvie, Blue Earth Diagnostics, Immunomic Therapeutics, Karyopharm, Kiyatec, Puma, Vascular Biogenics, Taiho, Deciphera, Tocagen. **DE GROOT**: Sanofi-Aventis, Astra Zeneca, EMD-Serono, Eli Lilly, Novartis, Deciphera Pharmaceuticals, Mundipharma, Ziopharm Oncology, Gilead, Celldex, Deciphara Pharmaceuticals, Abbvie, FivePrime Therapeutics, GW Pharma, Carthera, Eli Lilly, Kadmon, Boston Biomedical, Taiho Pharmaceuticals, Kairos Venture Investments, Syneos Health, Monteris, Agios, Mundipharma, GenomiCare, Blue Earth Diagnostics, Genentech, Foundation Medicine, Kazia Therapeutics, Astra Zeneca, Insys Therapeutics, Merck, Novella Clinical, Kiyatec, Vanquish Oncology, Orsenix. **BATTISTE**: Kazia Therapeutics. **GOLDLUST**: Cortice Bio, Wex Pharma, BMS, Cantex, Celldex, Northwest, Kazia Therapeutics, Diffusion, Novocare, Tocagen, Boston Bio., Cota. **GARNER**: Kazia Therapeutics. **SIMPSON**: Kazia Therapeutics, Bionomics. **OLIVERO**: Genentech, Roche, Merck, Kazia Therapeutics, Imugene, Aduro. **CLOUGHESY**: Tocagen, Kryopharm, DNAtrix, Amgen, Abbvie, Astra Zeneca, Boston Biomedical, Dicephara Pharmaceuticals, VBL, Agios, Merck, Roche, Boehringer Ingeiheim, VBI, Dicephara Pharmaceuticals, VBL, Agios, Merck, Roche, Genocea, Celgene, Puma, Eli Lilly, BMS, Cortice, Wellcome Trust, Novocure, Notable Laboratories, Kazia Therapeutics, Boston Biomedical, Sunovion, Human Longevity, Insys, ProNai, Pfizer, MedQIA.

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