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

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BACKGROUND

- **Paxalisib** (GDC-0084) is a potent, oral, selective, brain-penetrant inhibitor of class I phosphoinositide 3-kinase and mammalian target of rapamycin[1,2]
- The **PI3K pathway** is upregulated in ~85% of GBM cases per the Cancer Genome Atlas[3], and paxalisib has shown efficacy in a range of preclinical models
- A **phase I study** (NCT01547546) investigated paxalisib given once-daily as an oral (PO) dose in 47 patients with recurrent high-grade gliomas. The maximum tolerated dose (MTD) was 45mg once daily[4]

OBJECTIVES

The current **phase IIa study** (NCT03522298) aims to explore the safety, tolerability, and clinical activity of paxalisb in patients with **newly-diagnosed GBM** and **unmethylated MGMT promotor** status, following surgical resection and chemoradiotherapy.

METHODS

This is an open-label, single-arm, multicenter study in two parts, as shown in Figure 1.

- **Stage 1** – a dose escalation cohort to establish the MTD in newly-diagnosed unmethylated patients
- **Stage 2** – a dose expansion cohort to seek preliminary evidence of clinical activity in newly-diagnosed patients

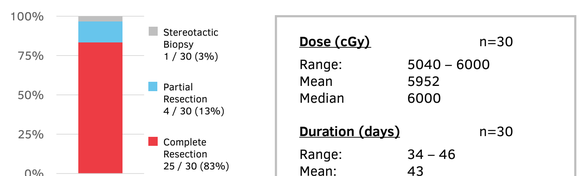
Figure 1: Study Design for Phase II study of GDC-0084

Stage 1: Dose Escalation	Stage 2: Expansion Cohort
Standard "3+3" design: • determine MTD in newly-diagnosed patients • further define safety, tolerability and PK	Two-arm, open-label design: • assess single agent activity of paxalisib • explore effect of fed vs. fasting state on PK
9 patients enrolled	21 patients enrolled

PATIENT POPULATION

Demographics (*n*=30)

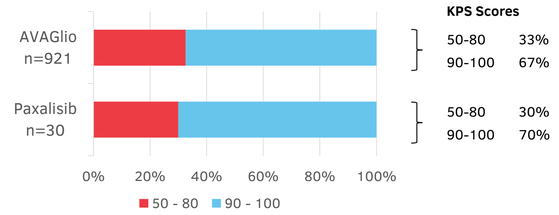
Figure 2: Key Demographic Parameters



Performance Status

Baseline **Karnofsky performance status** (KPS) appeared highly comparable to AVAGlio study (2014) in newly-diagnosed GBM[5], suggesting a broadly representative sample (Figure 3)

Figure 3: Baseline Performance Status



Prior Treatment

Figure 4: Surgical History

Figure 5: Radiotherapy History

Dose (cGy)	n=30
Range:	5040 – 6000
Mean	5952
Median	6000
Duration (days)	**n=30**
Range:	34 – 46
Mean:	43
Median:	43

INTERIM EFFICACY

- Recruitment was completed in February 2020. A number of patients remain on study drug and in post-treatment follow-up. Interim data are reported here
- For the entire study population, a median progression-free survival (PFS) of **8.5 months** was determined (Figure 6), and a median overall survival (OS) of **17.7 months** (Figure 7)
- One patient remains progression-free and on treatment twenty-two months after diagnosis [*as at May 2020*]

Figure 6: Kaplan-Meier Curve of Progression-Free Survival (PFS)

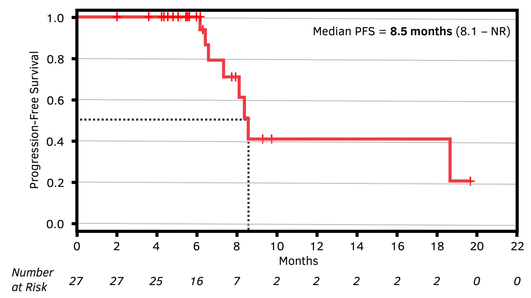
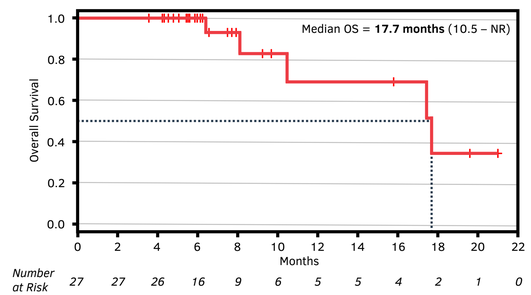


Figure 7: Kaplan-Meier Curve of Overall Survival (OS)



Analysis Cut-Off: 29 February 2020

DISCUSSION

Emerging Conclusions

- A maximum-tolerated dose (MTD) of **60mg** od has previously been reported. The principal toxicities were oral mucositis, hyperglycemia and skin rash, consistent with the class[6]
- The population of this study appears broadly representative of the wider glioblastoma population
- Encouraging signals of clinical efficacy have been observed, with a **PFS of 8.5 months** and an **OS of 17.7 months** on this analysis. The study remains ongoing

Directions for Future Research

- Paxalisib is expected to join the international GBM AGILE pivotal study (NCT03970447) in the second half of 2020
- Phase I studies are also underway in DIPG and DMGs (NCT03696355), and in brain metastases in combination with radiotherapy (NCT04192981), and phase II studies are in progress in brain metastases (NCT03994796), and in HER2+ breast cancer brain metastases (NCT03765983). Additional studies in other forms of brain cancer are under discussion
- Paxalisib has been granted orphan designation by FDA

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