Interim results of a Phase 2 study to evaluate the PI3K/mTOR inhibitor paxalisib (GDC-0084) given to newly diagnosed glioblastoma patients with unmethylated O^6-methylguanine-methyltransferase promoter

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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

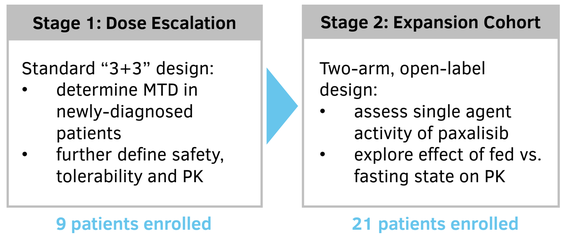
The current **phase IIa study** (NCT03522298) aims to explore the safety, tolerability, and clinical activity of paxalisb in patients with **newly-diagnosed GBM** and **unmethylated MGMT promotor** status, following surgical resection and chemoradiotherapy.

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



INTERIM SAFETY SUMMARY

- 24 patients received a dose of 60mg (3 in Stage1, 21 in Stage 2), and 6 patients received 75mg (all in Stage 1)
- The maximum tolerated dose was determined to be 60mg
- In general, toxicities were highly consistent with other PI3K / mTOR inhibitors, and with prior experience in this agent
- Most common AEs were rash, stomatitis, hyperglycemia, fatigue, nausea, and decreased appetite (Figure 2)
- Of note, no evidence of pneumonitis, cardiac toxicity, GI perforation, infection, CNS toxicity, or significant hepatotoxicity were seen

Figure 2: Number of Patients at 60mg (n=24) Experiencing AEs 'Possibly' or 'Likely' Related to Paxalisib (affecting ≥2 patients)

Term	Gr 1	Gr 2	Gr 3	Gr 4	Total (%)
Rash	4	6	7		17 (71%)
Fatigue	2	10	2		14 (58%)
Stomatitis	4	6	1		11 (46%)
Decr. appetite	5	5	1		11 (46%)
Nausea	3	5	1		9 (38%)
Hyperglycemia	1	2	5		8 (33%)
Diarrhea	5	1			6 (25%)
Decr. neutrophils	2	3		1	6 (25%)
Vomiting	3	2	1		6 (25%)
Decr. weight	3	2			5 (21%)
Decr. platelets	4	1			5 (21%)
Dehydration		4	1		5 (21%)
Dysgeusia		4			4 (17%)
Decr. lymphocytes	1	2			3 (13%)
Drug reaction			3		3 (13%)
Malaise	2	1			3 (18%)
Incr. cholesterol	2				2 (8%)
Pruritis	1		1		2 (8%)

INTERIM EFFICACY

- Recruitment was completed in February 2020. A number of patients remain on study drug and in post-treatment follow-up. Interim data as at **31 August 2020** are reported here
- For the entire study population, a median progression-free survival (PFS) of **8.4 months** was determined (Figure 3), and a median overall survival (OS) of **17.5 months** (Figure 4)
- One patient remains progression-free and on treatment twenty-seven months after diagnosis [*as at August 2020*]

Figure 3: Kaplan-Meier Curve of Progression-Free Survival (PFS)

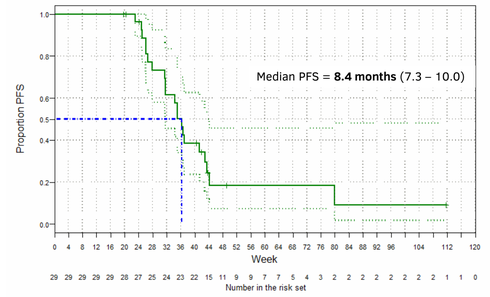
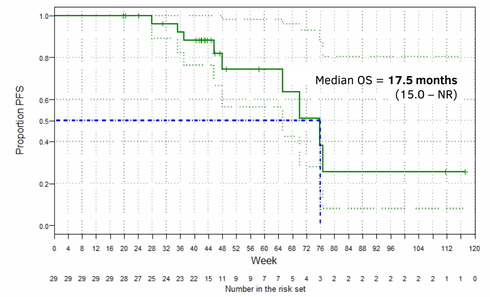


Figure 4: Kaplan-Meier Curve of Overall Survival (OS)



Analysis Cut-Off: 31 August 2020

DISCUSSION

Emerging Conclusions

- A maximum-tolerated dose (MTD) of **60mg** od has previously been reported. The dose-limiting toxicities at 75mg included hyperglycemia and mucositis[6]
- At 60mg, key toxicities of note include rash, stomatitis, hyperglycemia, consistent with other drugs in the PI3K / mTOR inhibitor classes
- Encouraging signals of clinical efficacy are consistent with prior interim analyses, with a **PFS of 8.4 months** and an **OS of 17.5 months** on this analysis. The study remains ongoing

Directions for Future Research

- Paxalisib has joined the international GBM AGILE study (NCT03970447) in newly-diagnosed and recurrent GBM
- 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), and in primary CNS lymphoma (TBD)

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