

A study of the focal adhesion kinase inhibitor GSK2256098 in patients with recurrent glioblastoma with evaluation of tumor penetration of [^{11}C]GSK2256098

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Background

GSK2256098 is a novel oral focal adhesion kinase (FAK) inhibitor. Preclinical studies demonstrate growth inhibition in glioblastoma cell lines. However, rodent studies indicate limited blood–brain barrier (BBB) penetration. In this expansion cohort within a phase I study, the safety, tolerability, pharmacokinetics (PK), and clinical activity of GSK2256098 were evaluated in patients with recurrent glioblastoma. Biodistribution and kinetics of [^{11}C]GSK2256098 were assessed in a substudy using positron-emission tomography (PET).

Methods

Patients were treated with GSK2256098 until disease progression or withdrawal due to adverse events (AEs). Serial PK samples were collected on day 1. On a single day between days 9 and 20, patients received a microdose of intravenous [^{11}C]GSK2256098 and were scanned with PET over 90 minutes with parallel PK sample collection. Response was assessed by MRI every 6 weeks.

Results

Thirteen patients were treated in 3 dose cohorts (1000 mg, 750 mg, 500 mg; all dosed twice daily). The maximum tolerated dose was 1000 mg twice daily. Dose-limiting toxicities were related to cerebral edema. Treatment-related AEs (>25%) were diarrhea, fatigue, and nausea. Eight patients participated in the PET substudy, with [^{11}C]GSK2256098 VT (volume of distribution) estimates of 0.9 in tumor tissue, 0.5 in surrounding T2 enhancing areas, and 0.4 in normal brain. Best response of stable disease was observed in 3 patients, including 1 patient on treatment for 11.3 months.

Conclusions

GSK2256098 was tolerable in patients with relapsed glioblastoma. GSK2256098 crossed the BBB at low levels into normal brain, but at markedly higher levels into tumor, consistent with tumor-associated BBB disruption. Additional clinical trials of GSK2256098 are ongoing.

Keywords: focal adhesion kinase, glioblastoma, GSK2256098, PET

Topic: positron-emission tomography, fatigue, glioblastoma, cerebral edema, focal adhesions, phosphotransferases, safety, brain, kinetics, neoplasms, pharmacokinetics, kinase inhibitors, toxic effect.

Importance of the study

This is the first clinical trial to evaluate a FAK inhibitor in glioblastoma. Increased FAK expression is observed in glioblastoma and is associated with a negative prognosis. While the FAK inhibitor GSK2256098 demonstrates preclinical activity in glioblastoma cell lines and xenografts, PK studies in rodents demonstrate limited central nervous system penetration in the presence of an intact BBB. We evaluated BBB penetration through assessment of [¹¹C]GSK2256098 biodistribution and kinetics. Tumor penetration of [¹¹C]GSK2256098 was observed in all participants with limited penetration into surrounding normal brain. Tumor concentrations of [¹¹C]GSK2256098 exceeded those associated with antitumor activity in preclinical studies. GSK2256098 was tolerated in patients with recurrent glioblastoma. These data support further clinical trials of GSK2256098 in patients with central nervous system tumors, which are ongoing.

Glioblastoma is the most common malignant primary brain tumor. Median survival is less than a year and standard treatment with surgery followed by radiotherapy and temozolomide chemotherapy results in a median survival of 14.6 months and 5-year overall survival of less than 10%.¹⁻³ Clinical trials of second-line therapies have yet to demonstrate a survival improvement.

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that functions within dynamic protein complexes called focal adhesions that are present at the site of attachment between cells and the extracellular matrix. FAK supports the assembly of focal adhesions and their consolidation of signals from integrins and growth factor receptors.^{4,5} FAK is phosphorylated at tyrosine 397 during activation, and phosphorylated (p)FAK forms a binary complex with the Src family kinases. FAK can trigger multiple downstream intracellular signaling cascades required for cell survival, growth, adhesion, migration, and invasion.⁴⁻⁶ In addition, FAK is associated with the protection of cells from anoikis through the sequestration of receptor-interacting protein from the death-receptor machinery, and with regulation of chemokine transcription.^{4,7}

Overexpression of FAK mRNA or protein is documented in many solid tumors, including glioblastoma.^{4,5,8-13} FAK expression is increased in metastatic disease compared with normal and early stage disease, indicating that it may be a marker of invasive potential.^{14,15} FAK protein expression is elevated in human glioblastoma relative to normal brain tissue.^{8,16} There is increased FAK and pFAK expression in higher-grade versus lower-grade gliomas; the former are associated with poorer survival.¹⁷ In addition, FAK expression is associated

with angiogenesis in high-grade gliomas but not in normal brain tissue, and there is evidence that FAK promotes angiogenesis in glioma by activating endothelial cell migration.⁹

GSK2256098 is a potent, ATP-competitive, reversible inhibitor of FAK with an enzymatic half-maximal inhibitory concentration value of 1.5 nmol/L. It has approximately 1000-fold specificity for FAK over the closest family member, Pyk2.¹⁸ In assays of 95 cancer cell lines, glioblastoma cell lines were some of the most sensitive to GSK2256098 (GlaxoSmithKline internal data). In preclinical studies, dose- and time-dependent inhibition of pFAK was observed in subcutaneous U87MG (human glioma) xenograft models, with correlation between pFAK inhibition and blood concentration of GSK2256098.¹⁸ Preclinical studies in rats indicate limited central nervous system (CNS) penetration of GSK2256098 in the presence of an intact blood–brain barrier (BBB), with brain:plasma concentrations of 0.08, 0.06, and 0.07 at 20, 40, and 60 minutes after a single oral dose, and 0.12, 0.35, and 0.45 at 6 hours post dose following a 6-hour i.v. infusion (6 mL/kg/h). GSK2256098 is a substrate of p-glycoprotein (Pgp), an efflux pump implicated in poor BBB penetration of many drugs. In *in vitro* studies with cell lines of MDCKII-MDR1 (Madin-Darby canine kidney type II–multidrug resistance protein 1) heterologously expressing human Pgp, GSK2256098 (3 μ M) was a Pgp substrate with a moderate efflux ratio of 5.0 and GSK2256098 (100 μ M) inhibited transport of digoxin (probe Pgp substrate) by 47% of the control value.¹⁹ However, in glioblastoma the BBB is disrupted,^{20–22} potentially permitting tumor penetration of GSK2256098.

A phase I open-label clinical trial of orally administered GSK2256098 was conducted in patients with advanced non-CNS cancers.²³ A total of 62 patients were enrolled into the study, comprising dose-escalation and expansion cohorts. GSK2256098 was well tolerated, and the declared maximum tolerated dose (MTD) was 1000 mg twice daily. Dose-limiting toxicities (DLTs) were grade 2 proteinuria (1000 mg), grade 2 nausea, vomiting, fatigue (1250 mg), and grade 3 asthenia and grade 2 fatigue (1500 mg). Minor responses were observed in 3 patients with mesothelioma and 1 patient with melanoma. These findings, combined with the encouraging preclinical evidence, raised the question of whether the drug was active in patients with glioblastoma. Here we report the safety and systemic and CNS pharmacokinetics (PK) of GSK2256098 in an expansion cohort of patients with glioblastoma. PET imaging was used to evaluate CNS and tumor penetration of [¹¹C]GSK2256098 in participants.

Methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, and applicable clinical trials regulations. Study conduct was approved by the London (Chelsea) Research Ethics Committee (11/LO/0551) and the Medicines and Healthcare Regulatory Agency and the Administration of Radioactive Substances Advisory Committee (ARSAC research certificate #RPC: 630/3925/28196), UK. All participants provided written informed consent prior to participation in the study. The trial was registered with ClinicalTrials.gov (NCT01138033).

Study Design and Patients

FAK113517 was a phase I open-label, nonrandomized, multicenter study of GSK2256098. In this expansion cohort, patients were recruited at 3 sites within the United Kingdom. GSK2256098 was administered at the MTD of 1000 mg twice daily, and at a dose of 750 mg or 500 mg twice daily to explore doses below the MTD. Dose reductions for toxicity were permitted.²³

Key eligibility criteria for recruitment: glioblastoma at first or second recurrence; progressive disease by Response Assessment in Neuro-Oncology (RANO) criteria; prior temozolomide-based chemoradiotherapy; measurable disease by RANO criteria; age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate hematologic, hepatic, and renal functions. Key exclusion criteria included active gastrointestinal disease that may impair drug absorption, prolonged QTc, and history of acute coronary syndrome or heart failure. CYP3A4, CYP2C8, CYP2C9, and OATP1B1 inhibitors and inducers were precluded prior to and during study participation.

Endpoints

The primary objectives of the study were to assess the safety and tolerability of GSK2256098 in patients with relapsed glioblastoma at the MTD determined in systemic cancers, with secondary objectives of characterizing PK and antitumor activity. The objectives of the PET imaging substudy were to assess the biodistribution and kinetics of [¹¹C]GSK2256098 and to estimate the quantity of [¹¹C]GSK2256098 in tumors and normal brain.

Assessments

Safety and tolerability

Pretreatment patient evaluation included medical history, physical examination, ECOG performance status, vital signs, blood tests (hematology, biochemistry, coagulation profiles), ECG, and urinalysis. These were repeated at specified timepoints throughout the study.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Toxicities occurring in the first 21 days of treatment were considered for determining DLTs.

Tumor assessment

Brain MRI with contrast was performed at baseline and every 6 weeks. Response evaluations were made according to the RANO criteria.²⁴

Pharmacokinetics

Blood samples were collected on Dried Blood Spot (DBS) cards for PK assessment predose and at 1, 1.5, 2, 3, and 4 hours following day 1 dose; and for predose on days 8, 15, 22, and 43. GSK2256098 concentrations in blood were quantified using a validated analytical method based on extraction from DBS on Whatman FTA (Flinders Technology Associates) paper, followed by ultra-high-performance liquid chromatography–tandem mass spectrometry (assay range, 10 to 10000 ng/mL). The PK parameters were derived by noncompartmental methods.

Imaging substudy

A PET-CT scan was performed on a single day between day 9 and day 20, after intravenous injection of carbon-11 radiolabeled [¹¹C]GSK2256098, about 2 hours after oral dosing of GSK2256098 (to coincide with expected peak plasma concentration). Initially, a CT scan of the head was performed to estimate tissue attenuation, immediately followed by a 90-minute cranial dynamic PET scan following intravenous administration of a bolus microdose (<10 µg) of [¹¹C]GSK2256098. Continuous arterial blood sampling was performed for the first 15 minutes of the scan for blood radioactivity measurements. Additionally, arterial blood samples for radioactivity counting and radio-HPLC (high performance liquid chromatography) metabolite analysis were collected during the PET scan. Blood was collected for PK sampling prior to oral dosing and at 1, 2, and 4 hours post oral dosing. Whole blood and plasma radioactivity measurements were used to calculate time-activity curves (TACs) of radioactivity concentration in blood and plasma. Measured radiometabolite data were used to correct these curves and derive the time course of [¹¹C]GSK2256098 in plasma. Supplementary Figures S1, S2, and S3 and [Supplementary Table S1](#) give additional PET protocols.

The dynamic PET images were reconstructed and corrected for attenuation and background randoms and scatter. The summed PET images for the full scan duration (0–90 min) was registered to each subject's baseline MR images and corrected for motion using a frame-to-frame registration process with a normalized mutual information cost function. Regions of

interest (ROIs) were manually delineated on the [^{11}C]GSK2256098 PET scan corresponding visually to areas of [^{11}C]GSK2256098 uptake in the PET scan (PET-enhanced regions) and in the normal brain tissue (*normal brain region*) away from the tumor. ROIs were also manually delineated on MR images obtained for clinical purposes on a day prior to the PET-CT scan and to correspond with gadolinium (Gd) enhancing regions on T1 postcontrast sequences (*T1 Gd-enhanced region*) and regions with increased T2 fluid attenuated inversion recovery (FLAIR) signal (*T2-FLAIR enhanced region*) indicating edematous regions. Given that the T1 Gd-enhanced region was typically a subset of the T2 FLAIR enhanced region, a third ROI was derived from the T2 FLAIR enhanced region that was not also enhanced on T1 post-Gd (*T2 FLAIR exc. Gd region*).

All the manually delineated regions were applied to the dynamic PET images to derive TACs for each of the regions defined. Tissue and plasma TACs were modeled to estimate the PET volume of distribution (V_T), which is the equilibrium partition coefficient of radioactivity between tissue and plasma for the tissue regions delineated.

Statistical Analysis

Descriptive statistics were used for safety, response, and PK data. Sample size was based on feasibility and not on power to test a statistical hypothesis. PET imaging data were analyzed using MIAKAT software version 3.3.8.

Results

Patients

Thirteen patients (median age 53 y) from 3 hospitals were enrolled and received at least one dose of GSK2256098 (Table 1). Eleven patients had a histological diagnosis of glioblastoma, 1 had a histological diagnosis of gliomatosis cerebri, and 1 had a previous histological diagnosis of anaplastic oligoastrocytoma with radiological evidence of subsequent transformation to glioblastoma. The median time from diagnosis of glioblastoma to study entry was 17 months, with a median time from last progression to study entry of 42 days. The median number of lines of previous chemotherapy was 2 (range, 1–3). All patients discontinued study treatment, most frequently due to disease progression (69%).

Table 1

Baseline patient characteristics

	500 mg b.i.d. (N = 3)	750 mg b.i.d. (N = 4)	1000 mg b.i.d. (N = 6)	Total (N = 13)
Age, y				
Mean	52.0	43.0	52.0	49.2
SD	11.36	12.75	8.99	10.70
Median (min, max)	57.0 (39, 60)	39.0 (33, 61)	53.0 (40, 65)	53.0 (33, 65)
Age group, n (%)				
18–64 y	3 (100)	4 (100)	5 (83)	12 (92)
65–74 y	0	0	1 (17)	1 (8)
Sex, n (%)				
Female	0	2 (50)	1 (17)	3 (23)
Male	3 (100)	2 (50)	5 (83)	10 (77)
Race, n (%)				
White—Arabic/North African heritage	1 (33)	0	0	1 (8)
White— White/Caucasian/European heritage	2 (67)	4 (100)	6 (100)	12 (92)
Number of prior chemotherapy regimens, n (%)				

	500 mg b.i.d. (N = 3)	750 mg b.i.d. (N = 4)	1000 mg b.i.d. (N = 6)	Total (N = 13)
1	0	0	2 (33)	2 (15)
2	2 (67)	3 (75)	3 (50)	8 (62)
3	1 (33)	1 (25)	1 (17)	3 (23)
Receiving steroids at baseline, n (%)				
Yes	3 (100)	2 (50)	5(83)	10 (77)
No	0	2 (50)	1 (17)	3 (23)
	500 mg b.i.d. (N = 3)	750 mg b.i.d. (N = 4)	1000 mg b.i.d. (N = 6)	Total (N = 13)
Age, y				
Mean	52.0	43.0	52.0	49.2
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Median (min, max)	57.0 (39, 60)	39.0 (33, 61)	53.0 (40, 65)	53.0 (33, 65)
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18–64 y	3 (100)	4 (100)	5 (83)	12 (92)
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	500 mg b.i.d. (N = 3)	750 mg b.i.d. (N = 4)	1000 mg b.i.d. (N = 6)	Total (N = 13)
Sex, <i>n</i> (%)				
Female	0	2 (50)	1 (17)	3 (23)
Male	3 (100)	2 (50)	5 (83)	10 (77)
Race, <i>n</i> (%)				
White—Arabic/North African heritage	1 (33)	0	0	1 (8)
White— White/Caucasian/European heritage	2 (67)	4 (100)	6 (100)	12 (92)
Number of prior chemotherapy regimens, <i>n</i> (%)				
1	0	0	2 (33)	2 (15)
2	2 (67)	3 (75)	3 (50)	8 (62)
3	1 (33)	1 (25)	1 (17)	3 (23)
Receiving steroids at baseline, <i>n</i> (%)				
Yes	3 (100)	2 (50)	5(83)	10 (77)
No	0	2 (50)	1 (17)	3 (23)

Safety and Tolerability

Patients were treated with GSK2256098 at 1000 mg (n = 6), 750 mg (n = 4), or 500 mg (n = 3) twice daily. A single DLT of grade 4 cerebral edema with associated grade 3 somnolence was observed in the 1000 mg cohort, and 1000 mg was determined as the MTD as defined by protocol criteria. Due to the observed cerebral edema, the investigators decided to explore treatment at dose levels below the MTD, to further characterize safety and tolerability and to investigate tumor penetration of [¹¹C]GSK2256098. One patient in the 750 mg cohort (n = 4) experienced grade 4 cerebral edema with associated grade 3 somnolence and grade 3 headache. There were no DLTs in patients in the 500 mg cohort (n = 3).

All patients reported at least one treatment-related adverse event (AE). The most frequent treatment-related AEs were diarrhea (38%), fatigue (31%), and nausea (31%). Treatment-related AEs by maximum toxicity grade are shown in Table 2. The majority of treatment-related AEs were grade 1 or 2. Brain edema was the only treatment-related grade 4 AE and was reported in 2 subjects. In both patients, the symptoms of brain edema improved following cessation of GSK2256098 and commencement of high-dose dexamethasone, but recurred following rechallenge with GSK2256098 at a dose reduction. In addition, there were 2 subjects with grade 3 AEs of fatigue and 2 with grade 2 AEs of somnolence that were reported as treatment related. All other treatment-related grades 3 and 4 AEs were reported for only one subject. No grade 3 or grade 4 treatment-related AEs occurred in more than one subject in the 500 mg cohort.

Table 2

Treatment-related adverse events

Discontinuation of GSK2256098 due to treatment-related AEs occurred in 2 patients due to grade 3 fatigue (n = 1) and grade 3 rise in alanine transaminase (n = 1). Dose reductions of GSK2256098 due to treatment-related AEs occurred in 1 patient in the 1000 mg cohort due to fatigue, and in 2 patients in the 1000 mg cohort (n = 1) and 750 mg cohort (n = 1) due to symptoms of cerebral edema. Two other patients had dose reductions (1 due to dosing error, and 1 per sponsor request). Twelve serious AEs occurred in 7 patients (54%); most were unrelated to GSK2256098 (58%). Treatment-related serious AEs included raised alanine transaminase (grade 3), somnolence (grade 3), lower respiratory tract infection (grade 3), and myalgia (grade 3).

Pharmacokinetics

All subjects participated in PK assessments on day 1 (Table 3). There was moderate to high intersubject variability. The results were not meaningfully different from those estimated for subjects in solid tumors in previous cohorts of this phase I trial with a difference in maximal concentration of 42% between the 2 groups following single or repeated doses across 750 mg and 1000 mg.²³

Table 3

Summary of GSK2256098 pharmacokinetic parameter values

%CVb = between-subject coefficient of variation; $AUC_{(0-4)}$ = area under the DBS concentration-time curve to the last quantifiable concentration; C_{avg} = average concentration over the dose interval; C_{max} = maximum observed concentration; DBS = dried blood spot.

Data reported as geometric mean (%CVb)

Clinical Activity

Eleven patients had imaging subsequent to commencing GSK2256098 and were evaluable for assessment of clinical activity. A best response of stable disease by RANO criteria was observed in 3 patients (27%), with progressive disease in 8 patients (73%). Median progression-free survival was 5.7 weeks (95% CI: 3.1–8.3 wk). Two patients were on study for over 90 days: 1 patient for 3.3 months (500 mg cohort) and 1 patient for 11.3 months (750 mg cohort).

[¹¹C]GSK2256098 Biodistribution and Kinetics

Eight patients participated in the PET imaging substudy. Tracer metabolism was moderate, with around 30%–55% of radioactivity in plasma at 90 minutes attributable to intact parent radiotracer ([Supplementary Figure S3](#)). Estimates of the regional PET V_T and images from a representative patient are shown in Table 4 and Fig. 1. Estimate of [¹¹C]GSK2256098 V_T was around 0.4 (range, 0.2–0.6) in normal brain, 0.9 (range, 0.4–1.7) in tumor tissue demonstrating [¹¹C]GSK2256098 uptake (PET-enhanced regions), and 0.5 (range, 0.2–0.7) in non-contrast enhancing disease (*T2 FLAIR exc. Gd region*). This indicates that at steady state, the concentration of GSK2256098 was approximately 0.4 times the corresponding concentration in plasma, and markedly higher (0.9) in tumor. Areas of high PET signal (indicating [¹¹C]GSK2256098 concentration) were spatially consistent with areas that were Gd enhancing on T1 MRI. Based on an estimate of GSK2256098 blood-to-plasma ratio of 0.84 from in vitro experiments in human blood, the measured blood concentrations of GSK2256098 were combined with estimated V_T values to produce estimates of tumor concentrations ranging from 448 ng/mL to 3482 ng/mL (Table 4). These drug concentrations do not take into account any potential contribution of radioactive metabolites to the PET tissue signal. No clear relationship was observed between dose of GSK2256098 and V_T . There was no significant association between estimated tumor concentration of GSK2256098 and radiological response or time on study, although of note the patient on treatment for 11.3 months had the highest estimated tumor concentration.

Table 4

Estimates of regional PET volume of distribution V_T and tumor concentration

Fig. 1

Discussion

This study demonstrates (i) that [^{11}C]GSK2256098 penetrates the BBB at low levels into normal brain but markedly higher levels were observed in tumor and (ii) that GSK2256098 is tolerable in patients with recurrent glioblastoma. One patient with recurrent glioblastoma in the 750 mg twice daily cohort received GSK2256098 treatment for 11.3 months until disease progression.

The MTD of GSK2256098 in patients with recurrent glioblastoma was 1000 mg twice daily, consistent with that defined in previous cohorts of this trial which evaluated GSK2256098 in patients with advanced systemic cancer. The observed DLTs in patients with glioblastoma were both related to cerebral edema, which had not been observed in previous studies of GSK2256098. However, previous cohorts had excluded patients with primary CNS malignancy and patients with brain metastases who were symptomatic or untreated or required corticosteroids or P450-inducing anti-epileptics. Cerebral edema is common in patients with glioblastoma and is primarily vasogenic rather than cytotoxic in nature due to BBB disruption.^{25,26} Cerebral edema (both vasogenic and cytotoxic) is associated with focal treatments for glioblastoma, including radiotherapy and carmustine wafers.^{27,28} Given the potential for cerebral edema, in future studies in patients with glioblastoma we would advocate initiating treatment with GSK2256098 at 500 mg twice daily, and uptitrating to 1000 mg twice daily as tolerated.

As yet, no small-molecule targeted inhibitor therapy has demonstrated sufficient clinical efficacy in glioblastoma to be approved for routine use.^{29–37} Effective treatment of glioblastoma requires a target that is present throughout the tumor, and adequate drug penetration through the BBB and into the tumor (not just to cells adjacent to blood vessels).^{38,39} Despite preclinical data indicating limited penetration and distribution of GSK2256098 into the intact rodent brain, PET scans of participants in this study demonstrated significant penetration of [^{11}C]GSK2256098 into tumors following microdose administration. There was limited penetration of [^{11}C]GSK2256098 into non–contrast enhancing disease areas (representing infiltrative disease or peritumoral edema⁴⁰), albeit at slightly higher levels than normal brain. The PET volume of distribution was not impacted by the different doses of oral GSK2256098 administered, suggesting no significant variation within the dose range explored in the saturation of membrane transporters (eg, Pgp) that

prevent BBB penetration. Combined with colocalization of the Gd-enhancing tissue on MRI, the PET signal is consistent with penetration of GSK2256098 being associated with a locally compromised BBB. An intact BBB is likely to limit penetration of radioactive metabolites due to the relatively hydrophilic nature of the observed metabolites. However, in areas of BBB disruption, there is a greater possibility that metabolites might contribute to the PET signal and thus confound estimates of tumor drug concentrations. Given the highly infiltrative nature of glioblastoma, limited penetration of GSK2256098 outside of contrast-enhancing areas may limit clinical effectiveness. This, along with the cytostatic nature of FAK inhibitors, supports combination therapy in future studies of GSK2256098 in glioblastoma.

In conclusion, this is the first study of a FAK inhibitor in glioblastoma. GSK2256098 achieved high tumor penetration in study participants, consistent with tumor-related BBB disruption. It was present at lower levels in normal brain tissue. Diarrhea, fatigue, and nausea were the most frequently observed treatment-related adverse events. While the MTD of GSK2256098 in patients with glioblastoma was 1000 mg twice daily, due to the potential for cerebral edema we would advocate initiating treatment at 500 mg twice daily and uptitrating as tolerated. Clinical trials of GSK2256098 as monotherapy and in combination with other agents in patients with brain tumors and other cancers are currently ongoing (NCT02428270, NCT02523014).

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Conflict of interest statement. J.T., L.Y., K.A., D.C. are employees of GlaxoSmithKline (GSK). R.F.R.F., L.L., A.S., C.P., Y.L., and G.S. are former employees of GSK. R.F.R.F., K.A., A.S., J.T. own stock in GSK. K.A. has a pending patent related to this study (WO 2013/003575 A1). C.P., G.S., Y.L., and A.S. are employees of Imanova UK (previously part of GSK), who performed and were paid for scanning services for this study and performed work for GSK outside of this study.

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