# First-in-human Phase I study to evaluate the brain-penetrant dual PI3K and mTOR inhibitor GDC-0084 in patients with progressive or recurrent high-grade glioma

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## Statement of Translational Relevance

Signaling through the phosphoinositide 3 kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway has been implicated in angiogenesis and cell growth in several types of cancer. The PI3K axis is abnormally activated in most high grade gliomas. We developed an oral, brain-penetrant small molecule inhibitor of phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) as a therapy for patients with high-grade glioma, where genomic alterations in this pathway occur in a majority of patients. A multi-center Phase I first-in-human study of GDC-0084 was conducted in patients with high-grade glioma. This Phase I study showed that GDC-0084 has good PK properties and acceptable safety profile with signs of pharmacodynamic effects in the CNS, as evidenced by FDG-PET. Our data suggests that clinical investigation of GDC-0084 in patients with high grade glioma in earlier lines of therapy or with other rational combination partners is warranted.

## Abstract

**Purpose:** GDC-0084 is an oral, brain-penetrant small molecule inhibitor of phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR). A first-in-human, Phase I study was conducted in patients with recurrent high-grade glioma.

**Experimental design:** GDC-0084 was administered orally, once-daily to evaluate safety, pharmacokinetics (PK) and activity. Fluorodeoxyglucose positron emission tomography (FDG-PET) was performed to measure metabolic responses.

**Results:** Forty-seven heavily pretreated patients enrolled in eight cohorts (2-65 mg). Dose-limiting toxicities (DLTs) included one case of Grade 2 bradycardia and Grade 3 myocardial ischemia (15 mg), Grade 3 stomatitis (45 mg) and 2 cases of Grade 3 mucosal inflammation (65 mg); the maximum tolerated dose (MTD) was 45 mg/day. GDC-0084 demonstrated linear and dose-proportional PK, with a half-life (~19 hr) supportive of once-daily dosing. At 45 mg/day, steady-state concentrations exceeded pre-clinical target concentrations producing antitumor activity in xenograft models. FDG-PET in 7 of 27 patients (26%) showed metabolic partial response. At doses ≥ 45 mg/day, a trend towards decreased median SUV in normal brain was observed, suggesting central nervous system penetration of drug. In 2 resection specimens, GDC-0084 was detected at similar levels in tumor and brain tissue, with a brain tissue/tumor to plasma ratio of > 1 and > 0.5 for total and free drug, respectively. Best overall response was stable disease in 19 patients (40%), and progressive disease in 26 patients (55%); 2 patients (4%) were non-evaluable.

**Conclusions:** GDC-0084 demonstrated classic PI3K/mTOR-inhibitor related toxicities. FDG-PET and concentration data from brain tumor tissue suggest that GDC-0084 crossed the blood-brain barrier.

## Background

Glioblastoma is the most common primary brain tumor, accounting for 15% of all brain and central nervous system tumors and approximately 56% of all gliomas (1). Evidence of common genetic abnormalities in signal transduction pathways that control angiogenesis and cell growth and survival have led to the development of new treatments that target molecules in these signaling pathways. However, prognosis remains poor with current standard of care, with few patients surviving beyond 5 years (2-5).

Activation of the phosphoinositide 3 kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway has been implicated in angiogenesis (6,7) and cell growth (8) in several types of cancer (9-11), including ≥ 80% of glioblastomas (12-15). Additionally, loss of phosphatase and tensin homolog (PTEN) expression or function, and dysregulation of receptor tyrosine kinases that exert downstream effects on PI3K are common in gliomas (16). Activating mutations in *PIK3CA* (the gene encoding the p110 catalytic subunit PI3Kα) and mutations in *PIK3R1* (the gene encoding the regulatory subunit p85) are also evident in gliomas (17).

GDC-0084 is a potent, oral, selective, brain-penetrant small molecule inhibitor of both phosphoinositide PI3K and mTOR kinase that was specifically designed for the treatment of brain cancer. GDC-0084 was designed to efficiently cross the blood brain barrier to achieve high drug exposure in the brain, thus maximizing its potential to treat brain cancers such as glioblastomas. In mouse xenograft models, GDC-0084 demonstrated dose-dependent tumor-growth inhibition (TGI), with 60% and 90% TGI observed at clinically relevant exposures (18,19).

Together, these data provided the rationale for investigating GDC-0084 for the treatment of patients with progressive or recurrent high-grade glioma. The primary objectives of this study

were to assess the safety, tolerability, and pharmacokinetics (PK) of GDC-0084 in patients with progressive or recurrent high-grade gliomas (WHO Grade III–IV), and to determine the maximum tolerated dose (MTD) of GDC-0084 and characterize the dose-limiting toxicities (DLTs). We also sought to characterize pharmacodynamic (PD) effects of GDC-0084 through assessment of change in glucose metabolism by means of $^{18}$F-Fluorodeoxyglucose positron emission tomography (FDG-PET) scans. Other objectives included a preliminary assessment of anti-tumor activity of GDC-0084.

## Patients and Methods

*Study design*

This was an open-label, multicenter, Phase I, dose-escalation study using a standard 3+3 design. GDC-0084 (supplied by Genentech, Inc.) was administered orally once-daily in cycles of 28 days, on a continuous dosing schedule at doses of 2-65 mg. Dose escalation followed a 3+3 design and continued until the MTD was exceeded, excessive pill burden was declared, or analysis of available PK data indicated that exposure was unlikely to increase with further increases in the dose of GDC-0084. The MTD was defined as the highest dose level at which < 33% of patients develop a DLT during Cycle 1 Days 1-28.

DLTs were defined as any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 Grade ≥ 3 non-hematologic toxicity unrelated to hyperglycemia or hyperlipidemia and is not due to disease progression or another clearly identifiable causes (excluding alopecia, nausea, vomiting, diarrhea, or electrolyte imbalance not managed with standard-of-care therapy, or asymptomatic lipase or creatine phosphokinase abnormality). Other DLTs included Grade ≥ 4 fasting hyperglycemia, Grade 3 symptomatic

fasting hyperglycemia (e.g., dehydration or acidosis requiring hospitalization), Grade 3 asymptomatic fasting hyperglycemia lasting ≥ 7 days after initiation of anti-hyperglycemic therapy, Grade ≥ 4 fasting hypercholesterolemia or triglyceridemia for ≥ 14 days despite intervention with a lipid-lowering agent, Grade 4 thrombocytopenia, Grade 3 thrombocytopenia lasting ≥ 7 days or is associated with clinically significant bleeding, and Grade 4 neutropenia lasting ≥ 7 days or accompanied by fever.

*Patients*

Eligible patients age ≥ 18 years with histologically documented high-grade gliomas (WHO Grade III–IV, by local pathology review) , with recurrent or progressive disease as defined by the Response Assessment in Neuro-Oncology (RANO) Criteria (20), and prior treatment with ≥ 1 regimen for gliomas (radiotherapy with or without chemotherapy for Grade III gliomas and radiotherapy with chemotherapy for Grade IV gliomas). Patients had be to ≥ 12 weeks from completion of adjuvant radiotherapy for gliomas to study entry, and baseline brain MRI scan performed within 14 days prior to initiation of study drug while either not receiving glucocorticoids or on a stable dose of glucocorticoids during the 5 consecutive days prior to the scan. Patients had to have Karnofsky Performance Status (KPS) of ≥ 70, adequate organ and bone marrow function (granulocyte count ≥ 1500/μL, platelet count ≥ 100,000/μL, AST, ALT, alkaline phosphatase and creatinine ≤ 1.5 × ULN), fasting plasma glucose less than 150 mg/dL, and QTc less than 500 milliseconds.

Patients were excluded if there was a history of prior treatment with a PI3K, mTOR, or PI3K/mTOR inhibitor in which the patient experienced a Grade ≥ 3 drug related or otherwise would be at increased risk for additional PI3K or mTOR related toxicity, anti-tumor therapy

within 4 weeks, requirement for chronic corticosteroid therapy consisting of > 2 mg dexamethasone per day or an equivalent dose of other corticosteroids, Grade ≥ 2 fasting hypercholesterolemia or hypertriglyceridemia, patients with a history of clinically significant cardiovascular events or medical disorders, and treatment with enzyme-inducing anti-epileptic agents or warfarin. There were no molecular eligibility criteria.

The study protocol was approved by local Institutional Review Boards prior to patient recruitment and was conducted in accordance with the Declaration of Helsinki International Conference on Harmonization E6 Guidelines for Good Clinical Practice. Written informed consent was obtained for all patients prior to performing study-related procedures in accordance with federal and institutional guidelines. The study was registered on ClinicalTrials.gov (NCT01547546).

*Safety assessments*

Safety assessments were determined weekly during Cycle 1 and then every 2 weeks thereafter using NCI CTCAE v4.0. Cycle 1 was the DLT assessment window.

*Pharmacokinetic assessments*

Frequent blood samples for PK analysis were collected on Days 1 and 8, or Day 15 of Cycle 1. A validated liquid chromatographic-tandem mass spectrometry (LC/MS-MS) method with a lower limit of quantitation of 0.00052 μM was used to measure the concentration of GDC-0084 in plasma samples. PK parameters were estimated using non-compartmental analysis (Phoenix WinNonlin 6.4; Cetara, Princeton, NJ).

*Brain penetration*

Brain-to-plasma ratios were estimated from two patients (post hoc analysis and not from a pre-specified cohort). Tumor, adjacent brain tissue and plasma samples from one patient were obtained ~5.5 hr (plasma) and 7 hr (brain) after 45 mg QD dosing to steady-state. Post-mortem tumor and brain samples were collected from another patient taking 45 mg QD (last dose was 11 days prior to death) and plasma concentrations at the time of death were estimated using this patient's observed plasma half-life. GDC-0084 in plasma and brain samples were measured using LC/MS-MS.

*Activity outcomes*

Disease status was assessed using RANO criteria for high-grade gliomas (20) at screening, on Day 1 of Cycle 2, every 8 weeks thereafter, and ≥ 4 weeks after the occurrence of a complete or partial response (all +/- 7 days). Time on study was defined as time from first GDC-0084 dose to study discontinuation.

*Biomarker assessments*

To demonstrate the ability of GDC-0084 to exert biologic effects in tumor tissue and aid in the dose selection, FDG-PET was performed at baseline and on-treatment either on Day 1 of Cycle 2 (+7 days), or Day 8 of Cycle 1 (+ 7 days), within 1-4 hours of dosing. In general, patient preparation and FDG-PET data acquisition procedures followed guidelines by the National Cancer Institute (21,22). Reconstructed FDG-PET images were converted into standardized uptake value (SUV) maps. Regions of interest (ROIs) were delineated for each MRI enhancing lesion and the maximum SUV ($SUV_{max}$) within each ROI was computed. The percent change on

the average $SUV_{max}$ across all patient lesions was used as quantitative measure of treatment effect on disease metabolic activity. A decrease in disease metabolic activity of at least 20% constituted a partial metabolic response. Median SUV in non-enhancing brain tissue was also computed as a measure of metabolic activity in normal brain.

Pre-treatment tumor tissue, when available, was profiled for PTEN expression using immunohistochemical methods, as previously described (23), and using a targeted next generation sequencing gene panel, as previously described (24). O6-methylguanine-DNA methyltransferase status was not formally assessed as part of the study.

*Statistical methods*

A 3+3 dose escalation design was used to determine the MTD. No formal statistical hypotheses were tested in this study. Design considerations were not made with regard to explicit power and type I error, but to obtain preliminary safety, PK, and PD information. For the safety analysis and the activity analysis, all patients who received ≥ 1 dose of GDC-0084 were included. Descriptive statistics were used throughout the study.

*Data sharing*

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here

(https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)

## Results

*Patient characteristics*

Forty-seven patients were enrolled in 8 successive dose escalation cohorts (2-65 mg GDC-0084). The baseline characteristics of the patient population are shown in Table 1. The median age was 50 years (range 29-73) with more males (72%) enrolled than females. At study enrollment 14 patients (30%) were classified as WHO Grade III glioma and 33 patients (70%) were classified as WHO Grade IV glioma. Median KPS was 90 (range of 70-100). The mean number of prior systemic therapies was 3 (range 1-5), and 23 patients (48%) received bevacizumab in the immediate prior line of therapy.

*Safety, tolerability, and adverse events*

The most frequent AEs attributed to GDC-0084 were fatigue, hyperglycemia, nausea, rash, hypertriglyceridemia, mucositis, hypophosphatemia, decreased appetite, and diarrhea (Table 2). Nine patients (19%) experienced Grade 3 AEs related to GDC-0084, including hyperglycemia (4 patients [9%]) and mucositis (3 patients [6%]).

Overall, 4 patients experienced DLTs in this study. In the 15 mg dose group, 1 patient experienced Grade 2 bradycardia and Grade 3 myocardial ischemia. In the 45 mg dose group, 1 of 8 patients experienced Grade 3 stomatitis. In the 65 mg dose group, 2 of 6 patients experienced Grade 3 mucosal inflammation. All DLTs were considered related to GDC-0084. The MTD was determined to be 45 mg GDC-0084 given orally once-daily in 28 day cycles.

Seven of 47 patients (15%) experienced serious AEs (SAEs) related to GDC-0084. Five patients (11%) reported Grade 3 SAEs related to GDC-0084 (dry skin, fatigue, hyperglycemia, myocardial ischaemia, pneumocystis jirovecii pneumonia, pruritus, and stomatitis). There were no SAEs related to GDC-0084 that were higher than Grade 3.

Six patients (13%) experienced AEs that led to dose reduction or dose discontinuation of GDC-0084. Three patients (6%) experienced mucositis and all other AEs leading to dose reduction or dose discontinuation were reported by 1 patient at most.

Seven patients (15%) experienced GDC-0084-related AEs of special interest; 4 patients (9%) experienced hyperglycemia, 3 patients (6%) experienced mucositis and 1 patient each (2%) experienced bradycardia, myocardial ischaemia, and pruritus. One death was reported in this trial due to disease progression, which was deemed not related to GDC-0084.

*Pharmacokinetic analysis*

PK analyses using plasma samples GDC-0084 was rapidly absorbed ($T_{max}$ ~2 hours) and displayed an approximately linear and dose proportional increase in $C_{max}$ and $AUC_{0-24}$, with a half-life of ~18.7 hours, which is supportive of once-daily dosing (Figure 1A). The accumulation ratio had a mean value of 2.1 ± 0.9, which was consistent with the theoretical accumulation based upon half-life estimates and the once-daily dosing interval. Exposure of GDC-0084 observed at the MTD of 45 mg QD exceeds the pre-clinically predicted exposure associated with efficacy (60% TGI) in 7 of 8 patients (Figure 1B).

*Brain penetration*

In surgical and post-mortem samples from two patients dosed at 45 mg QD, GDC-0084 was detected at similar levels in brain tumor and tissue (surgical samples: 0.80 uM [tumor], 0.86 uM [brain]; post-mortem: 1.79 nM [tumor], 0.97 nM [brain]). In the surgical samples, the brain tumor to plasma and brain tissue to plasma ratios were >1.43 and >1.54 for total drug and >0.48 and >0.51 for free drug, respectively. In the post-mortem samples the brain tumor to plasma and brain tissue to plasma ratios were estimated to be ~1.1 and ~0.6 for total drug and ~0.60 and ~0.21 for free drug, respectively.

*Clinical activity*

Of the patients with evaluable FDG-PET data, 7 of 27 (26%) patients had a metabolic partial response (Figure 2). At doses of ≥ 45 mg QD, a trend towards decreased median SUV in normal brain was observed, suggesting CNS penetration of study drug.

Overall in this heavily pretreated population, no objective response as assessed by RANO criteria were observed (Figure 3), and best response was limited to stable disease in 19 patients (40%) in the 2, 4, 8, 15, 45, and 65 mg cohorts. Twenty-six patients (55%) had progressive disease. Two patients (4%) did not have evaluable post-treatment response assessment. Three patients (6%) stayed on study for at least 6 months (Figure 4).

*Biomarker analysis*

PTEN tissue expression was assessed in 36 patients (Figure 3). Overall, 20 patients had PTEN loss and/or a PIK3CA mutation. Complete loss of PTEN protein was observed in 1 patient and low expression was observed in 15 patients (42%). Normal PTEN expression was observed in 20 patients with no data available for 11 patients.

A targeted next generation sequencing panel was run on patients with remaining tissue. Twenty-two patients had sufficient tissue that passed quality control that generated somatic mutation results. Seven PTEN mutations were identified, one of which had complete loss of PTEN protein expression, 2 had low PTEN expression and 4 had normal PTEN expression. Six *PIK3CA* mutations were identified in the tumor samples, 4 of which were hotspot mutations (E542K, E545G and H1047R) and 2 were non-hotspot mutations (S774F and R949Q).

Two patients were identified as *PIK3CA* mutant by the local test. One activating AKT1 mutation (E17K) and 1 non-spot mutation (D32G) were identified. Seven unique mutations in the PI3K regulatory domain, PIK3R2, were also identified. Finally, 1 EGFR single nucleotide variant mutation and 1 deletion mutation were found in tumor samples from 2 patients (E829K and V592del). There was no clear correlation between the genomic status of the tumor and outcomes in this Phase I study.

**Discussion**

In this first-in-human Phase I study of GDC-0084 in a population of heavily pretreated patients with recurrent high-grade gliomas the reported AEs were generally consistent with the established PI3K-mTOR inhibitor class effects. Mucositis was the predominant dose-limiting toxicity. The MTD of GDC-0084 was determined to be 45 mg/day with 1 of 8 patients experiencing a DLT (mucositis). At this dose 7 of 8 patients had drug exposures consistent with anti-tumor activity in pre-clinical models. GDC-0084 was rapidly absorbed and demonstrated linear- and dose-proportional increases in exposure, with a half-life supportive of once-daily dosing. Although data was limited, drug concentrations obtained from one patient who underwent resection of recurrent tumor while receiving GDC-0084, and another patient whose

post-mortem brain was available for analysis, suggested that GDC-0084 crossed the blood brain barrier, with a brain tumor to plasma and brain to plasma ratios in excess of 1. Data from the FDG-PET studies showing a metabolic partial response in 26% of evaluated patients, and a trend towards decreased median SUV in normal brain at doses of ≥ 45 mg daily also supported CNS penetration of GDC-0084. Though the PET studies were exploratory, the results are interesting and suggest a dose responsiveness to GDC-0084. Unlike other PI3K inhibitors that cross the blood-brain barrier such as buparlisib (25), there were no neuropsychiatric complications. This suggests that these previously reported toxicities were not a class effect of brain penetrant PI3K inhibitors, but more likely related specifically to buparlisib.

In this heavily pretreated unselected patient population in which patients had a median of 3 prior therapies and 48% of patients received bevacizumab in the immediate prior line of therapy, the single-agent anti-tumor activity was limited. Fifty-five percent of patients demonstrated a best response of progressive disease and 40% of patients had stable disease. Two patients did not have evaluable post-treatment response assessment. It is possible the GDC-0084 may have more activity in a less heavily pretreated population or in the first-line setting where the tumors may be less mutated and heterogenous.

To evaluate whether patients with PI3K pathway activation had a better outcome, tissue was obtained from a subset of patients to determine PTEN expression and the presence of PI3K mutations. Only 36 of 47 patients had tissue available for analysis of PTEN expression and 22 of 47 patients had tissue of adequate quality for somatic mutational analysis. There was no clear correlation between PTEN loss or PI3K mutations and response to GDC-0084. However, since the tissues were usually obtained from the initial surgery, and not surgery following the most recent recurrence, it is unclear whether the molecular alterations that were determined accurately

reflected the situation in the tumor at the time the patients received GDC-0084. The lack of correlation of efficacy to *PIK3CA* status is similar to mTOR inhibitors in breast cancer. Everolimus activity in the breast cancer patient population is not linked to alterations in gene expression or signaling pathways in HR+ HER2- tumors, or *PIK3CA*/WT mutation status (26,27).

Despite the importance of the PI3K-mTOR pathway in glioblastoma (15), there have been a paucity of agents inhibiting this pathway that adequately crosses the blood-brain barrier. Cloughesy et al (28) administered voxtalisib (XL765), a pan PI3K/mTOR inhibitor or XL147, a pan PI3K inhibitor, to patients with recurrent glioblastoma and showed that voxtalisib had better tumor penetration than XL147, although both drugs produced significant reduction of pS6K1 compared to archived tumor and reduction of Ki-67, suggesting that some inhibition of the PI3K pathway was achieved. Wen et al (29) subsequently conducted a Phase I trial of voxtalisib with temozolomide, with or without radiation therapy in patients with high-grade gliomas. The MTD was 90 mg once daily or 40 mg twice daily. However, drug development was suspended and additional studies were not performed. Kaley et al (30) evaluated perifosine, an AKT inhibitor, in a Phase II trial involving 16 GBM and 14 anaplastic astrocytoma patients. The agent was reasonably well tolerated but showed no efficacy in the GBM cohort with no responses, PFS6 of 0% and a median survival of 3.68 months. One patient with anaplastic astrocytoma had a partial response.

Pitz et al reported aPhase III trial of a brain penetrant PI3K inhibitor PX-366 in 33 unselected glioblastoma patients (31). The agent was fairly well-tolerated but there was only 1 (3%) partial response and 8 (24%) patients had stable disease. The 6 month progression free survival was 18%. Only a minority of patients had adequate tissue for evaluation of molecular

biomarkers and no statistically significant association was found between stable disease and PTEN status, *EGFRvIII* mutation, *PIK3CA* mutation status or *PIK3R1* mutation status. The study did not confirm whether therapeutic concentrations of the drug were achieved in the tumor or whether the PI3K pathway was inhibited. More recently, Wen et al reported that the pan-PI3K inhibitor buparlisib crossed the blood brain barrier well with tumor-to-plasma patios in excess of 1, but the drug failed to inhibit the PI3K pathway adequately (25). At the recommended Phase II dose of 100 mg daily, buparlisib inhibited phosphorylated $AKT^{S473}$ in 6 of 14 patients (43%), but had no effect on phosphoribosomal protein $S6^{S235/236}$ or tumor proliferation. This was reflected in the lack of clinical activity of the drug with no responders and a 6 month PFS of only 8%. It therefore remains unknown whether a PI3K inhibitor that can cross the blood brain barrier and adequately inhibit the pathway will have activity or whether the heterogeneity of the tumor and the presence of redundant pathways will require combination therapies.

There have also been a number of prior studies of mTOR inhibitors in recurrent glioblastoma (231-35). Most of the trials that have been reported targeted mTORC1 and were ineffective, possibly because of incomplete inhibition of mTORC1, and release of mTORC1-mediated restraints on PI3K/mTORC2/AKT signaling, resulting in resurgent AKT signaling (36,37). Agents that target both mTORC1 and 2, such as GDC-0084, are potentially more effective and studies with these agents in glioblastoma are ongoing. It is possible that by inhibiting both PI3K and mTOR, GDC-0084 will inhibit the PI3K pathway more effectively than agents inhibiting only one of these targets.

In summary, GDC-0084 is reasonably well-tolerated at 45 mg daily, a dose which exceeds the pre-clinically predicted exposure associated with efficacy and appears to cross the blood brain barrier. These data support further development of GDC-0084. The exploration of

rational GDC-0084 combinations in patient-derived glioblastoma organoid models may be of value (38, 39). This agent is being evaluated in a Phase I/II trial in patients with newly-diagnosed glioblastoma with unmethylated DNA-methylguanine- methyltransferase promoter status as adjuvant therapy following surgical resection and initial chemoradiation with temozolomide (NCT03522298), and in Phase II trials in diffuse intrinsic pontine glioma and diffuse midline gliomas (NCT03696355), HER2 positive breast cancer brain metastases (NCT03765983) and brain metastases with PI3K pathway activation (NCT03994796).

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Table 1. Patient demographics and disease characteristics.

| **Characteristic** | **2 mg (n=7)** | **4 mg (n=4)** | **8 mg (n=5)** | **15 mg (n=6)** | **20 mg (n=4)** | **30 mg (n=7)** | **45 mg (n=8)** | **65 mg (n=6)** | **All Patients (N=47)** |
|---|---|---|---|---|---|---|---|---|---|
| Age in years, median (range) | 58 (32–63) | 61 (30–64) | 44 (38–59) | 57 (38–62) | 38 (30–50) | 56 (44–73) | 49 (31-62) | 42 (29–59) | 50 (29–73) |
| Sex (male) | 5 (71%) | 3 (75%) | 5 (100%) | 4 (67%) | 2 (50%) | 3 (43%) | 6 (75%) | 6 (100%) | 34 (72%) |
| Time from primary diagnosis (mo.), median (range) | 56 (13–182) | 37 (22–47) | 53 (22–67) | 43 (14–87) | 24 (18–132) | 20 (11–45) | 97 (23–190) | 35 (12–100) | 41 (11–190) |
| No. prior systemic therapies, median (range) | 4 (1-4) | 3.5 (2-5) | 3 (1-5) | 3.5 (1-5) | 2 (2-3) | 3 (2-5) | 3 (2-5) | 3 (2-4) | 3 (1-5) |
| WHO Grade | | | | | | | | | |
| III | 3 (43%) | 1 (25%) | 1 (20%) | 1 (17%) | 1 (25%) | - | 5 (63%) | 2 (33%) | 14 (30%) |
| IV | 4 (57%) | 3 (75%) | 4 (80%) | 5 (83%) | 3 (75%) | 7 (100%) | 3 (38%) | 4 (67%) | 33 (70%) |
| Baseline KPS scale score | | | | | | | | | |
| 70 | 1 (14%) | - | 1 (20%) | - | 1 (25%) | 2 (29%) | 3 (38%) | 1 (17%) | 9 (19%) |
| 80 | 4 (57%) | 1 (25%) | 1 (20%) | 1 (17%) | 1 (25%) | 3 (43%) | - | 2 (33%) | 13 (28%) |
| 90 | 2 (29%) | 3 (75%) | 3 (60%) | 5 (83%) | 2 (50%) | 2 (29%) | 4 (50%) | 3 (50%) | 24 (51%) |
| 100 | - | - | - | - | - | - | 1 (13%) | - | 1 (2%) |

WHO=World Health Organization; KPS=Karnofski Performance Status.

Table 2. Adverse events related to GDC-0084 occurring in ≥ 2 patients.

| | 2 mg (n=7) | | 4 mg (n=4) | | 8 mg (n=5) | | 15 mg (n=6) | | 20 mg (n=4) | | 30 mg (n=7) | | 45 mg (n=8) | | 65 mg (n=6) | | All Patients (N=47) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade | Grade 3 | All Grade |
| Any adverse events | 0 | 1 (14%) | 0 | 3 (75%) | 0 | 3 (60%) | 1 (17%) | 4 (67%) | 0 | 4 (100%) | 2 (29%) | 6 (86%) | 2 (25%) | 7 (88%) | 4 (67%) | 5 (83%) | 9 (19%) | 33 (70%) |
| Fatigue [a] | 0 | 0 | 0 | 0 | 0 | 1 (20%) | 0 | 2 (33%) | 0 | 1 (25%) | 1 (14%) | 2 (29%) | 0 | 5 (62%) | 0 | 3 (50%) | 1 (2%) | 14 (30%) |
| Hyperglycemia | 0 | 0 | 0 | 1 (25%) | 0 | 1 (20%) | 1 (17%) | 3 (50%) | 0 | 0 | 1 (14%) | 3 (43%) | 0 | 2 (25%) | 2 (33%) | 3 (50%) | 4 (9%) | 13 (28%) |
| Nausea | 0 | 0 | 0 | 2 (50%) | 0 | 1 (20%) | 0 | 0 | 0 | 3 (75%) | 0 | 1 (14%) | 0 | 2 (25%) | 0 | 2 (33%) | 0 | 11 (23%) |
| Rash [b] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (38%) | 0 | 5 (83%) | 0 | 8 (17%) |
| Hypertriglyceridemia | 0 | 0 | 0 | 1 (25%) | 0 | 0 | 0 | 1 (17%) | 0 | 0 | 0 | 2 (29%) | 0 | 2 (25%) | 0 | 1 (17%) | 0 | 7 (15%) |
| Mucositis [c] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (12%) | 4 (50%) | 2 (33%) | 3 (50%) | 3 (6%) | 7 (15%) |
| Hypophosphatemia | 0 | 0 | 0 | 1 (25%) | 0 | 2 (40%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (25%) | 1 (17%) | 1 (17%) | 1 (2%) | 6 (13%) |
| Decreased appetite | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (25%) | 0 | 0 | 0 | 4 (50%) | 0 | 0 | 0 | 5 (11%) |
| Diarrhea | 0 | 0 | 0 | 1 (25%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14%) | 0 | 1 (12%) | 0 | 2 (33%) | 0 | 5 (11%) |
| Vomiting | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (50%) | 0 | 0 | 0 | 1 (12%) | 0 | 1 (17%) | 0 | 4 (9%) |
| Cholesterol increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (29%) | 0 | 1 (12%) | 0 | 0 | 0 | 3 (6%) |
| Hypercholesterolemia | 0 | 0 | 0 | 1 (25%) | 0 | 0 | 0 | 1 (17%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (17%) | 0 | 3 (6%) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (25%) | 0 | 1 (17%) | 0 | 3 (6%) |

No Grade 4 or 5 drug-related AEs were reported. [a] Fatigue includes fatigue and asthenia. [b] Rash includes rash and rash maculo-paular. [c] Mucositis includes mucosal inflammation and stomatitis.

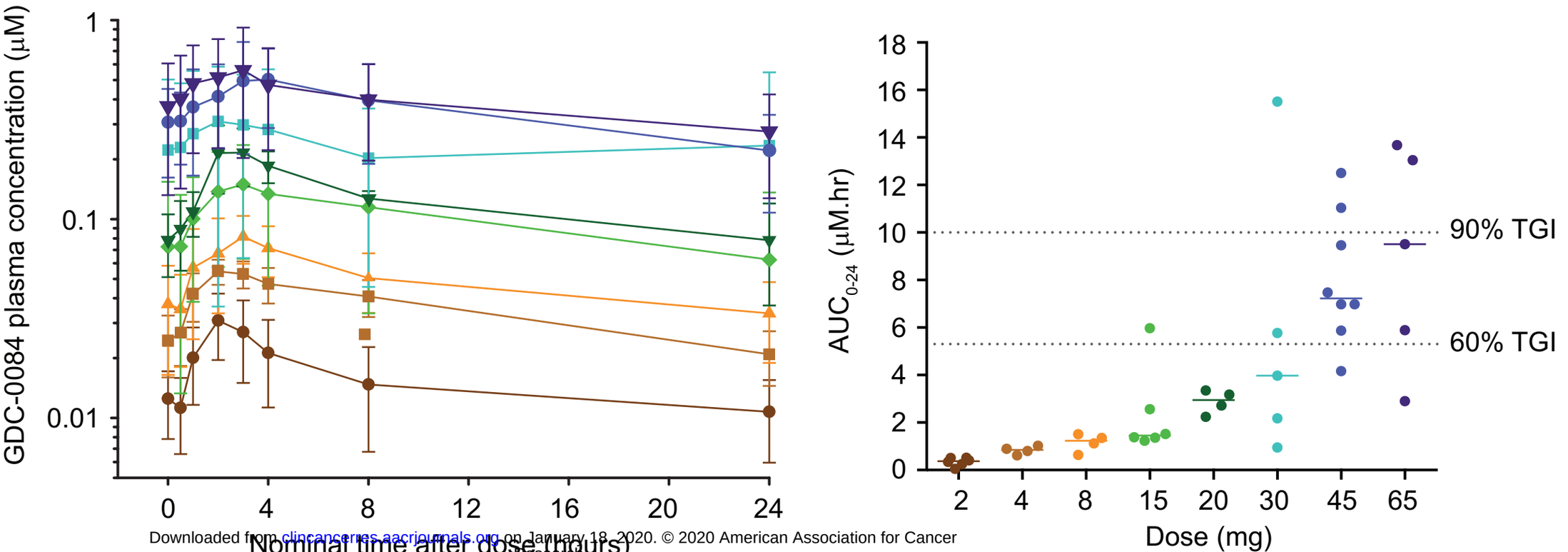
**Figure Legends**

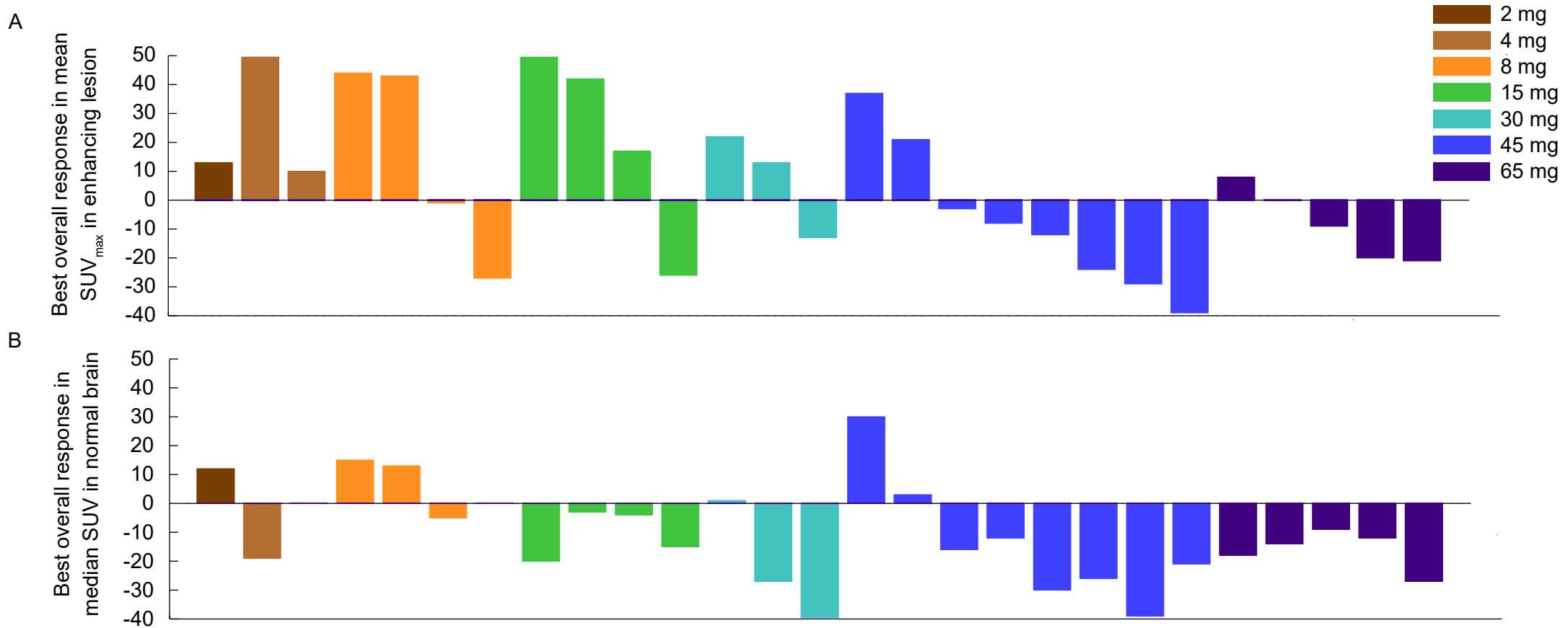
Figure 1. GDC-0084 pharmacokinetics. (A) Mean (± SD) steady-state plasma concentrations of GDC-0084 (B) Observed individual steady-state area under the curve ($AUC_{0-24}$) values by dose level. Horizontal lines indicate exposures that correlate to percent tumor growth inhibition (TGI) exposure targets from a U87 (PTEN null) subcutaneous xenograft model (40).

Figure 2. FDG-PET assessments. (A) change in mean standard update value (SUVmax) in tumor, and (B) median SUV in normal brain. IHC=immunohistochemistry; WT=wild type; MUT=mutant; ND=not detected, MUT* = local assessment.

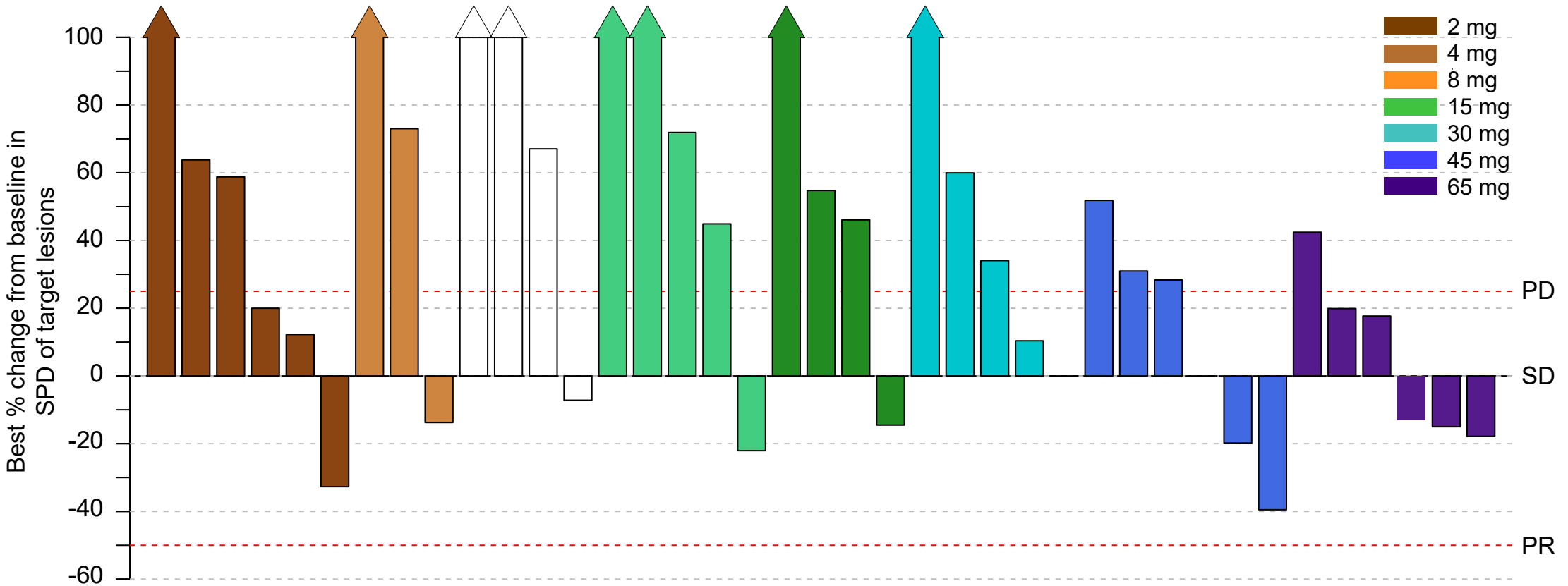
Figure 3. Objective response estimated for patients with disease measurable by response assessment in neuro-oncology criteria (RANO) guidelines. SPD=sum of products of diameters; PD=progressive disease; SD=stable disease; PR=partial response; IHC=immunohistochemistry; WT=wild type; MUT=mutant; ND=not detected; MUT* = local assessment. Best change in sum of product of diameters of target lesions is displayed by dose level.

Figure 4. GDC-0084 time on study. Patients are grouped by dose levels. WHO glioma Grade (III or IV) is noted for each patient.

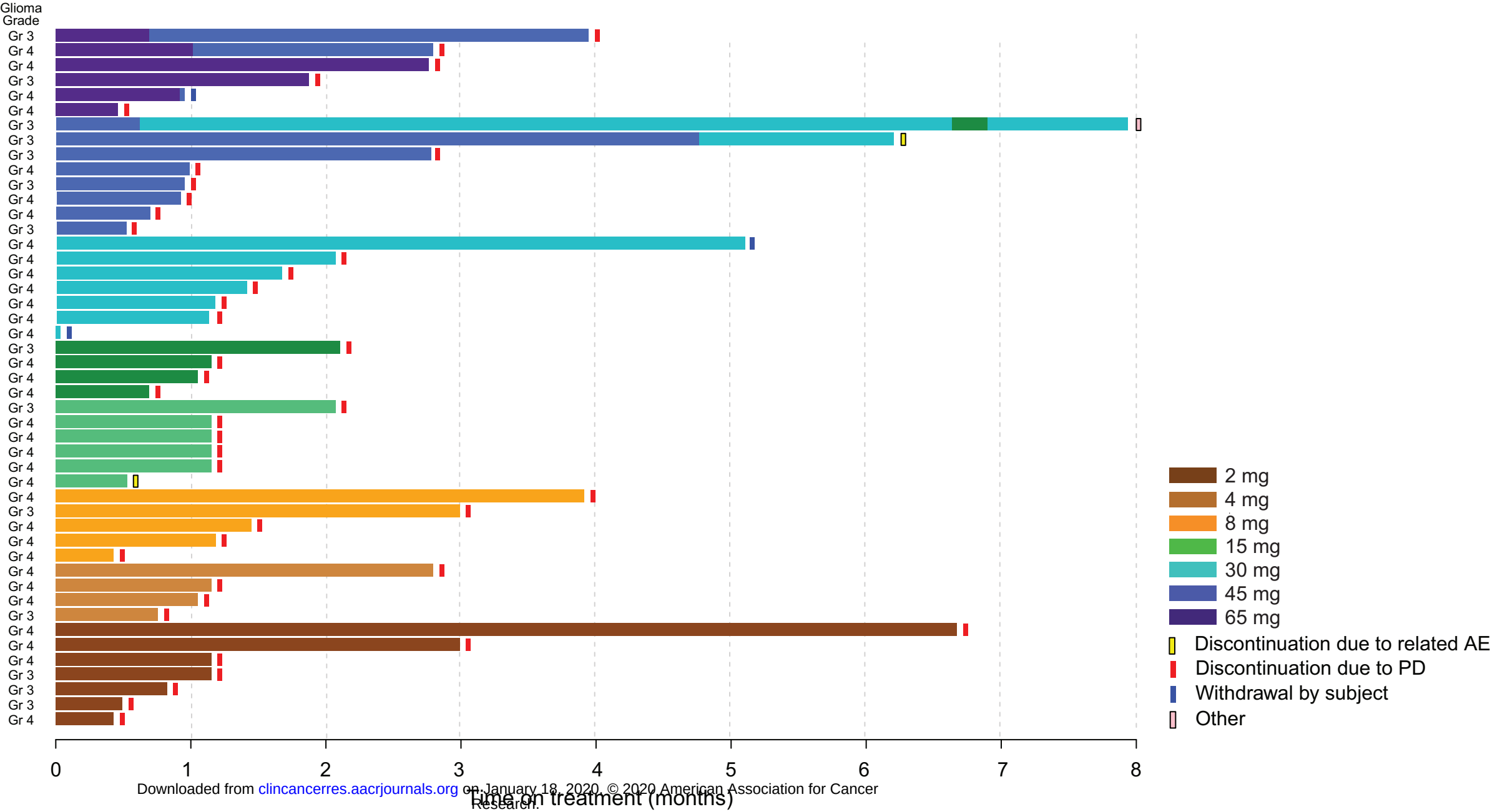





| Time on GDC-0084 (mo.) | 6.7 | 0.8 | 1.1 | 3 | 1.2 | 3.9 | 1.4 | 1.1 | 1.1 | 1.1 | 2.1 | 2.1 | 1.7 | 1.4 | 1 | 0.7 | 0.4 | 2.8 | 8 | 1 | 6.2 | 1 | 1.9 | 1 | 0.5 | 2.8 | 3.9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PTEN IHC | LOW | WT | LOW | WT | FAIL | WT | WT | WT | WT | WT | WT | ND | FAIL | LOW | WT | ND | LOW | FAIL | WT | LOW | WT | WT | LOW | WT | FAIL | LOW | WT |
| PIK3CA | ND | ND | WT | MUT* | WT | ND | ND | WT | MUT | WT | MUT* | ND | ND | ND | WT | ND | MUT | WT | WT | ND | ND | WT | WT | WT | WT | ND | WT |




| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Enhancing lesion volume at screening ($cm^3$) | 35 | 2.7 | 39 | 0.4 | 24 | 2.8 | 8.3 | 13 | 29 | 49 | 5.1 | 33 | 8.7 | 4.3 | 7.2 | 0.5 | 34 | 20 | 2 | 13 | 16 | 0 | 5 | 10 | 26 | 28 | 70 | 38 | 11 | 29 | 73 | 11 | 3.7 | 77 | 3.9 | 64 | 11 | 1.4 | 2.8 |
| Time on GDC-0084 (mo.) | 1.2 | 1.1 | 0.4 | 3 | 0.8 | 6.7 | 1.1 | 1.1 | 2.8 | 0.4 | 1.4 | 1.2 | 3 | 1.1 | 1.1 | 1.1 | 1.1 | 0.5 | 1.1 | 1.1 | 0.7 | 2.1 | 1.2 | 1.2 | 1.4 | 2.1 | 1.7 | 0.4 | 1 | 0.7 | 1 | 2.8 | 6.2 | 0.5 | 2.8 | 2.8 | 1.9 | 3.9 | 1 |
| PTEN IHC | WT | LOW | LOW | WT | LOW | LOW | NULL | LOW | LOW | LOW | WT | FAIL | WT | WT | WT | WT | WT | ND | LOW | FAIL | FAIL | LOW | WT | ND | LOW | ND | FAIL | LOW | LOW | ND | WT | FAIL | WT | FAIL | LOW | LOW | LOW | WT | WT |
| PTEN | WT | ND | MUT | ND | ND | ND | MUT | WT | ND | ND | ND | WT | ND | MUT | WT | WT | MUT | ND | ND | ND | ND | WT | MUT | ND | ND | ND | ND | WT | ND | ND | WT | WT | ND | WT | MUT | ND | WT | WT | WT |
| PIK3CA | WT | ND | MUT | ND | ND | ND | MUT | WT | ND | ND | ND | WT | MUT* | WT | MUT | MUT | WT | ND | ND | ND | ND | WT | WT | ND | ND | ND | ND | MUT | ND | ND | WT | WT | ND | WT | MUT | ND | WT | WT | WT |
| AKT1 | WT | ND | WT | ND | ND | ND | WT | WT | ND | ND | ND | WT | ND | WT | WT | WT | WT | ND | ND | ND | ND | WT | WT | ND | ND | ND | ND | MUT | ND | ND | WT | WT | ND | WT | WT | ND | MUT | WT | WT |
| PIK3R2 | WT | ND | WT | ND | ND | ND | MUT | WT | ND | ND | ND | MUT | ND | WT | WT | WT | WT | ND | ND | ND | ND | MUT | WT | ND | ND | ND | ND | WT | ND | ND | WT | WT | ND | MUT | WT | ND | WT | WT | MUT |
| EGFR | WT | ND | WT | ND | ND | ND | WT | WT | ND | ND | ND | WT | ND | WT | WT | MUT | WT | ND | ND | ND | ND | WT | WT | ND | ND | ND | ND | WT | ND | ND | WT | WT | ND | WT | WT | ND | WT | WT | WT |



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# First-in-human Phase I study to evaluate the brain-penetrant PI3K/mTOR inhibitor GDC-0084 in patients with progressive or recurrent high-grade glioma

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