Afatinib and radiotherapy, with or without temozolomide, in patients with newly diagnosed glioblastoma: results of a phase I trial

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Abstract

Background Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults. Amplification or overexpression of the epidermal growth factor receptor gene, part of the ErbB family, occur in approximately 40% and 60% of patients with GBM, respectively. We present data from a dose-finding study of the ErbB inhibitor afatinib in combination with radiotherapy (RT), with or without temozolomide (TMZ), in patients with GBM.

Methods This was a phase I, open-label, 3 + 3 dose-escalation trial in patients with newly-diagnosed, histologically-confirmed grade 4 malignant glioma and proven O6-methylguanine-DNA methyltransferase gene promoter methylation status. The primary endpoint was the maximum tolerated dose (MTD) of continuous daily afatinib when given in combination with RT, with (regimen M) or without (regimen U) concomitant TMZ treatment.

Results Fifty-five patients were enrolled; 36 received ≥ 1 dose of trial medication (regimen M, n = 20, regimen U, n = 16). Afatinib was discontinued by all patients during the study. Reasons for afatinib discontinuation (regimen M/U) included disease progression (45%/50%), dose-limiting toxicity (10%/0%), and other adverse events (AEs; 35%/38%). The most frequently reported AEs with either regimen were diarrhea and rash, with no new safety signals identified. The MTD was determined as afatinib 30 mg in combination with daily TMZ and RT, and afatinib 40 mg in combination with RT alone.

Conclusions This study identified the MTD for afatinib in combination with RT, with and without TMZ, in patients with GBM. Further studies of afatinib in patients with GBM are warranted and should be based on appropriate biomarker-based preselection.

Trial registration NCT00977431 (first posted September 15, 2009).

Keywords Glioblastoma · Afatinib · Dose-escalation · Temozolomide · Radiotherapy

Agnieszka Cseh passed away in May 2021.

Frank Saran and Michael Brada have contributed equally to this work.
Introduction

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults [1] and is associated with a poor prognosis, with a median progression-free survival (PFS) of 7.4–10.7 months [2–4] and median overall survival (OS) of 14.6 months [5]. Limited progress has been made in improving outcomes for patients with GBM in recent decades [1]. First-line therapy for newly diagnosed patients is maximal safe surgical resection, followed by radiotherapy (RT) and temozolomide (TMZ) [6]. However, response to TMZ treatment can vary depending on the methylation status of the methyl-guanine methyl transferase (MGMT) enzyme promoter [7, 8]. Additionally, most glioblastomas become resistant to first-line therapies, which can occur via several mechanisms, including activation of DNA repair mechanisms, evasion of apoptosis, and adaptation of the cell cycle [9, 10]. As survival rates remain low, there is a large unmet need in GBM, particularly for patients with unmethylated MGMT promoters, for whom standard treatments are less effective [1, 11]. Consequently, several biomarker-driven therapeutic targets have been investigated to date, including the ErbB family of receptors.

Dysregulation of the ErbB pathway has been reported to contribute to GBM progression [12], with mutation, rearrangement, altered splicing and/or focal amplification of the epidermal growth factor receptor (EGFR) gene observed in over half of GBM cases [13–15]. Some studies have indicated that overexpression of EGFR may be associated with worse outcomes following RT in patients with GBM [16, 17]. EGFR tyrosine kinase inhibitors (TKI) have therefore been investigated in patients with malignant glioma or GBM, but have so far shown little activity in this setting [18]. Afatinib is an ErbB-family blocker that is approved for use in patients with NSCLC [19, 20]; it irreversibly binds to and blocks EGFR (ErbB1), HER2 (ErbB2), and ErbB4. Afatinib is therefore considered to have a wider inhibitory profile than first-generation EGFR TKIs [21, 22]. Furthermore, brain penetrance is recognized as a potential hurdle in the utilization of EGFR TKIs in GBM [23, 24]. Preclinical data indicate that afatinib has a moderate capacity to penetrate the BBB, supporting its use against central nervous system (CNS) malignancies [25, 26]. Indeed, 35–82% of patients with NSCLC and CNS metastases who were treated with afatinib monotherapy experienced a CNS response [27–30]. Thus, given the wider inhibitory profile of afatinib than first-generation TKIs, and its potential for CNS penetration, afatinib represents a possible treatment for GBM.

In a phase I/II study of afatinib with or without TMZ versus TMZ alone in patients with recurrent GBM, afatinib showed a manageable safety profile and modest efficacy in this hard-to-treat population [31]. There was no difference in OS between the treatment arms in the overall trial population; however, in the small number of patients assessed by biomarker subgroup analysis, there was a non-statistically significant trend towards increased PFS in afatinib-treated patients expressing the EGFR-variant III (EGFR-vIII) mutation, an EGFR variant frequently found in GBM [14]. Given that EGFR overexpression or mutation may contribute to poor outcomes and progression of GBM, and that preclinical and clinical data have highlighted potential for afatinib to elicit antitumor activity in GBM, we hypothesized that addition of afatinib to RT and TMZ may improve tumor responses and/or delay resistance to GBM treatment. The purpose of this trial was to define the toxicity and maximum tolerated dose (MTD) of afatinib in combination with RT, with and without TMZ, for the treatment of patients with newly diagnosed GBM.

Materials and methods

Study design and patient population

The study (NCT00977431) was a phase I, open-label, 3 + 3 dose-escalation trial in patients with newly-diagnosed malignant glioma. The trial was conducted at five sites in the United Kingdom.

Eligible patients were aged ≥ 18 and < 70 years, with newly-diagnosed, histologically-confirmed World Health Organization grade 4 malignant glioma and proven MGMT gene promoter methylation status (or tumor material available for testing). Exclusion criteria included: surgery within 2 weeks prior to the start of treatment or planned during the trial; placement of a Giladel® wafer at surgery, prior to or radiosurgery for GBM); and treatment with other investigational drugs concomitantly with the study.

The trial was carried out in compliance with the clinical trial protocol, in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, and in line with applicable regulatory requirements and Boehringer Ingelheim standard operating procedures. Prior to the initiation of any trial-related procedure, all patients were informed about the trial verbally and in writing by the investigator and provided written informed consent according to ICH-GCP and local legal requirements.

Treatment

This study included two treatment regimens: regimen M, afatinib + TMZ in combination with RT; and regimen U,
afatinib in combination with RT without TMZ. During the
dose-finding phase, patients with methylated MGMT status
were treated with regimen M, and patients with unmethyl-
ated MGMT gene promoters were treated with regimen U. The
protocol was amended following the emergence of evi-
dence demonstrating the efficacy of TMZ in patients with
GBM regardless of MGMT methylation status [32]. Once the
MTD in regimen U had been determined, all new patients
were assigned to regimen M regardless of methylation status.

In both regimens, RT was administered to patients at a
dose of 2 Grays (Gy) per fraction on 5 days per week for
6 weeks (total dose of 60 Gy) in an initial RT phase. Afatinib
was administered in dose escalation cohorts of 20, 30, and
40 mg/day (single oral dose) during the RT phase (i.e., days
1–42), and then at 40 mg/day following RT (maintenance
phase) until investigator-assessed disease progression or
undue adverse reaction, whichever occurred first. For regi-
men M, patients received TMZ 75 mg/m² daily (single oral
dose) during the RT phase. A 4-week TMZ-free phase fol-
lowed the RT phase, after which TMZ was administered for
up to six 28-day cycles (maintenance phase: TMZ single
oral dose once daily on days 1–5: 150 mg/m² in cycle 1 and
200 mg/m² in cycles 2–6).

Afatinib treatment was paused whenever a patient expe-
rienced an adverse event (AE) that met the criteria for dose-
limiting toxicity (DLT), regardless of the cycle. DLT was
defined as an AE or laboratory abnormality considered to
be related to afatinib and meeting pre-specified criteria (see
Supplementary Methods). Upon recovery of the AE to base-
line or National Cancer Institute Common Terminology Cri-
teria for Adverse Events (CTCAE) grade 1 (whichever was
higher) within 14 days, treatment could be continued at a
reduced dose. Otherwise, the patient was discontinued from
trial medication, except for patients with obvious clinical
benefit according to the investigator’s judgment.

Endpoints and assessments

The primary endpoint was the MTD of continuous daily
afatinib when given in combination with RT in patients with
newly diagnosed GBM, with or without concomitant TMZ
treatment. Secondary endpoints were the incidence and
intensity of AEs, objective tumor response rate, and phar-
macokinetics of afatinib (afatinib concentration at steady
state, pre-dose: Days 8, 15, and 29; please see Supplemental
Methods).

MTD was defined as the highest afatinib dose level at
which no more than one of six patients experienced DLT,
i.e., the highest afatinib dose with a DLT incidence ≤ 17%,
during the 6-week RT phase. Patients who, for any reasons
other than DLT, did not receive trial medication during the
RT phase, for more than 5 consecutive days or more than
8 non-consecutive days, could stay in the trial, but were
removed from the MTD assessment and replaced by addi-
tional patients.

Safety was assessed by physical examination, hemat-
ologic and chemistry laboratory values, vital signs, and elec-
trocardiography scans. AEs were graded by CTCAE ver-
sion 3.0. Serious AEs (SAEs) were defined as any AE that
resulted in death, was immediately life threatening, resulted
in persistent or significant disability, required or prolonged
patient hospitalization, was a congenital anomaly/birth
defect, or was deemed serious for any other reason.

Objective tumor response rate was assessed by the inves-
tigator according to the Macdonald criteria [33], as meas-
ured by cerebral gadolinium-enhanced MRI. Assessment of
objective response was conducted during the maintenance
phase, (i.e., following completion of radiotherapy). MRIs
were performed between days 21–28 of cycles 1, 3, 5, 8, 10,
and 12 for regimen M, and of cycles 2, 4, 6, 8, 10, and 12 for
regimen U. In the second year, MRIs were performed every
3 months (cycles 15, 18, 21 and 24), and every 6 months
thereafter. Objective response was defined as the best over-
all response [complete response (CR) or partial response]
recorded since the first administration of treatment until
disease progression, death, or treatment discontinuation.
Unplanned post hoc analysis was performed to determine
time to disease progression (TTP). TTP was calculated as
the time between the first treatment date to the day follow-
ning the first date with recorded progressive disease. Patients
without progressive disease were censored at their most
recent imaging date. The median and 95% confidence inter-
val (CI) were calculated using Kaplan–Meier methodology.

Statistical analyses

Safety, pharmacokinetic, and efficacy parameters were sum-
marized descriptively; no formal statistical hypothesis test-
ing was conducted. All patients who were administered at
least one dose of any study treatment were included in the
efficacy and safety analyses.

Results

Patient disposition and characteristics

Between November 2009 and October 2012, 55 patients
were enrolled onto the trial. Of these, 36 patients received
at least one dose of trial medication; 20 and 16 patients
were treated with regimens M and U, respectively. Key
baseline characteristics were similar between the two
treatment arms, except for median tumor size, which was
greater in patients receiving regimen U (Table 1). Patients
who received regimen M were predominantly male (70%)
and white (95%), with a median time from first histological
diagnosis of 38 days (range 28–67) and a median tumor size (sum of largest cross-section post-surgery) of 89 mm² (range 0–2088). Patients who received regimen U were also predominantly male (69%) and white (100%), with a median time from first histological diagnosis of 36 days (range 28–51) and median tumor size of 978 mm² (range 0–2331).

With regimen M, 20 patients were treated and 15 patients continued afatinib beyond the RT phase. With regimen U, 16 patients were treated and 13 continued afatinib beyond the RT phase (Fig. 1). The median (range) durations of afatinib treatment for regimens M and U were 150 (6–2340) days and 167 (1–397) days, respectively. Afatinib was discontinued by all patients during the study. Reasons for afatinib discontinuation with regimen M included disease progression (45%), DLT (10%), and other AEs (35%) (Fig. 1). One patient who received regimen M had not experienced disease progression at data cut-off and was switched to commercially supplied afatinib; he remained on treatment for more than 6 years. With regimen U, reasons for afatinib discontinuation included disease progression (50%), and AEs other than DLTs (38%); no patients receiving regimen U discontinued afatinib treatment due to DLTs.

### MTD of afatinib with concomitant RT

Overall, 17 of 20 patients who received regimen M were evaluable for MTD determination (Fig. 2). In the first dose cohort (afatinib 20 mg/day), one of six evaluable patients had a DLT during the RT phase (grade 4 thrombocytopenia). The afatinib dose was therefore escalated to 40 mg/day; two of five patients (seven patients were treated; two were not evaluable) had DLTs: one patient had grade 4 thrombocytopenia and one patient had grade 3 vomiting. The afatinib dose was reduced to 20 mg/day and an intermediate dose level of 30 mg/day was explored; none of the six treated patients had DLTs. Accordingly, afatinib 30 mg was determined as the MTD in combination with daily TMZ and RT.

With regimen U, nine of 16 patients treated were evaluable for MTD determination. In the first dose cohort (afatinib 20 mg/day), three patients were treated without any DLT during the RT phase. The afatinib dose was subsequently escalated to 40 mg/day; one of six patients had a DLT (grade 3 diarrhea). Thus, afatinib 40 mg was determined as the MTD in combination with RT.

For pharmacokinetic data, please see Supplemental Results.

### Safety profile of each regimen

The most frequently reported AEs with regimen M were diarrhea (85%), nausea (75%), and rash (65%). Of patients receiving regimen M, 95% had at least one drug-related AE (Table 2); the most common drug-related AEs were diarrhea (80%), rash (65%), nausea (45%), and fatigue (45%; Supplementary Table 1). Nine (45%) patients had AEs that led to discontinuation of afatinib; AEs (preferred terms) reported in more than one patient were diarrhea, fatigue, rash, and thrombocytopenia (two patients each). All other AEs leading to afatinib discontinuation were reported in single patients only; these were skin toxicity, skin ulcer, alanine aminotransferase increased, and postoperative wound infection.

With regimen U, the most frequently reported AEs were diarrhea (94%), rash (75%), and headache (63%). Of patients

| Table 1 Patient baseline demographics and clinical characteristics |
|---------------------------------------------------------------|
| Regimen M Afatinib + TMZ + RT N = 20 | Regimen U Afatinib + RT N = 16 |
| Male, n (%) | 14 (70) | 11 (69) |
| Race, n (%) | | |
| White | 19 (95) | 16 (100) |
| Asian | 1 (5) | 0 |
| Age in years, median (range) | 52.5 (25–66) | 53.5 (34–68) |
| BMI in kg/m², median (range) | 27.3 (20.6–33.8) | 28.7 (21.7–38.8) |
| Smoking history, n (%) | | |
| Never smoked | 15 (75) | 13 (81) |
| Ex-smoker | 4 (20) | 2 (13) |
| Currently smokes | 1 (5) | 1 (6) |
| Time from first histological diagnosis in days, median (range) | 38.0 (28–67) | 36.0 (28–51) |
| Karnofsky performance score, median (range) | − 10.0 (− 50–0) | − 20.0 (− 50–0) |
| Sum of largest cross-section post-surgery in mm², median (range) | 89.0 (0–2088) | 978.3 (0–2331) |
| Unilocular, n (%) | 18 (90) | 15 (94) |

BMI body mass index, RT radiotherapy, TMZ temozolomide
receiving regimen U, 94% of patients had at least one drug-related AE (Table 2); the most frequently reported drug-related AEs were diarrhea (81%), rash (75%), and fatigue (45%; Supplementary Table 1). Ten patients (63%) had AEs that led to discontinuation of afatinib; these were diarrhea, dermatitis acneiform, rash, pneumonia, pulmonary embolism, generalized tonic–clonic seizure, increased intracranial pressure, lethargy, malignant neoplasm progression, and disease progression (one patient each).

Frequencies of grade ≥ 3 drug-related AEs and SAEs by treatment regimen and dose are shown in Table 2. SAEs were reported in 12 (60%) patients who received regimen M and 12 (75%) patients who received regimen U. There were no fatal AEs reported for patients who received regimen M. Fatal AEs were reported in three patients (19%) who received regimen U. The causes of death in these patients were bacterial meningitis, pneumonia, and disease progression. For all three deaths, none were considered to be drug-related.

Response to therapy

Of 20 evaluable patients who received regimen M, five (25%) patients achieved an objective response, including one CR, and 11 (55%) patients had stable disease. With regimen U, one (6%) of 16 evaluable patients had an objective response and eight (50%) had stable disease according to the Macdonald response assessment criteria [33]. The best overall responses by afatinib dose with regimens M and U are shown in Table 3. The median time to disease progression for evaluable patients who received regimens M and U were 434 days (95% CI 205–NA, n = 18) and 211 days (95% CI 101–NA, n = 14), respectively. Insufficient data were available to calculate upper 95% CIs.

Discussion

In this open-label, phase I dose-escalation trial in newly diagnosed patients with GBM, the MTD of afatinib was 30 mg/day in combination with RT and TMZ (regimen M; methylated MGMT promoter), and 40 mg/day in combination with RT (regimen U; unmethylated MGMT promoter).

The most frequently reported drug-related AEs in this trial with regimens M/U were diarrhea (81/81%), rash (75%), and fatigue (45%; Supplementary Table 1). Ten patients (63%) had AEs that led to discontinuation of afatinib; these were diarrhea, dermatitis acneiform, rash, pneumonia, pulmonary embolism, generalized tonic–clonic seizure, increased intracranial pressure, lethargy, malignant neoplasm progression, and disease progression (one patient each).
The key aim of this study was not to investigate efficacy; however, disease control observed at RT completion was indicative of modest efficacy for both treatment regimens in patients with newly diagnosed GBM. It is unclear whether treatment with afatinib was a contributing factor, as it was administered in combination with treatments with known efficacy in GBM [5, 32]. Moreover, previous studies of ErbB pathways inhibitors in GBM have shown little efficacy when given alone [31, 36]. In a phase Ib/II trial of afatinib with or without TMZ in patients with recurrent GBM, the 6-month PFS rate was significantly lower with afatinib monotherapy than with afatinib plus TMZ or TMZ alone (afatinib alone: 3%; afatinib + TMZ: 10%; TMZ alone: 23%) [31]. However, median PFS was longer in afatinib-treated patients with EGFR-overexpressing tumors (3.35 months) than those with EGFR levels within a normal range (0.99 months).

Similar results have been observed with other EGFR TKIs. Gefitinib (with or without chemotherapy) was associated with response rates of up to 14% and 6-month PFS rates of 5–24% in patients with recurrent glioma [36–39]. Similarly, response rates of up to 8% have been achieved with erlotinib, with little impact on overall response or PFS in patients with recurrent malignant glioma compared with TMZ (with or without chemotherapy) [40–43]. While previous studies have indicated minimal activity of ErbB family inhibitors in GBM, a case of prolonged response to afatinib has been reported previously in a patient with recurrent GBM in this study. This patient, who had several EGFR mutations, EGFR gene amplification, and EGFR-vIII seropositivity, survived for around 5 years from recurrence, nearly sixfold longer than expected in patients with recurrent GBM [44, 45]. The patient was switched to commercial supply and was still on treatment at the time of the database lock. A further two patients with GBM who had long-term responses (> 12 months) to afatinib harbored mutations in specific combinations of alleles that are causal of EGFR addiction [44, 46]. For example, one patient had a PTPN11 mutation thought to drive EGFR addiction and, hence, response to afatinib, and another patient had a tumor that was EGFR amplified and carried an additional allele on the amplicon, potentially underlying the sustained response observed [46].

These findings suggest that afatinib may be of most benefit in patients with GBM harboring EGFR aberrations.

Given that alterations affecting EGFR, e.g. EGFR overexpression, have been identified previously in tumors of patients with GBM, including in long-term responders to afatinib [16, 17, 44, 46], a potential limitation of the present study is that patients were not selected based on biomarker analysis. Patients were not selected in this manner as EGFR genetic testing was not routinely performed when the trial was initiated. In future trials, selection of patients based upon specific biomarkers, such as EGFR mutations or amplification, may assist in identifying patients who are more likely to benefit from EGFR-targeted therapies. Another limitation of this study is that, similar to other trials to date, it has not been possible to distinguish the efficacy of afatinib from the known effectiveness of RT and TMZ [31]. Additionally, response to therapy was evaluated using Macdonald criteria, which were in widespread use at the time of the design of this study. These criteria have

### Fig. 2 Determination of the maximum tolerated dose based on the occurrence of dose limiting toxicities during the 6-week radiotherapy phase. MTD maximum tolerated dose, RT radiotherapy, TMZ temozolomide. *In Regimen M, one patient was replaced in the 20 mg afatinib group and one patient was replaced in the 40 mg afatinib group
largely been superseded by response assessment in neuro-oncology (RANO) criteria [47, 48].

This dose-finding study identified the MTD for afatinib in combination with RT and TMZ for patients with methylation of the MGMT promoter (30 mg/day during RT; 40 mg/day maintenance phase; regimen M), and in combination with RT for patients without methylation of the MGMT promoter (40 mg/day in RT and maintenance phases; regimen U). Treatment with both regimens was associated with a manageable AE profile that was consistent with the known safety profiles of the individual agents; the pharmacokinetic profile of afatinib was also in line with previous afatinib monotherapy studies at all dose levels. While this study only included a small number of patients, and efficacy was not the primary endpoint, antitumor activity was observed in a subset of each treatment group. Given the relationship between EGFR aberrations and poor response to treatment in GBM, the ErbB pathway remains a plausible therapeutic target in GBM. Research into the safety and pharmacokinetics of afatinib in patients with previously treated brain cancer is ongoing in a phase I study (NCT02423525). In future studies, biomarker analysis should be utilized to guide preselection of patients most likely to benefit from afatinib treatment.
### Supplementary Information
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### Author contributions
FS, LW, AJ, CM, SJ and FH substantially contributed to the acquisition, analysis, or interpretation of data for the work. RG and MB substantially contributed to the conception or design of the work. KP, JS, SB and AC substantially contributed to the conception or design of the work and to the acquisition, analysis, or interpretation of data for the work. All authors drafted the work/revised it critically for important intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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### Data availability
To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (see [https://www.mystudywindow.com/msw/datasharing](https://www.mystudywindow.com/msw/datasharing)). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Researchers should use the [https://vivli.org/](https://vivli.org/) link to request access to study data and visit [https://www.mystudywindow.com/msw/datasharing](https://www.mystudywindow.com/msw/datasharing) for further information.

### Code availability
(software application or custom code): not applicable.

### Declarations

#### Conflict of interest
SJ reports having a private medical practice for CNS and Thyroid tumors, having an investment in Genesis Cancer Care at Newmarket within a Limited Company – Saunders and Jef-feries Consultancy, and undertaking medicolegal work (one-two cases per year). KP declares being a Global project Manager working for Boehringer Ingelheim. JS declares employment with Boehringer Ingelheim Pharma GmbH & Co KG. SB declares employment with Boehringer Ingelheim Pharmaceuticals, Inc. AC declares employment with Boehringer Ingelheim International GmbH. All remaining authors declare no potential conflict of interest. The authors did not receive payment related to the development of the manuscript.

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### Table 3  Summary of treatment response

| Regimen | CR | PR | SD | PD | Missing | Objective response | Disease control rate |
|---------|----|----|----|----|----------|--------------------|---------------------|
| M Afatinib (20 mg) + TMZ + RT N = 7 | 0 | 2 (29) | 5 (71) | 0 | 0 | 2 (29) | 7 (100) |
| M Afatinib (30 mg) + TMZ + RT N = 6 | 1 (17) | 2 (33) | 2 (33) | 1 (17) | 0 | 3 (50) | 5 (83) |
| M Afatinib (40 mg) + TMZ + RT N = 7 | 0 | 4 (57) | 11 (55) | 2 (10) | 2 (29) | 4 (57) | 16 (80) |
| M Afatinib (total) + TMZ + RT N = 20 | 1 (5) | 4 (20) | 11 (55) | 2 (10) | 2 (29) | 4 (57) | 16 (80) |

CR: complete response, PD: progressive disease, PR: partial response, RT: radiotherapy, SD: stable disease, TMZ: temozolomide
Ethical approval The study was approved by the Ethics Committee of the NHS Health Research Authority London (West London and Gene Therapy Advisory Committee). All patients provided written informed consent according to International Conference on Harmonization Good Clinical Practice and local legal regulations. Patients included in the current study provided written consent for the usage of their data for research purposes.

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