Phase I study of afatinib and radiotherapy with or without temozolomide in newly diagnosed glioblastoma

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Background

- Glioblastoma, the most common primary brain tumor in adults, is associated with a particularly poor prognosis, with little progress in patient response outcomes in recent decades[1]
- ErbB pathway dysregulation plays a key role in the pathogenesis of glioblastoma
  - Overexpression of *EGFR* has been reported in ~50% of patients[2]
  - In many cases, *EGFR* is mutated; the most common *EGFR* mutation is the oncogenic variant III of the receptor (*EGFRvIII*) in ~40% of patients[3]
- Radiotherapy + temozolomide (TMZ) is considered the mainstay of maintenance therapy in patients with newly diagnosed glioblastoma[4]
  - Patients harboring tumors with the methylated methyl-guanine methyl transferase (*MGMT*) gene promoter benefitted from the addition of TMZ to standard radiotherapy whilst patients with an unmethylated *MGMT* promoter had minimal responses

EGFR, epidermal growth factor receptor

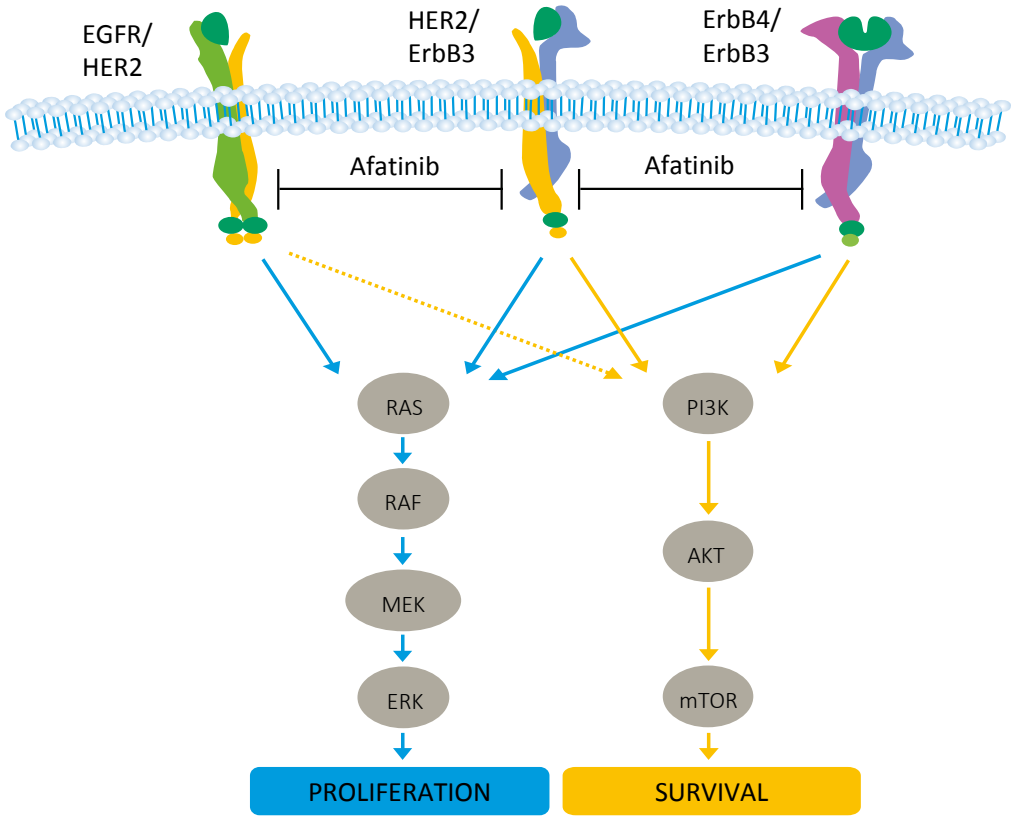
Background (cont'd)

- EGFR activation has been associated with resistance to radiotherapy[5,6]
- Afatinib irreversibly inhibits signaling from all ErbB family receptor homodimers and heterodimers (EGFR/ErbB1, HER2/ErbB2, ErbB3 and ErbB4)[7]
- The addition of afatinib to the RT + TMZ regimen is a potential approach to improve response and delay the onset of resistance in glioblastoma treatment
- This Phase I dose-escalation trial was conducted to determine the maximum tolerated dose (MTD), safety, efficacy and pharmacokinetics (PK) of afatinib and radiotherapy ± TMZ in newly diagnosed glioblastoma patients

HER2, human epidermal growth factor receptor 2

Background (cont'd)

Afatinib mechanism of action[8]



AKT, protein kinase B, *ERK,* extracellular signal-regulated kinase, *HER2,* human epidermal growth factor receptor 2; (ErbB2), *MEK* mitogen-activated protein kinase kinase; *mTOR,* mammalian target of rapamycin; *PI3K*, phosphoinositide 3-kinase; *RAF*, rapidly accelerated fibrosarcoma; *RAS*, rat sarcoma

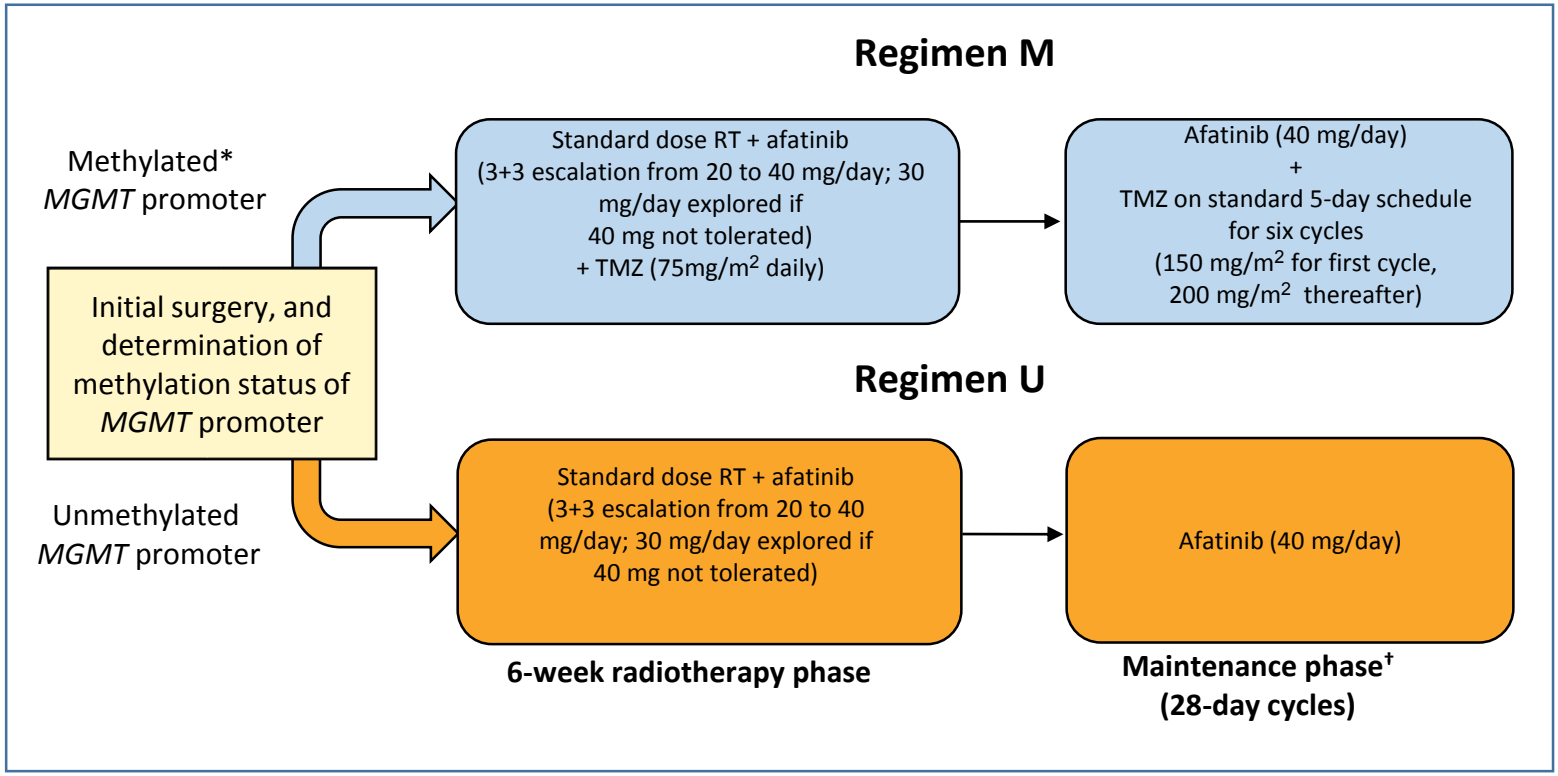
Methods

Study design and patients

- This Phase I open-label trial used a 3+3 dose escalation design (see Study schema)
- The MTD for afatinib in combination with radiotherapy ± TMZ was determined during the radiotherapy phase, based on dose-limiting toxicities (DLTs)
- Patients aged ≥18 years and <70 years with newly diagnosed WHO Grade IV malignant glioma, proven MGMT gene promoter methylation status, early postoperative Gd-enhanced magnetic resonance imaging and Karnofsky performance score ≥70% were recruited at 5 centers in the United Kingdom

Methods (cont'd)

Study schema



*Once the MTD in Regimen U had been determined, all further patients were assigned to Regimen M regardless of the methylation status; †Until disease progression or undue adverse events; RT, radiotherapy

Methods (cont'd)

Endpoints and statistical analysis

Primary	MTD of afatinib in combination with RT (Regimen U) and in combination with RT and TMZ (Regimen M)
Secondary	**Safety**: Incidence and intensity of adverse events according to CTCAE version 3 **Efficacy:** Objective tumor response as assessed by the investigator according to the Macdonald criteria **PK:** Afatinib $C_{pre,ss}$ on Days 8, 15 and 29

CTCAE, Common Terminology Criteria for Adverse Events; $C_{pre,ss}$, pre-dose concentration at steady state; RT, radiotherapy

Patient demographics and baseline characteristics

	Regimen M (n=20)	Regimen U (n=16)
Median age, years (range)	52.5 (25–66)	53.5 (34–68)
Male, n (%)	14 (70)	11 (69)
White, n (%)	19 (95)	16 (100)
Never smoked, n (%)	15 (75)	13 (81)
Prior surgery, n (%)	14 (70)	14 (88)

Results

Patient exposure and disposition

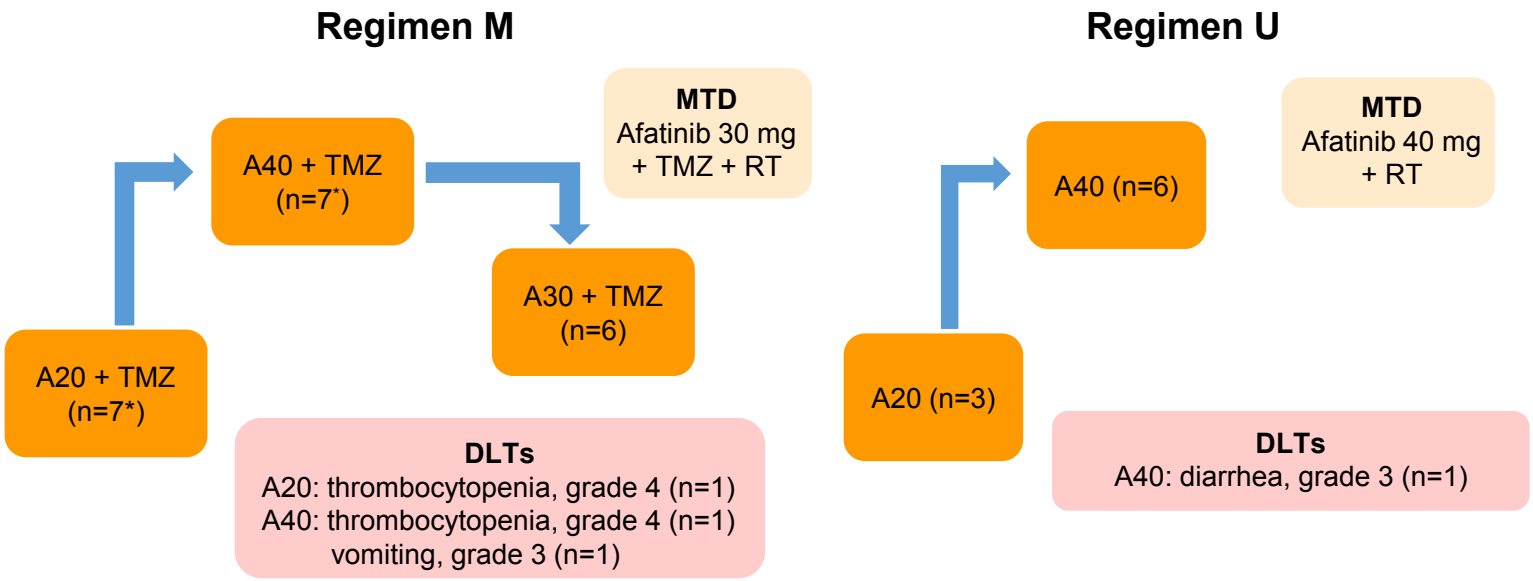
n (%)	Regimen M (n=20)	Regimen U (n=16)
Continued afatinib beyond RT phase	15 (75)	13 (81)
Discontinued due to progressive disease	9 (45)	8 (50)
Discontinued due to DLT	2 (10)	0
Discontinued due to other AEs	7 (35)	6 (38)
Discontinued due to non-compliance	1 (5)	0
Discontinued for other reasons	1 (5)	2 (13)

- Median extent of treatment exposure: Regimen M: 151 days (range: 6–2340); Regimen U: 168 days (range: 1–397)
- At final data cut-off (September 12, 2017), 35 patients had discontinued study treatment, primarily due to progressive disease (47%) or AEs other than DLTs (36%)
  - One patient, without progressive disease at data cut-off, was switched to commercially provided afatinib and remained on treatment for >6 years

AE, adverse event

Results (cont'd)

Determination of MTD based on the occurrence of DLTs†



*One patient was replaced; †During the six-week radiotherapy phase; A, afatinib

Results (cont'd)

Overall summary of AEs

n (%)	Regimen M (n=20)	Regimen U (n=16)
Any AE	20 (100)	16 (100)
Drug-related AE	19 (95)	15 (94)
Grade ≥3 AE	16 (80)	12 (75)
AEs leading to afatinib discontinuation	9 (45)	10 (63)
Serious AEs	12 (60)*†	12 (75)
Drug-related serious AEs	6 (30)	1 (6)
Deaths	0	3 (19)‡
Drug-related deaths	0	0

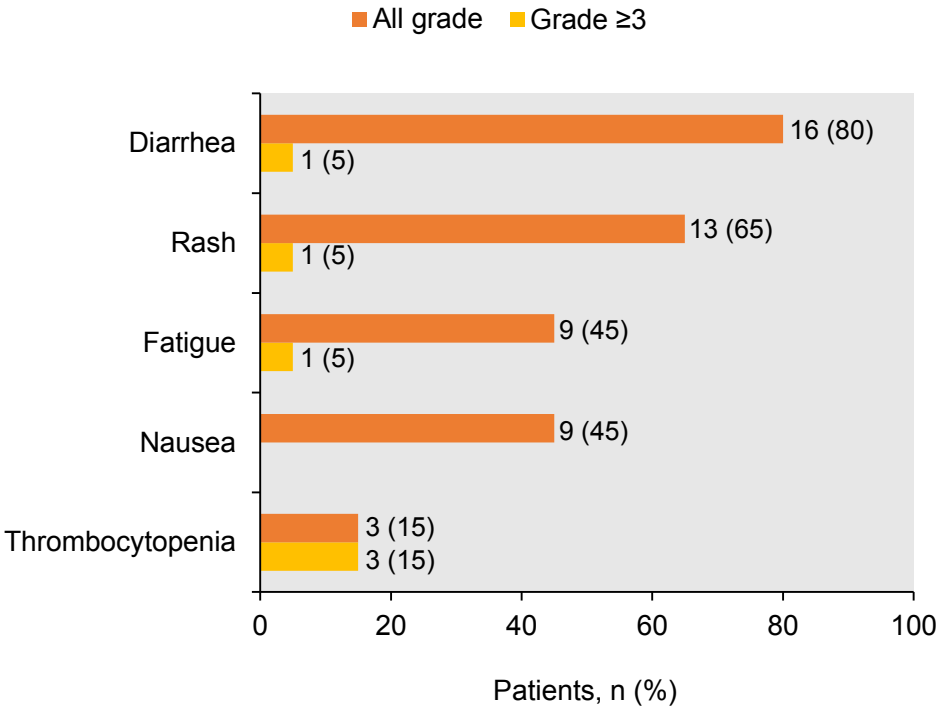
- As patient numbers are small, no firm conclusions can be made about the difference in occurrence of deaths between the regimens

*More than one seriousness criterion might be given for each patient; †No AEs that led to disability or incapacity and no AEs that were congenital anomalies were observed in this trial; ‡Deaths were caused by malignant neoplasm progression, pneumonia and bacterial meningitis, reported in one patient each (6%)

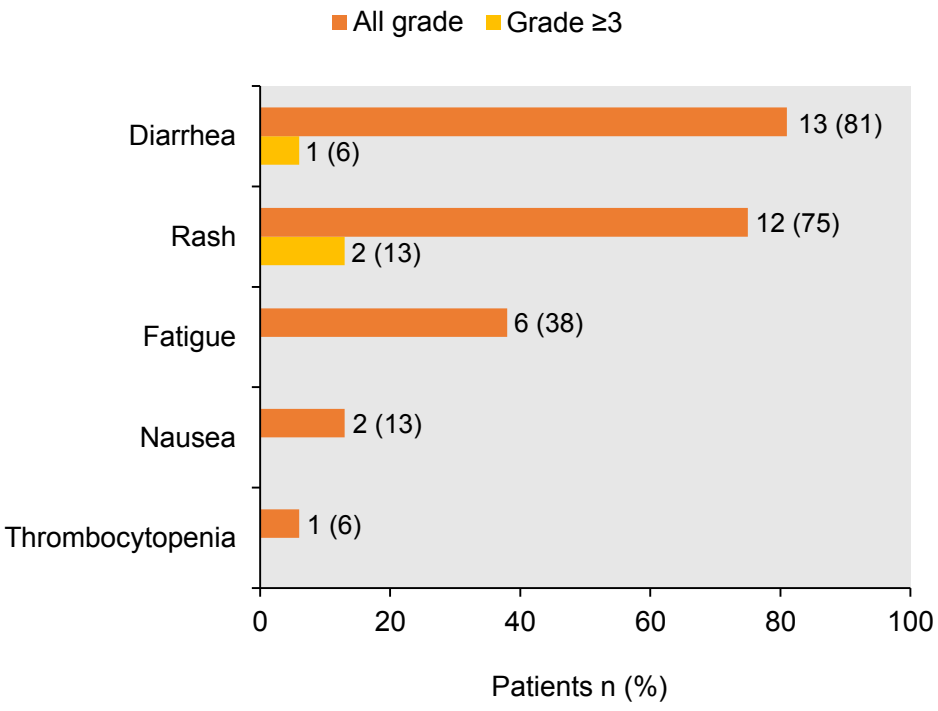
Results (cont'd)

Incidence and intensity of drug-related AEs

Most common drug-related AEs (preferred term) by maximum CTCAE grade in Regimen M (n=20)



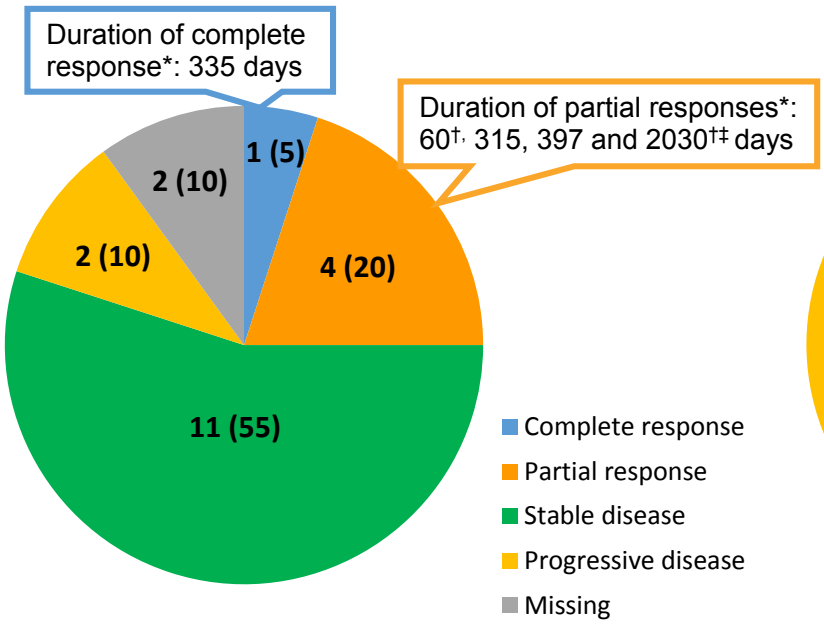
Most common drug-related AEs (preferred term) by maximum CTCAE grade in Regimen U (n=16)



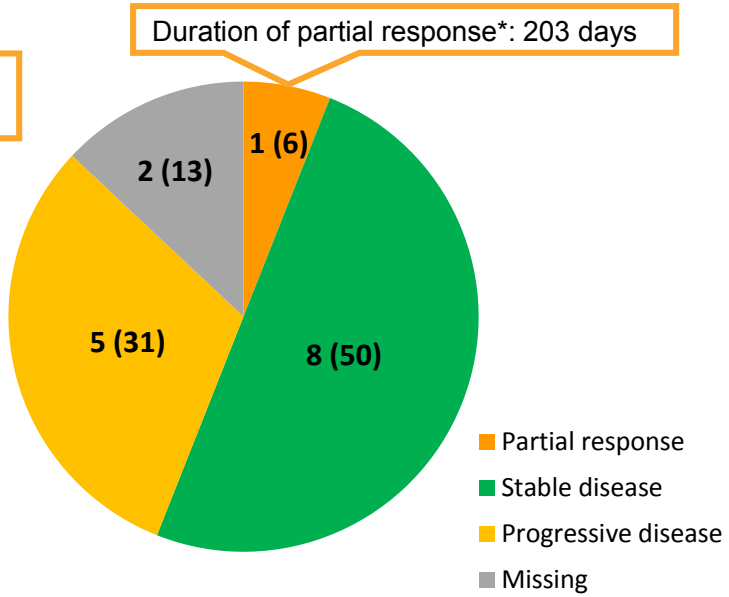
Results (cont'd)

Anti-tumor activity

Best overall response: Regimen M, n (%)



Best overall response: Regimen U, n (%)



*Not pre-specified in the clinical trial protocol or statistical analysis plan; †Censored observations; ‡Switched to commercial supply after data cut-off

Results (cont'd)

Pharmacokinetics

Geometric mean afatinib pre-dose steady-state plasma concentrations on Days 8, 15 and 29 in Regimen M

	Afatinib 20 mg/day + TMZ			Afatinib 30 mg/day + TMZ			Afatinib 40 mg/day + TMZ		
	n	gMean	gCV (%)	n	gMean	gCV (%)	n	gMean	gCV (%)
$C_{pre,ss,8}$ (ng/mL)	3	4.37	40.20	5	10.70	70.30	5	15.70	32.80
$C_{pre,ss,15}$ (ng/mL)	4	5.61	55.10	6	9.64	54.30	4	16.80	59.50
$C_{pre,ss,29}$ (ng/mL)	4	5.31	92.00	6	17.80	15.60	3	17.40	56.10

Geometric mean afatinib pre-dose steady-state plasma concentrations on Days 8, 15 and 29 in Regimen U

	Afatinib 20 mg/day			Afatinib 40 mg/day		
	n	gMean	gCV (%)	n	gMean	gCV (%)
$C_{pre,ss,8}$ (ng/mL)	3	4.88	32.90	12	16.70	40.20
$C_{pre,ss,15}$ (ng/mL)	3	4.43	177.00	10	18.90	35.50
$C_{pre,ss,29}$ (ng/mL)	3	5.01	53.30	9	16.10	40.70

- Afatinib trough plasma concentrations appeared stable over the observed treatment period

$C_{pre,ss,N}$, pre-dose concentration at steady state Day N; gCV, geometric coefficient of variation; gMean, geometic mean

Conclusions

- The MTD was determined as afatinib 30 mg/day when combined with radiotherapy and TMZ (Regimen M), and afatinib 40 mg/day when given with radiotherapy alone (Regimen U)
- The overall AE profile was consistent with the known safety profiles of afatinib, TMZ and radiotherapy
- Afatinib and radiotherapy ± TMZ appeared well-tolerated with manageable AEs
- The most common treatment-related AEs were diarrhea, rash and fatigue
- This dose-finding study conducted in a small number of patients suggested beneficial anti-tumor activity when patients were treated with afatinib and radiotherapy ± TMZ
- Afatinib steady-state plasma concentrations were comparable with or without co-administration of TMZ

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