

Phase II open-label study of nintedanib in patients with recurrent glioblastoma multiforme

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Abstract Nintedanib (BIBF 1120) is a small, orally available, triple angiokinase inhibitor in phase III development (various indications) that targets VEGFR 1–3, FGFR 1–3, and PDGFR- α/β . This open-label, uncontrolled, phase II study assessed the efficacy and safety of nintedanib in patients with recurrent glioblastoma multiforme (GBM) who had previously failed radiotherapy plus temozolomide as first-line therapy (STUPP), or the same regimen with subsequent bevacizumab-based therapy as second-line treatment (BEV). Patients with a performance status of 0–1, histologically proven GBM, and measurable disease (by RANO) were enrolled. Nintedanib was given orally at a dose of 200 mg twice daily (bid), with magnetic resonance imaging undertaken every 8 weeks. The primary endpoint was objective response rate. The study was stopped prematurely following a preplanned futility analysis after inclusion of 13 patients in the STUPP arm and 12 in the BEV arm. Best response was stable disease (SD) in three patients (12 %); all other patients progressed within the first four 28-day cycles. One patient in the BEV arm has had SD for 17+ months. Median progression-free survival was 1 month and median overall survival was 6 months. Nintedanib had an acceptable safety profile, with no CTCAE grade 3–4 adverse events. Common adverse events were CTCAE grade 1–2 fatigue, loss of appetite,

diarrhea, and nausea. Single-agent nintedanib (200 mg bid) demonstrated limited, but clinically non-relevant antitumor activity in patients with recurrent GBM who had failed 1–2 prior lines of therapy.

Keywords Glioblastoma · Nintedanib (BIBF 1120) · Angiogenesis inhibitors · Phase II clinical trial

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant neoplasm of the central nervous system (CNS) in adults [1]. Current primary treatment is maximal surgical resection followed by the ‘STUPP’ regimen [2]: brain irradiation (60 Gy in 30 fractions) concurrent with temozolomide (TMZ) over 6 weeks, followed by adjuvant TMZ monotherapy for up to 6 months [3, 4]. Median overall survival (OS) associated with this regimen was 14.6 months [2]. Patients who progress through initial treatment, however, have a dismal prognosis with a median OS of about 6 months [5]. For these patients there is no established treatment.

GBM is a highly vascularized tumor and vascular endothelial growth factor (VEGF) is highly expressed in GBM, where it induces angiogenesis primarily by stimulating VEGF receptor-2 (VEGFR-2) on tumor vessels [6]. Additionally, overexpression or amplification of the epidermal growth factor receptor (EGFR) and its truncated variant, EGFRvIII, is often seen in primary GBM [7], while overexpression of the platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), p53, and IDH1 is more common in secondary GBM [8–10]. Activation and overexpression of these signaling molecules is believed to facilitate angiogenesis and

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growth in this highly aggressive malignancy. *PTEN* mutations, contributing to abnormally high activity in the PI3 K/AKT/mTOR pathway, are also often seen in GBM tumors [11].

Although the angiogenic process is poorly understood, inhibition of the VEGF axis, in combination with other implicated growth factor receptors might have a synergistic inhibitory effect on tumor angiogenesis [12]. Targeting VEGF signaling alone with the monoclonal antibody, bevacizumab (which is approved for use in recurrent GBM in the USA), has resulted in modest clinical benefits (response rates of 28–35 % and median OS of 7.7–9.2 months when used in monotherapy) in patients with recurrent GBM in first/second relapse [13–15]. These limited effects may be a consequence of escape mechanisms for tumor angiogenesis, whereby PDGFRs and FGFRs compensate for the disruption of the VEGF pathway [16]. A multitargeted approach may therefore be more beneficial.

Nintedanib (BIBF 1120; Boehringer Ingelheim, Germany) is a potent, oral triple angiokinase inhibitor in phase III development that targets VEGFRs, PDGFRs, FGFRs, Flt3, RET, and Src [16]. In preclinical models, the specific and simultaneous abrogation of these pathways resulted in effective growth inhibition of both endothelial and perivascular cells [16]. Nintedanib may therefore be a more effective inhibitor of angiogenesis than agents that solely target the VEGF pathway and thus may have a potential role in GBM. Phase I/II monotherapy studies in various tumour types (including advanced non-small cell lung cancer and ovarian cancer) and idiopathic pulmonary fibrosis show that nintedanib is generally well tolerated with mild-to-moderate adverse effects, such as gastrointestinal symptoms and reversible elevations of liver enzymes [17–20]. Initial signs of clinical activity, including encouraging tumor stabilization rates of 46–76 %, have also been observed during phase I/II development [17, 20, 21]. From these studies, the recommended dose for continuous daily monotherapy is 200–250 mg twice daily (bid) [17, 21].

As nintedanib might present as a new treatment option for GBM, this phase II study was initiated to investigate the antitumor activity and safety of this agent in patients with primary GBM who had failed primary or secondary treatment for recurrent disease.

Patients and methods

Patient selection

Adult patients aged >18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and histologically proven GBM were enrolled. All patients had

previously failed standard radiotherapy plus TMZ as first-line therapy (STUPP), or the same regimen with subsequent bevacizumab-based therapy as second-line treatment (BEV). Patients also had available archival tissue blocks, measurable disease (according to Revised Assessment in Neuro-Oncology [RANO] guidelines), progressive disease (documented by a magnetic resonance imaging [MRI] scan obtained within 14 days prior to enrolment), and had provided informed consent. Patients undergoing recent resection (>6 weeks) for recurrent tumors were eligible, but residual disease was required for inclusion. Fertile women had to use appropriate contraceptive methods.

Key exclusion criteria included: prior treatment with nintedanib or any other VEGFR inhibitor, except bevacizumab; inadequate hematologic function (absolute neutrophil count <1,500/ml, platelets <100,000/ml, or hemoglobin <9.0 g/dl); insufficient coagulation (international normalized ratio ≥ 2 or prothrombin time/partial thromboplastin time >50 % of the deviation of the institutional upper limit of normal [ULN]); inadequate hepatic function (alanine transaminase/aspartate transaminase >1.5 \times ULN or total bilirubin outside of normal limits); significant cardiovascular disease (uncontrolled hypertension, unstable angina, history of myocardial infarction in the 12 months prior to the start of treatment, congestive heart failure > New York Heart Association Class 2, pericardial effusion, or serious cardiac arrhythmia); hemorrhagic or thromboembolic events in the past 6 months; and major injuries in the 10 days prior to start of the study. Patients with active serious infection requiring systemic antimicrobial therapy, or patients with active or chronic hepatitis C or B infection were also ineligible.

This investigator-initiated study (clinicaltrial.gov identifier: NCT01251484) was supported by a research grant from Boehringer Ingelheim, who provided the study medication. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. Protocol approval was obtained from the local Ethics Committee and Danish Medicines Agency.

Treatment plan

This was an investigator-initiated, single-center, non-randomized, open-label, two-stage phase II study of single-agent nintedanib in patients with recurrent primary GBM who had failed primary (first-line radiotherapy plus TMZ; STUPP arm) or secondary (STUPP regimen followed by second-line bevacizumab-based therapy; BEV arm) treatment for recurrent disease. The study was designed so that 32 patients would be enrolled into both the STUPP and BEV arms. The two-stage design included a stopping rule

if three or fewer patients achieved an objective response once 16 patients had been enrolled into each arm.

All patients were treated continuously with nintedanib at a dose of 200 mg bid (two capsules twice daily). One cycle was 28 days, with treatment continued until disease progression (PD) or unacceptable toxicity.

Evaluation of response

Neuro-imaging with MRI, including pre-contrast T1, T2/FLAIR and post-contrast T1, with two orthogonal planes and T2-weighted flair, was performed at baseline, before the first treatment cycle, and every 8 weeks thereafter. Tumor size was measured in two dimensions, according to RANO criteria [22].

Safety assessment

All adverse events occurring during the course of the trial and for up to 2 months after the last dose of study medication were collected, documented, and reported. Toxicity was graded every 2 weeks for the first two cycles and every 4 weeks thereafter, according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [23]). A toxicity and dose-reduction management plan was followed according to the investigators' brochure.

Biomarker Analyses

Although biomarker analyses were pre-planned, utilizing archival tissue blocks and collected plasma samples to assess vascular and immune system parameters, none were undertaken due to early termination of the study.

Statistical analysis

The primary endpoint was the objective tumor response rate (complete remission [CR] + partial remission [PR]), assessed according to RANO criteria [22]. Secondary endpoints included progression-free survival (PFS), OS, safety, and evaluation of biomarkers.

It was estimated that a total of 32 patients per arm would be required to provide 76 % power to be able to detect a treatment effect on response rate at a one-sided significance level of $\alpha = 0.05$. The proportion of responders under the null hypothesis (no drug effect) was assumed to be 10 %, while under the alternative hypothesis (drug effect), the proportion was assumed to be 25 %.

A preplanned safety analysis was undertaken when the first 10 patients had received a minimum of two cycles (8 weeks) of treatment. A futility analysis was also planned once 16 patients were evaluable for response in each arm

(stage 1), or earlier if clinically indicated. An objective response in at $>3/16$ patients in either arm was required to proceed to stage 2, where a total of 32 patients would be recruited per arm. This would result in a probability of early termination of >75 % when the true response rate was <10 %.

Response rates were calculated in the intention-to-treat (ITT) population, with confidence intervals estimated using the Clopper-Pearson method. PFS and OS analyses were also performed in the ITT population using the Kaplan–Meier log-rank method. PFS was defined as the time between the start of treatment and first occurrence of disease progression or death; data were censored at last follow-up if the patient remained alive without PD. Safety data are summarized for all treated patients. The Kaplan–Meier method was used to analyze time-to event data and the log-rank test was used to compare PFS and OS (SPSS version 18.0) analyses.

Results

Patient characteristics

Twenty five patients were enrolled between January 2011 and July 2011. Baseline demographics and patient characteristics are shown in Table 1.

The study was stopped prematurely for futility after inclusion of 13 patients in the STUPP arm and 12 patients in the BEV arm, since no responses were observed in either arm. Median follow-up was 14 months (range 10–15 months) and median number of treatment cycles administered was 2 (range 1–17, Table 2).

Efficacy

The objective response rate (CR + PR) to nintedanib 200 mg bid among all patients in the ITT population was 0 % (Table 2). The best radiographic response was SD in three patients (12 %): two patients in the STUPP arm and one patient in the BEV arm. PD was observed in the remaining 22 patients (88 %). One patient in the BEV arm has had SD for 17 months (Fig. 1), while all other patients progressed within the first four cycles. Analyses of possible correlations with biomarkers were not performed due to the lack of response.

Six-month PFS was 4 % ($n = 1$; 95 % CI 0.1–20.4 %). Median PFS was estimated to be 1 month (95 % CI 0.7–1.3 months), and no significant differences were observed between the two arms. Estimated median OS was 6 months (95 % CI, 3.6–8.4 months). A significant difference in OS was observed between the STUPP and BEV arms (median OS: 8.1 [95 % CI 1.5–14.8] vs. 1.3

Table 1 Baseline demographics and patient characteristics

	All patients (<i>N</i> = 25)	STUPP arm (<i>N</i> = 13)	BEV arm (<i>N</i> = 12)
Gender, <i>n</i> (%)			
Male	15 (60)	7 (54)	8 (67)
Female	10 (40)	6 (46)	4 (33)
Median age, years (range)	55 (31–72)	56 (33–72)	52 (31–68)
ECOG PS, <i>n</i> (%)			
0	4 (16)	2 (15)	2 (17)
1	21 (84)	11 (85)	10 (83)
Use of corticosteroids, <i>n</i> (%)	11 (44)	3 (23)	8 (67)
Salvage surgery prior to entry, <i>n</i> (%)	11 (44)	10 (77)	1 (8)

ECOG PS eastern cooperative oncology group performance status

Table 2 Efficacy outcomes, treatment exposure and follow-up

	All patients (<i>N</i> = 25)	STUPP arm (<i>N</i> = 13)	BEV arm (<i>N</i> = 12)
Best response (RANO criteria), <i>n</i> (%)			
CR or PR	0 (0)	0 (0)	0 (0)
SD	3 (12.0)	2 (15.4)	1 (8.3)
PD	22 (88.0)	11 (84.6)	11 (84.6)
Median number of cycles, <i>n</i> (range)	2 (1–17)	2 (1–4)	1.5 (1–17)
Median follow-up, months (range)	14 (10–15)	14 (1–15)	14.5 (11–15)
PFS at 6 months, % (95 % CI)	4.0 (0.1–20.4)	0 (0–24.7)	8.3 (0.2–38.5)
Median OS, months (95 % CI)	6 (3.6–8.4)	10 (4.3–15.5)	2 ^a (0.3–3.7)

^a This difference was statistically significant versus STUPP ($p < 0.02$, Fischer's exact test). CI confidence interval; CR complete response; OS overall survival; PD progressive disease; PFS, progression-free survival; PR partial response; RANO revised assessment in neuro-oncology; SD stable disease

[95 % CI 0.0–4.9] months, respectively [$p < 0.02$], (Fig. 2). Six patients were alive at the time of the analyses, five in STUPP and one in BEV arm.

Only patients who maintained a good performance status (0–1) were retreated at progression after receiving nintedanib. Patients in the STUPP arm were subsequently treated with bevacizumab or TMZ induction therapy. Eligible patients in the BEV arm went on to receive re-irradiation in an ongoing trial. Among five patients in the STUPP arm who were subsequently treated with bevacizumab, four responded with a response duration

between 4 and >10 months. Among two patients who received TMZ, one achieved PR for >6 months prior to progression. Only two patients in the BEV arm were retreated after nintedanib; both were re-irradiated, but neither responded to treatment.

Adverse events

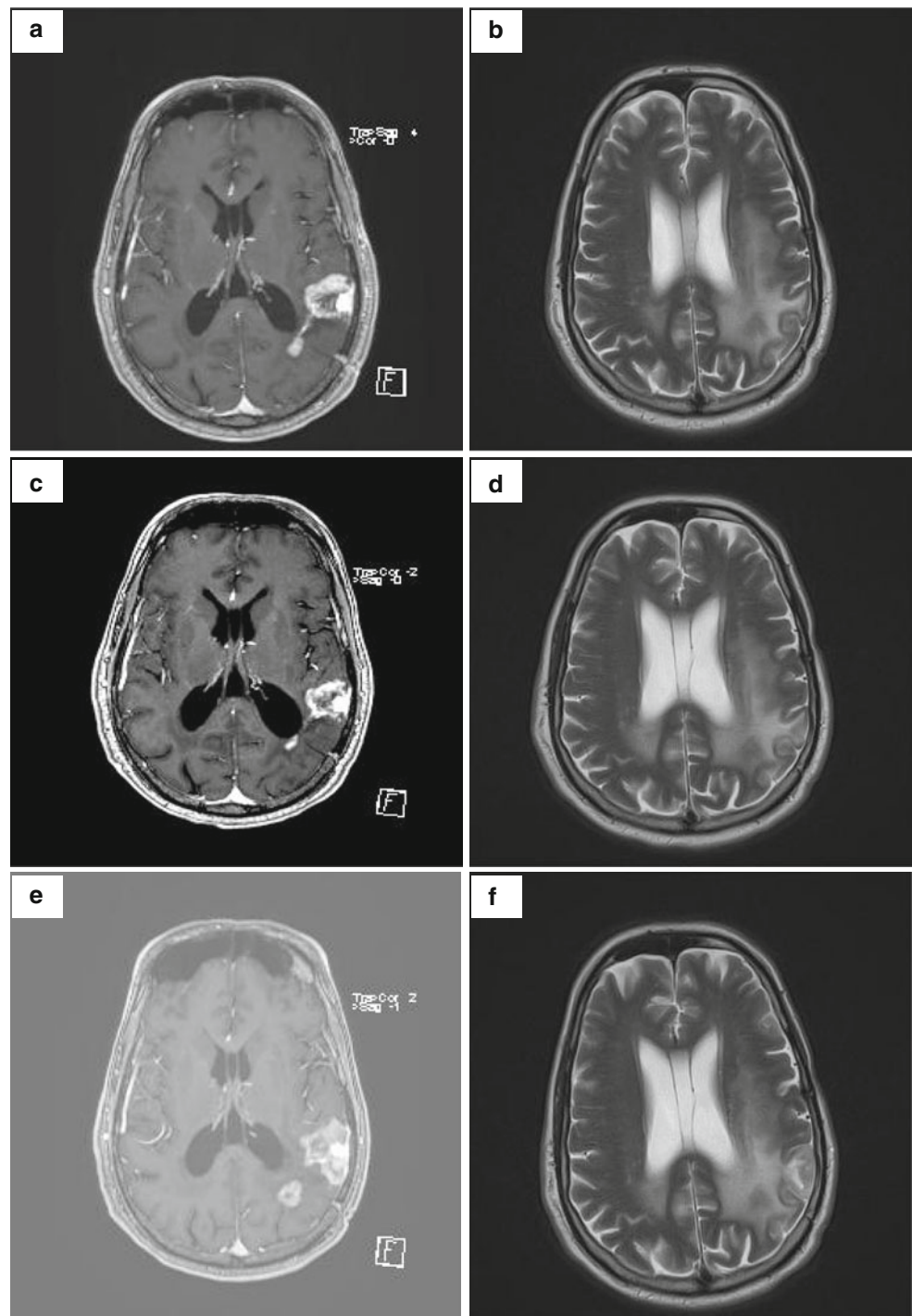
Single-agent nintedanib treatment was well tolerated (Table 3). Grade 3–4 adverse events were not observed and there were no study-related deaths or episodes of intracranial hemorrhage. The most frequently reported adverse events were grade 1–2 fatigue ($n = 24$; 96 %), loss of appetite ($n = 6$; 24 %), diarrhoea ($n = 9$; 36 %), and nausea ($n = 5$; 20 %). There were no significant differences in adverse events between the STUPP and BEV arms, and no dose reductions were reported.

Discussion

Data from this phase II trial show that nintedanib 200 mg bid is well tolerated, but with limited, clinically non-relevant activity in patients with recurrent GBM who have failed primary or secondary treatment for recurrent disease. At the time of the futility analysis (which resulted in early closure of the trial), no responses had been reported and just 3/25 patients had achieved tumor stabilization. Median PFS was 1 month and median OS was 6 months. As expected, patients who had received nintedanib as third-line therapy had significantly shorter median OS than those who had received the drug as second-line therapy (2 vs 10 months, respectively; $p < 0.02$), reflecting the poorer prognosis of patients with more refractory disease. Despite this, one patient did achieve an extended period of disease stabilization (17 + months), which suggests that some patients may benefit from treatment. It also suggests that time to progression or SD may be better endpoints in studies of angiogenesis inhibitors.

This is the first study to evaluate objective responses to single-agent nintedanib in patients with recurrent GBM. In preclinical models, nintedanib predominately inhibits VEGFR 1–3 and PDGFR- α/β at nanomolar concentrations, with sustained VEGFR blockade lasting for >32 h [16, 24]. In addition, drug activity has been observed in cells that are predominately activated through FGFRs [16]; although the exact mechanism that underlies this effect is unknown [24]. Inhibition of pro-angiogenic receptor tyrosine kinases, such as PDGFR and FGFR, also appears to be relevant [25]. However, the lack of activity observed in the present study indicates that a potential blockade of the activity of VEGFR, PDGFR, and FGFR kinases by nintedanib does not inhibit angiogenesis in patients with recurrent GBM.

Fig. 1 Baseline MRI (January 2011) from a patient with stable disease for 17 months showing contrast-enhanced lesion in the left temporo-parietal region ($2.7 \times 2.5 \times 2.4$ cm [AP \times SS \times CC] (a). T2 changes covered 8.8 cm anterior-posterior (b). After 12 cycles (February 2012) contrast-enhanced lesion in the left temporo-parietal region stable disease ($2.7 \times 2.5 \times 2.7$ cm [AP \times SS \times CC] (c). T2 changes covered 8.0 cm (d). At progression after 17 months the contrast-enhanced lesion increased in size (e), whereas the T2 changes remained unchanged (f). However, the patient also progressed clinically



One reason for this could be that glioma cells rely on other redundant pathways to support angiogenesis [26]. Consistently, a number of previous studies utilizing small molecule, dual-VEGFR/PDGFR inhibitors (sunitinib, sorafenib, vatalanib, cediranib, and pazopanib) also failed to demonstrate any clinically relevant activity in recurrent GBM [27–31]. Other authors have reported lower response rates and shorter disease control rates using bevacizumab after

patients have relapsed on another prior anti-VEGF therapy [32]. This could not be confirmed in our study, since we observed several, durable responses to bevacizumab in patients previously treated with nintedanib.

Restricted delivery of targeted agents across the blood–brain barrier may also reduce their efficacy against brain tumors. Several tyrosine kinase inhibitors, including cediranib, gefitinib, erlotinib, and lapatinib, have been shown

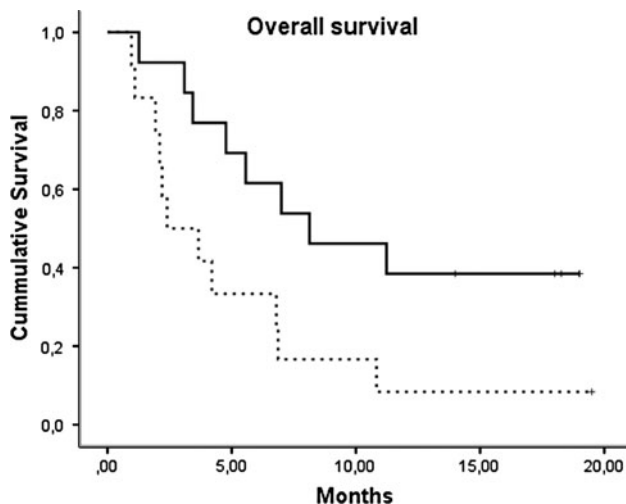


Fig. 2 A significant difference in overall survival was observed between the STUPP (*solid line*) and BEV (*dotted line*) arms (median OS: 8.1 [95 % CI 1.5–14.8] vs 1.3 [95 % CI 0.0–4.9] months, respectively [$p < 0.02$], log-rank test). Six patients were alive at the time of the analyses, five in STUPP and one in BEV arm

Table 3 Treatment-related adverse events reported among all 25 patients, according to CTCAE version 4.0

Adverse event (preferred term)	Grade $\frac{1}{2}$ n (%)	Grade $\frac{3}{4}$ n (%)
Fatigue	24 (96)	0 (0)
Diarrhea	9 (36)	0 (0)
Loss of appetite	6 (24)	0 (0)
Nausea	5 (20)	0 (0)
Infection	4 (16)	0 (0)
Skin reaction	4 (16)	0 (0)
Weight loss	4 (16)	0 (0)
Stomatitis	3 (12)	0 (0)
Vomiting	2 (8)	0 (0)
Bleeding	1 (4)	0 (0)

CTCAE national cancer institute common terminology criteria for adverse events

to be substrates for two important efflux transporters at the blood–brain barrier, P-gp/Bcrp, which restricts their CNS penetration [33–36]. Consistently, preclinical whole-body autoradiography studies show that nintedanib (molecular weight 539 Da) does not cross the blood–brain barrier in normal rat brain (investigator’s brochure U03-1563), as is generally expected for molecules >300 Da. Nonetheless, molecules >300 Da can reach intracranial tumor lesions with disrupted blood–brain barriers in tumor vessels, as is the case for bevacizumab [37]. Studies are now required to investigate if adequate concentrations of nintedanib are achievable in the brain or if nintedanib’s lack of activity is due to compensatory pro-angiogenic or other mechanisms.

Several publications have shown that anti-VEGF therapy, either with bevacizumab alone or in combination with

chemotherapy induces responses in 25–68 % of patients with recurrent GBM [14, 38–41]. Response duration can be months, but most patients eventually become resistant to treatment and their tumors progress [14, 38–41]. The reasons for this are not entirely clear; although it has been postulated the recurrent phenotype might be more invasive and infiltrative than de novo GBM. In addition, resistance might develop due to up-regulation of PDGF and recruitment of pericytes, which stabilizes the neovasculature. It has therefore been suggested that a combination of VEGFR inhibition and PDGFR inhibition might overcome this resistance [42]. Furthermore, inhibition of FGF’s pro-angiogenic effect might facilitate inhibition of tumor neovascularization [34]. Unfortunately, the lack of response to nintedanib does not support these propositions. However, the lack of activity is consistent with that seen with other multikinase inhibitors [41, 43].

Phase I studies have shown that the maximum tolerated dose of nintedanib is 200–250 mg (administered once or twice daily) with other studies demonstrating moderate response rates at doses up to 250 mg bid in various metastatic tumors [17–19, 21]. In the present study, we used a dose of 200 mg bid, which is within the range of the optimal dose. At this dose, nintedanib was well tolerated. The reported incidence of adverse events was low compared to published reports in other malignancies [19]. Additionally, we did not observe many of the common toxicities usually associated with anti-VEGF therapy, which is consistent with previous data on nintedanib [17–19, 21].

Conclusion

Nintedanib is well tolerated in patients with recurrent GBM who have failed 1–2 prior lines of therapy, but does not demonstrate any clinically relevant antitumor activity.

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Conflicts of interest No authors have conflicts of interest.

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