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EORTC study 26041-22041: Phase I/II study on concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) with PTK787/ZK222584 (PTK/ZK) in newly diagnosed glioblastoma

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ABSTRACT

Background: Glioblastoma is a highly vascularised tumour with a high expression of both vascular endothelial growth factor (VEGF) and VEGFR. PTK787/ZK222584 (PTK/ZK, vatalanib), a multiple VEGF receptor inhibitor, blocks the intracellular tyrosine kinase activity of all known VEGF receptors and is therefore suitable for long-term therapy of pathologic tumour neovascularisation.

Patients and methods: The study was designed as an open-label, phase I/II study. A classic 3 + 3 design was selected. PTK/ZK was added to standard concomitant and adjuvant treatment, beginning in the morning of day 1 of radiotherapy (RT), and given continuously until disease progression or toxicity. PTK/ZK doses started from 500 mg with subsequent escalations to 1000 and 1250 mg/d. Adjuvant or maintenance PTK after the end of radiochemotherapy was given at a previously established dose of 750 mg twice daily continuously with TMZ at the standard adjuvant dose.

Results: Twenty patients were enrolled. Dose-limiting toxicities at a once daily dose of 1250 mg were grade 3 diarrhoea ($n = 1$), grade 3 ALT increase ($n = 2$), and myelosuppression with grade 4 thrombocytopenia and neutropenia ($n = 1$). The recommended dose of PTK/ZK in combination with radiotherapy and temozolomide (TMZ) is 1000 mg once a day. This treatment is safe and well tolerated.

Conclusion: In our phase I study once daily administration of up to 1000 mg of PTK/ZK in conjunction with concomitant temozolomide and radiotherapy was feasible and safe. Prolonged administration of this oral agent is manageable. The planned randomised phase II trial was discontinued right at its onset due to industry decision not to further develop this agent.

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1. Introduction

Temozolomide (TMZ) concomitant and adjuvant to radiotherapy (RT) has become the new standard of care in 2004 for newly diagnosed glioblastoma (GBM) based on a large randomised trial.[1] After a long term follow-up of 45.9 months, the survival advantage conferred by the addition of temozolomide to radiotherapy remains highly significant the 2-, 3- and 4-year survivals being 10.9%, 4.4% and 3% in the radiotherapy arm, versus 27.2%, 16.7% and 12.1% in the concomitant arm ($p < 0.0001$).[2] However, despite surgery, radiotherapy and concomitant and adjuvant chemotherapy, GBM invariably recurs and ultimately leads to patients' death.[1,2] Further trials exploring new combinations are urgently needed.

Vascular endothelial growth factor (VEGF) is a target for tumour growth inhibition, as it is a major regulator of angiogenesis. Malignant gliomas are highly vascularised and infiltrative tumours are strongly dependent on endothelial cell proliferation regulated by proangiogenic cytokines. GBM has a high expression of both VEGF and VEGFR. PTK/ZK, a multiple VEGF receptor inhibitor, blocks the intracellular tyrosine kinase activity of all known VEGF receptors and is therefore suitable for long-term therapy of pathologic tumour neovascularisation.

As demonstrated in a phase I study,[3] continuous daily administration of oral PTK/ZK (1500 mg/d) can be safely combined with TMZ, without the MTD being reached.

Moreover, preclinical and clinical evidence suggests that antiangiogenic treatment may work best in combination with chemotherapy and radiotherapy. Ionising radiation induces overexpression of VEGF[4,5] in both tumour cells and endothelial cells. Radiotherapy-induced increase of VEGF expression promotes the survival and migration of endothelial cells following radiotherapy, which leads to an increased tumour angiogenesis after radiotherapy.[6] The inhibition of these VEGF-dependent pathways during radiotherapy increases endothelial cell apoptosis and abrogates the increased migration and invasion of endothelial cells following radiotherapy.[4,5,7] Theoretically, co-administration of radiotherapy, anti-VEGF drugs and other angiogenesis-inhibiting drugs are an attractive approach as the combination may increase the anti-tumour effects of radiotherapy, compared to treatment with RT or with antiangiogenetic treatment alone.

The European Organisation for Research and Treatment of Cancer (EORTC), Brain Tumour and Radiation Oncology Groups planned a phase I/II study in which PTK/ZK is combined with standard RT and concomitant TMZ. The results of the safety and dose-finding run-in phase I part of the triple combination are reported here.

2. Patient and methods

2.1. Patient eligibility

Eligible patients were 18 to 70 years of age with newly diagnosed and histologically confirmed glioblastoma (World Health Organisation [WHO] grade IV astrocytoma) with a WHO performance status of 2 or less, with adequate haematologic, renal, and hepatic function (absolute neutrophil count, $\geqslant 1.500 \times 10^9$ cells/l; platelet count, $\geqslant 100 \times 10^9$ cells/l; serum creatinine level, $\leqslant$1.5 times the upper limit of normal in the laboratory where it was measured; total serum bilirubin level, $\leqslant$1.5 times the upper limit of normal; and liver-function values, <3 times the upper limit of normal for the laboratory), and who had clinically normal cardiac function without history of ischaemic heart disease in the past 6 months. Patients who were receiving corticosteroids were eligible if their required daily dose was stable or decreasing for at least 14 d before randomisation.

Patients with previous or current malignancies at other sites with the exception of cone biopsied carcinoma of the cervix and adequately treated basal or squamous cell skin carcinoma were excluded; similarly patients with a history of uncontrolled systemic disease, uncontrolled hypertension, and active uncontrolled infections were ineligible. Concomitant treatment with warfarine or other coumarine derivatives or other investigational drugs was not permitted. Patients receiving EIADs were ineligible. Patients under EIADS were switched to no EIADs prior study entry. The protocol was approved by the EORTC protocol review committee, and by national and institutional review boards of the participating centres according to European, national and local regulations. All patients provided written informed consent. The trial was registered with www.ClinicalTrials.gov, identification number NCT00128700.

2.2. Study design and treatments

The study was designed as an open-label, phase I/II study. PTK/ZK was added to standard concomitant and adjuvant treatment, beginning in the morning of day 1 of radiotherapy, and given continuously until disease progression or toxicity. PTK787/ZK222584 (PTK/ZK) was to be taken once daily during RT, doses were escalated in cohorts of 3–6 patients depending on toxicity. PTK/ZK starting dose was 500 mg with subsequent escalations to 1000 and 1250 mg/d. After completion of concomitant chemoradiotherapy, maintenance (adjuvant) PTK/ZK was given at a previously established dose of 750 mg twice daily continuously with TMZ given at a dose of 150–200 mg/m^2 for 5 d every 28 d. PTK787/ZK222584 was continued as maintenance treatment until disease progression.

Radiotherapy consisting of fractionated focal irradiation at a dose of 2 Gy per fraction was given once daily 5 d per week over a period of 6 weeks, for a total dose of 60 Gy. The GTV consists of the entire enhanced visible tumour on CT or MRI prior to surgery. The CTV comprises a 2–3 cm margin for microscopic tumour extension. Radiotherapy was planned with dedicated computer tomography and three-dimensional planning systems; conformal radiotherapy was delivered with linear accelerators with nominal energy of 6 MV or more. Concomitant chemotherapy consisted of temozolomide at a daily dose of 75 mg/m^2, given 7 d per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 d. After a 4-week break, patients were then to receive up to six cycles of adjuvant temozolomide according to the standard 5-d schedule every 28 d. The daily dose was 150 mg/m^2 for the first cycle and was increased to 200 mg/m^2 beginning with the second cycle, in the absence of significant toxicity. During the radiotherapy/temozolomide

phase, patients were to receive prophylaxis against *Pneumocystis carinii jierovicii* pneumonia, with either inhaled pentamidine or oral trimethoprim–sulfamethoxazole. Antiemetic prophylaxis with metoclopramide or a 5-hydroxytryptamine 3 antagonist was recommended before the initial doses of concomitant temozolomide and was required during the adjuvant 5-d courses of temozolomide. Treatment is summarised in Fig. 1.

2.3. Patient evaluations

Within 14 d prior to the start of the treatment, each patient had a baseline evaluation consisting of medical history and physical examination, neurologic examination (including Mini-Mental State Examination), complete blood count, serum chemistries, and magnetic resonance imaging. During radiotherapy, patients were to be seen every week. Twenty-one to 28 d after the completion of radiotherapy and every 3 months thereafter, patients underwent a comprehensive evaluation, including administration of the MMSE and radiologic assessment of the tumour. During adjuvant and maintenance part, patients underwent a monthly clinical evaluation. Tumour progression was defined according to MacDonald's criteria[8] as an increase in tumour size by 25%, the appearance of new lesions, or an increased need for corticosteroids. When there was tumour progression or after two years' of follow-up, patients were treated at the investigator's discretion, and the type of second-line therapy was recorded. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (CTC), version 3.0.

2.4. Statistical considerations

A classic 3 + 3 design was selected. A minimum of 3 patients was included at each dose level. In case of the occurrence of Dose Limiting Toxicity (DLT) in 1 patient, up to 3 additional patients were enrolled. If 2 or more patients experienced DLT ($\geqslant$33%) this was considered the maximally tolerated dose, and the dose level below would be considered the recommended dosage for phase II. A minimum of 6 patients was treated at the recommended dose. DLT was defined as: an absolute neutrophil count less than 500 (grade 4) for $\geqslant$7 d, febrile neutropenia, thrombocytopenia grade 4, any grade 3–4 non-haematological toxicity except alopecia, nausea, vomiting and fever which can be rapidly controlled with appropriate measures. Only toxicity occurring during concomitant chemoradiotherapy and the subsequent 2 weeks were considered for DLT assessments. Kaplan–Meier technique was used to compute estimates for progression free and overall survival parameters and their 95% confidence intervals (CIs). In the whole cohort, overall survival was compared to EORTC glioblastoma historical dataset.[1] The Cox regression was used to assess the effect of PTK/ZK over TMZ/RT alone after adjustment for possible confounding effects (age, WHO performance status, MMSE and administration of corticosteroids).

3. Results

3.1. Patients

Between June 2005 and May 2007, a total of 20 patients were accrued in this phase I/II trial. However, due to lack of efficacy in colorectal cancer trials the sponsoring manufacturer of PTK/ZK decided to discontinue all development of this agent, and we had to close this trial prematurely in June 2007. Eighteen patients were included in the phase I part of the protocol, and 2 patients at the recommended phase II dose. Three escalating dose levels were explored with concomitant radiochemotherapy (see Table 1). Four patients were treated at 500 mg, 8 at 1000 mg (6 in the phase I, 2 in the phase II) and 7 at 1250 mg as well as 1 patient even when allocated to 1250 mg did not start treatment. Safety data are thus reported on 19 patients. Table 1 shows treatment allocation, and Table 2 patients' characteristics at baseline.

3.2. Sequence of dose levels studied and DLTs

Dose level 1 (PTK/ZK 500 mg) enrolled 4 patients. No DLT was reported. Dose level 2 (PTK/ZK 1000 mg) enrolled 6 patients.

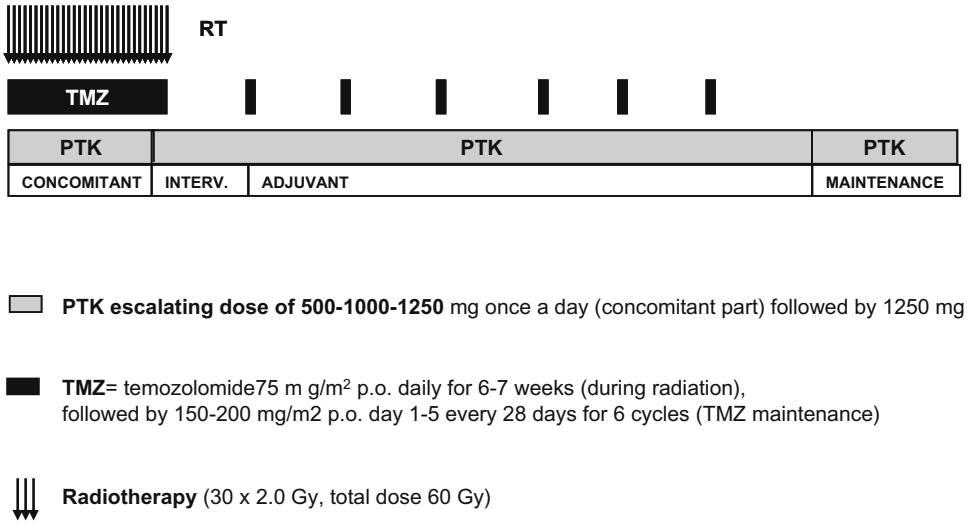
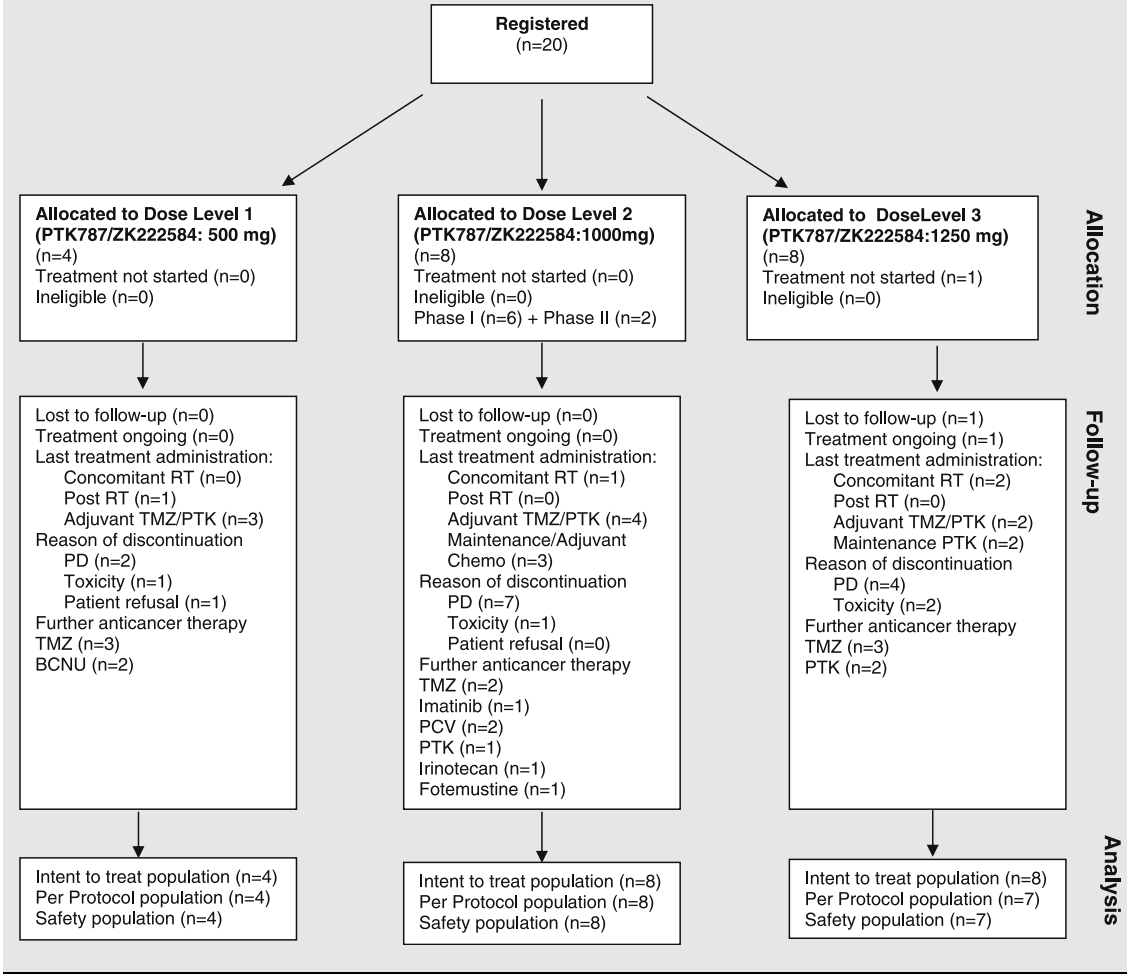


Fig. 1 – Phase I treatment schema.

Table 1 – Consort table.



One patient out of the first 3 experienced DLTs: grade 3 hyponatremia and grade 3 liver dysfunction. No additional DLT were observed in the second triplet. Dose limiting toxicity was reached at the subsequent dose level 3 (PTK/ZK 1250 mg). Eight patients were allocated to this dose, one did not start treatment, and DLTs were observed in four: grade 3 diarrhoea ($n = 1$), grade 3 ALT increase ($n = 2$), grade 4 thrombocytopenia ($n = 1$) and prolonged grade 4 neutropenia ($n = 1$). Dose level sequence is describe on Table 3. Consequently a dose of 1000 mg once daily was recommended for the phase II part of the study, and two additional patients were treated at this dose level before trial closure.

3.3. *Disposition of patients and delivery of treatment*

The addition of PTK/ZK to standard treatment did not affect the delivery of concomitant temozolomide/radiotherapy treatment. Radiotherapy was administered at the planned dose and duration in all patients. Sixteen patients completed the full course of concomitant temozolomide as planned. Three patients interrupted treatment one grade II rash, one for hepatic toxicity and one for haematological toxicity, after 25, 38, and 28 d, respectively. In one of these 3 patients adjuvant TMZ was prescribed. Median relative dose intensity for PTK/ZK during the concomitant phase was 100% in all dose levels. After radiotherapy, 15 patients (79%) started maintenance part with a median of 5 cycles (range, 1–6) being administered; 6 (40%) patients completed all the 6 cycles of planned chemotherapy. The main reason for not completing adjuvant therapy was disease progression (67%). Only 2 patients discontinued adjuvant temozolomide because of toxic effects (grade 3 rash and acute hepatitis).

A total of six patients started maintenance part of treatment (3 in dose level 2, and 3 in dose level 3). None of them interrupted treatment for toxicity. Table 4 summarises the details of treatment.

3.4. *Safety and tolerability*

Nineteen patients were assessable for toxicity, and all experienced at least one drug-related adverse event (AEs) during the study. We analysed AEs during whole treatment period and are reported in Table 5.

Treatment was discontinued due to toxicity in 2 patients (10%) after the concomitant part (1 patient for grade 3 hepatic toxicity, and 1 patient for grade 4 thrombocytopenia), and in 2

Table 2 – Patient characteristics (*n* = 20).

Characteristic	Patients	
	No.	%
Age, years		
Median	53.5	
Range	33–67	
Sex		
Male	12	60
Female	8	40
Performance status		
0	10	50
1	10	50
MMSE		
27–30	19	95
<27	1	5
Histological review		
GBM	16	80
Missing	4	20
Antiepileptic treatment		
Yes, EIADS	4	20
Yes Non-EIADS	15	75
No	1	5
Corticosteroids		
Yes	15	75
No	5	25

patients (14%) during adjuvant part (1 patient for acute hepatitis, and 1 patient for grade 3 rash). Rash, diarrhoea and liver dysfunction grade 3 were the main causes of PTK/ZK dose reduction or interruption (see Table 5).

3.5. *Efficacy*

After a median follow-up for surviving patients of 24 months, 3 out of 4 patients at dose level 1 (500 mg) had disease progression and died, 1 patient was still alive and progression free. All the 8 patients at dose level 2 (1000 mg) presented disease progression, and 7 of them died. Among 7 patients treated at dose level 3 (1250 mg), 4 had disease progression and 5 patients were alive. Overall, 15 (79%) patients had disease progression, and 7 (37%) were alive at time of the analysis of data. The median PFS was 6.8 months (95% CI 5.7–30.1), the PFS at 6 and 12 months were 63.2% (95% CI 37.9–80.4), and 31.6% (95% CI 12.9–52.2), respectively. Median, 1 and 2-year survival were 17.3 months (95% CI 11.7–32.4), and 63.2% (95% CI 37.9–80.4) and 33.5 (95% CI 13.4–55.2), respectively. All deaths were due to disease progression.

4. Discussion

PTK/ZK in combination with temozolomide concomitant and adjuvant to radiotherapy is safe and well tolerated. MTD has been reached at 1250 mg and the recommended dose of PTK/ZK in combination with radiotherapy and temozolomide is 1000 mg once a day. The observed dose limiting toxicities were: grade 3 hyponatremia, transaminase elevation, diarrhoea, and prolonged grade 4 neutropenia. Haematological toxicity was manageable, grade 3–4 adverse events being reported in 10% of treated patients. The most common grade 3–4 non-haematological toxicity during treatment was transaminase elevation in 37% of patients. This adverse event seems to be related to the combination of PTK/ZK with temozolomide, as it was not previously been observed in our prior large-scale experience with this regimen without PTK/ZK.[1] Notably one patient developed histologically confirmed grade 3 acute hepatitis during adjuvant treatment. This patient at baseline showed a non-active chronic hepatitis B, and during adjuvant treatment developed an acute infection due to virus reactivation. However, virus reactivation is likely due to TMZ immunosuppression rather than PTK/ZK induced toxicity. Although toxicity was modest, treatment interruptions due to toxicity after concomitant (10%) and adjuvant treatment (14%) were higher than that reported after standard treatment (5–8%).[1]

Antiangiogenic drugs (i.e. bevacizumab, cediranib) given as single agent or in combination with chemotherapy showed encouraging results in recurrent in malignant gliomas, with radiographic response rates up to 50% and median PFS of 24 weeks.[9] These promising data from phase II studies on recurrent tumours suggest that up-front treatment of newly diagnosed GBM with antiangiogenic drugs might be more

Table 3 – Dose levels' description during TMZ/RT.

DL	mg/d	*n* pts	Number of pts with DLT	DLT description
1	500	4	No DLT	No DLT
2	1000	8[a]	1 out of 6	G3 hyponatremia G3 liver dysfunction
3	1250	7	4 out of 7	G3 AST G3 ALT G3 AST G4 leucopenia G4thrombocytopenia G4 neutropenia[b] G3 diarrhoea

a *Note*: 2 pts treated in phase II.
b Of more than 7 d.

Table 4 – Disposition of Patients and Intensity of Treatment.

	DL1 (*n* = 4)	DL2 (*n* = 8)	DL3 (*n* = 7)
Radiotherapy			
Dose Gy			
Median	60.0	60.0	60.0
Range	59.8–60.0	58.0–60.0	60.0–60.0
Early discontinuation of radiotherapy – no. (%)	1 (25.0)	1 (12.5)	0 (0.0)
Concomitant temozolomide			
Relative dose intensity (%)			
Median (range)	99.1	99.3	99.0
Range	95.4–103.6	97.0–100.8	47.7–101.9
Early discontinuation of temozolomide – no. (%)	0 (0.0)	1 (12.5)	2 (28.6)
Concomitant PTK787/ZK222584			
Relative dose intensity (%)			
Median	100.0	100.0	100.0
Range	95.6–100.0	92.2–100.0	66.4–100.0
Early discontinuation of PTK787/ZK222584 — no. (%)	0 (0.0)	2 (25.0)	4 (57.1)
4 weeks PTK787/ZK222584	DL1 (*n* = 4)	DL2 (*n* = 8)	DL3 (*n* = 7)
Relative dose intensity (%)			
Median	74.2	83.3	92.6
Range	46.0–83.3	0.0–100.0	0.0–100.0
Early discontinuation of PTK787/ZK222584 – no. (%)	0	0	0
Adjuvant-therapy period	DL1 (*n* = 3)	DL2 (*n* = 7)	DL3 (*n* = 5)
Adjuvant not started – no. (%)	1 (25)	1 (12.5)	2 (28.6)
Cycles of therapy			
Median	2	5	6
Range	1–5	1–6	1–6
Adjuvant Temozolomide	DL1 (*n* = 3)	DL2 (*n* = 7)	DL3 (*n* = 5)
Relative dose intensity (%)			
Median	99.8	99.1	99.6
Range	85.7–100.0	85.8–100.9	92.2–102.9
Adjuvant PTK787/ZK222584	DL1 (*n* = 3)	DL2 (*n* = 7)	DL3 (*n* = 5)
Relative dose intensity (%)			
Median	83.3	86.4	83.1
Range	66.7–83.3	82.8–100.0	69.1–100.0
Maintenance PTK787/ZK222584	DL1 (*n* = 0)	DL2 (*n* = 3)	DL3 (*n* = 3)
Cycles of PTK787/ZK222584			
Median	0	5	12
Range	0	4–21	3–17
Relative dose intensity (%)			
Median	0	86.8	100.0
Range	0	76.3–100.0	97.1–100.0
Treatment interrupted/stopped	0	1 (33.3)	1 (33.3)

Note: One patient did not start allocate treatment.

advantageous than at recurrence. An additional advantage of using antiangiogenic treatment in association with radiochemotherapy is that they should stabilise the blood–brain barrier (BBB), decreasing peritumoural oedema and intratumoural pressure. However, it has been postulated that the penetration of chemotherapeutic agents might be compromised if combined with agents that normalise the blood–brain barrier, and some animal experiments have failed to show that the outcome is improved by combining radiotherapy with antiangiogenic drugs.[5]

Unlike bevacizumab,[9–11] PTK/ZK, appears not to induce thromboembolic or haemorrhagic events. In our study, in which no concomitant treatment with warfarine or other coumarine derivatives was permitted (prophylactic administration of low-molecular heparins was allowed), no patients developed grade 3–4 haemorrhagic events during treatment, and only 1 patient developed a grade 2 deep venous thrombosis during adjuvant treatment. However, due to the small numbers of treated patients a low incidence of such toxicity cannot be excluded.

In our phase I study the addition of PTK/ZK to standard chemoradiotherapy was feasible and safe, with no evident increase in toxicity compared to prior experience with chemoradiotherapy alone. Successful antiangiogenic therapy requires continuous drug exposure over long periods of time, ideally with an oral agent.

Our phase II study has been prematurely closed due to drug company's management decision independent of the

Table 5 – Grade 3–4 toxicity per patient.

	DL1 ($n = 4$) n	DL2 ($n = 8$) n	DL3 ($n = 7$) n	Total ($n = 19$) n (%)
Neutropenia	1	0	2	3 (16)
Thrombocytopenia	0	0	1	1 (5)
Anaemia	0	0	1	2 (10)
SGPT	1	3	3	7 (37)
SGOT	1	0	1	2 (10)
Infection	1	2	0	3 (16)
Hypertension	0	0	1	1 (5)
Abdominal pain	0	1	1	2 (10)
Hypocalcemia	0	1	0	1 (5)
Hyponatremia	0	1	0	1 (5)
Rash/Dermatitis	0	1	1	2 (10)
Fatigue	0	2	1	3 (16)
Diarrhoea	0	0	1	1 (5)
Viral hepatitis	1	0	0	1 (5)

current experience in glioma. In view of the promising results obtained by antiangiogenic approaches in high grade gliomas, and of the safety profile demonstrated by PTK/ZK in addition to temozolomide concomitant and adjuvant to radiotherapy, further randomised studies assessing the efficacy of antiangiogenic agents in combination with temozolomide concomitant and adjuvant to radiotherapy are warranted.

Conflict of interest statement

Dr. Mirimanoff declares an Advisory Role and Honoraria with Schering Plough.

All other authors have no conflict of interest to declare.

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