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[Eur J Cancer](#). 2009 Nov 27. [Epub ahead of print]

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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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 500mg with subsequent escalations to 1000 and 1250mg/d. Adjuvant or maintenance PTK after the end of radiochemotherapy was given at a previously established dose of 750mg twice daily continuously with TMZ at the standard adjuvant dose. **RESULTS:** Twenty patients were enrolled. Dose-limiting toxicities at a once daily dose of 1250mg 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 1000mg once a day. This treatment is safe and well tolerated. **CONCLUSION:** In our phase I study once daily administration of up to 1000mg 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.

PMID: 19945857 [PubMed - as supplied by publisher]

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