

Activity of temozolomide in patients with advanced chemorefractory colorectal cancer and *MGMT* promoter methylation

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Background: No evidence-based treatment options are available for patients with advanced colorectal cancer (CRC) progressing after standard therapies. *MGMT* is involved in repair of DNA damage and *MGMT* promoter methylation may predict benefit from alkylating agents such as temozolomide. The aim of our study was to evaluate the activity of temozolomide in terms of response rate in patients with metastatic CRC and *MGMT* methylation, after failure of approved treatments.

Patients and methods: Patients were enrolled in a monocentre, open-label, phase II study and treated with temozolomide at a dose of 150 mg/m²/day for 5 consecutive days in 4-weekly cycles. The treatment was continued for at least six cycles or until progressive disease.

Results: Thirty-two patients were enrolled from August 2012 to July 2013. Treatment was well tolerated with one grade 4 thrombocytopenia and no other grade ≥ 3 toxicities. No complete response occurred. The objective response rate was 12%, reaching the pre-specified level for promising activity. Median progression-free survival and overall survival were 1.8 and 8.4 months, respectively. Patients with KRAS, BRAF and NRAS wild-type CRC showed significantly higher response when compared with those with any RAS or BRAF mutation (44% versus 0%; $P = 0.004$). TP53 status had no influence on the primary end point.

Conclusions: Temozolomide is tolerable and active in heavily pre-treated patients with advanced CRC and *MGMT* promoter methylation. Further studies in biomolecularly enriched populations or in a randomized setting are necessary to demonstrate the efficacy of temozolomide after failure of standard treatments.