EPIGENETIC SILENCING OF THE OF THE *O-6-METHYLGUANINE-DNA METHYLTRANSFERASE* GENE IN GLIOBLASTOMA IS REQUIRED FOR RESPONSIVENESS TO THE ALKYLATING AGENT TEMOZOLOMIDE; TRANSLATIONAL RESEARCH EFFORT TO A RANDOMIZED, PROSPECTIVE CLINICAL TRIAL

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Epigenetic silencing of the *O-6-methylguanine-DNA methyltransferase* (*MGMT*) gene by promoter methylation has been recognized as an important factor to predict good outcome in glioblastoma patients treated with alkylating agents. *MGMT* codes for an excision repair enzyme removing alkyl-groups from the O6-position of guanine, one of the targets of alkylating agents. To take it one step further and to establish the methylation status of the *MGMT* promoter as a predictive factor for TMZ treatment, rather than solely a prognostic marker we needed to demonstrate the absence of a positive prognostic effect in patients with a methylated *MGMT* promoter not receiving alkylating agent chemotherapy.

Here we tested the relationship of *MGMT* silencing with outcome in patients randomized either to initial therapy with the alkylating agent TMZ and radiotherapy (RT) or RT only (EORTC 26981/22981 & NCIC CE.3). The *MGMT* promoter was methylated in glioblastoma of 45% of 206 patients. In this group the 2-year overall survival rate was 46% when randomized to TMZ/RT compared to only 23% in the RT-arm (p=0.007,log-rank test). Patients with an unmethylated *MGMT* show a much smaller and statistically not significant difference between treatment arms. (p=0.067, log-rank test).

Here we establish the methylation status of the *MGMT* promoter as a specific predictive factor for treatment response to TMZ chemotherapy. For the first time patients unlikely to respond can be identified and alternative treatments be proposed. The *MGMT* methylation status determination is an important towards molecular diagnostics and tailored and individualized treatments.