EG-11. DYSREGULATION OF MGMT IN GLIOBLASTOMA: FRIEND OR FOE?
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Glioblastoma (GBM) is the most common and lethal form of brain cancer (median survival <15 months). The DNA alkylating agent, temozolomide, is used as the standard chemotherapeutic agent, resulting in mispairing of guanine with thymidine that leads to cellular arrest. However, in GBM patients the O6-methylguanine-DNA methyltransferase (MGMT) protein protects DNA from damage induced by temozolomide. Nevertheless, loss of MGMT expression is a frequent event in human malignancies and typically the result of MGMT promoter methylation. MGMT methylation has been strongly associated with the T-allele of the rs16906252 SNP (C/T) in colorectal carcinoma, pleural mesothelioma, and lung cancers. We therefore examined the T-allele and MGMT methylation in temozolomide-treated GBM patients. In 255 temozolomide-treated GBM patients, we found that the T-allele was significantly more frequent in patients with a methylated MGMT promoter. The unadjusted hazard ratio for death in carriers of the T-allele compared to wild-type, irrespective of methylation status, was 0.39 (95% CI: 0.21-0.73; p = 0.003), indicating a 61% relative reduction in the risk for death of T-allele carriers. Surprisingly, GBM patients harboring the T-allele in the absence of MGMT methylation showed a survival benefit comparable to those with MGMT methylation (median survival: 15.5 months) and significantly better than the median survival of wild-type, unmethylated patients (median survival: 10.3 months). This suggests that the T-allele may reduce MGMT activity by mechanisms independent of methylation. Genotyping of 451 healthy controls indicated the frequency of carriage of the T-allele was 13% (MAF 0.065). In contrast, carriage of the T-allele in 160 GBM patients was 17%. Significantly, elevated risks were associated with carriage of the T-allele and development of GBM (odds ratio of 2.62 [95% CI: 1.7-4.2]). We report that the T-allele (rs16906252) has predictive (response to temozolomide) and prognostic value (MGMT methylation and longer survival), but conversely may be a predisposing factor for the development of GBM.
NOW ENROLLING
Phase 2b study of IGV-001 in patients with newly diagnosed glioblastoma (NCT04485949)

**OBJECTIVES**
- PRIMARY OBJECTIVE: Progression-free survival
- SECONDARY OBJECTIVE: Overall survival
- SAFETY OBJECTIVE: Safety and tolerability

**Key Inclusion Criteria**
Patients who take part in the trial* must:
- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

**Key Exclusion Criteria**
Patients are not allowed to participate* in the trial if they have:
- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn's disease)
- Heart disease or history of heart issues

*Additional criteria apply. Please refer to protocol 14379-201 for full inclusion and exclusion criteria. †Patients can participate if they had some skin cancers, superficial bladder cancer (cancer that was only on the surface of the lining of the bladder), or carcinoma in situ (cancer that had not spread) of the cervix or breast that had been cured.

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IGF-1R, insulin-like growth factor 1 receptor; KPS, Karnofsky Performance Scale; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

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