Glioblastoma (GBM) is an incurable disease, which challenges innovation for significant therapeutic progress. TG6002 is a recombinant oncolytic vaccinia virus deleted in two genes (Thymidine Kinase and Ribonucleotide Reductase) and expressing the suicide gene FCU1 which catalyzes the direct conversion of the nontoxic 5-fluorocytosine (5-FC) into the toxic metabolites 5-fluorouracil (5-FU) and 5-fluorouridine monophosphate (5-FUMP). TG6002 demonstrated strong tumor selectivity and retained full capacity to replicate and lyse human cancer cell lines. The expression of the FCU1 gene by the recombinant virus provided a targeted chemotherapy within the tumor, with a higher level of efficiency and selectivity than traditional treatment with 5-FU.

Prior to initiating clinical development, the anti-tumor activity of the TG6002/5-FC combination was investigated, using U-87MG human GBM cell line and glioblastoma stem cells (GSC). The growth of U-87MG subcutaneous tumors implanted in nude mice was inhibited by a single systemic administration of TG6002. In an orthotopic brain tumor model, mice survived significantly longer when treated intravenously by TG6002 alone, and oral 5-FU added a significant survival benefit. GSC retrieved from patients are much less sensitive than U-87MG cells to anti-cancer agents. However, when exposed in vitro to TG6002, evidence of virus replication and cell killing was found. In addition, TG6002 yielded a synergistic GSC killing effect when combined with temozolomide in this model, suggesting a potential benefit of this combination in the clinic.

A dose-escalation Phase I safety trial of intravenous TG6002 delivery in combination with 5-FC was initiated in patients with recurrent glioblastoma (NCT03294486).

**HUMAN GliOBLASTOMA CELL LINES: IN VITRO**

**HUMAN GliOBLASTOMA CELL LINES: SUBCUTANEOUS MODEL**

**HUMAN GliOBLASTOMA CELL LINES: ORTHOTOPIC MODEL**

**CONCLUSION**

In human glioblastoma tumor models, after intravenous injection, TG6002 demonstrated specific replication and high efficacy. TG6002 showed a potent antitumor activity due to its strong oncolytic activity. Treatment with 5-FC further provided an enhanced anti-tumor activity in orthotopic models. TG6002 also demonstrated efficient activity in several GSC which are known to be resistant to standard radio and chemotherapies and may be the source of cancer recurrence. Moreover, the combination of TMZ/TG6002 displayed a synergistic killing effect suggesting a potential benefit of this combination in the clinic.

Following these promising preclinical results, a dose-escalation Phase I safety trial of intravenous TG6002 delivery in combination with 5-FC was initiated in patients with recurrent glioblastoma (NCT03294486).