Background Glioblastoma multiforme (GBM) is an incurable glial tumor affecting the central nervous system. The reported median survival and the percentage of patient surviving up to 2-years in the unfavorable patients' subgroup with unmethylated (u)MGMT promoter is 12.7 months and less than then 15% (Stupp et al., 2009), respectively. Despite immunotherapies being able to slow or eradicate numerous tumors, even those metastasized to the brain, none so far have extended survival in GBM.

Methods We have developed a personalized hematopoietic stem cell-based immunotherapy platform delivering immunotherapeutic payloads into the TME through a subset of tumor infiltrating macrophages. Specifically, Temferon has been designed to deliver IFN-α2 within the TME by Tie-2 expressing macrophages (TEMs). Temferon is currently under testing in an open-label, Phase 1/2a dose-escalation study (NCT03866109) evaluating its safety, and biological activity in up to 27 newly diagnosed GBM patients with uMGMT. Temferon is administered by ASCT after the RTx treatment without the concurrent administration of Temozolomide, whose survival benefit is known to be marginal in the uMGMT population.

Results As of June 2023, 4 incremental doses of Temferon (0.5–3.0 x10⁶ cells/kg) have been tested across 21 patients (median age at enrolment 57) assigned to seven cohorts. Median Overall Survival (OS)) after 1st surgery is 15 months (5–40 months). The haematological recovery occurred in all the patients irrespective of dose administered. The percentage of transduced cells found in the BM, reached for the highest dose tested up to the 50% at 1 month and persisted at detectable level in the long-term. Very low median concentrations of IFNα were detected in the plasma, indicating tight regulation of vector expression. Notably, as predicted by TEMs biological behaviour, in the CSF the concentration of IFNa increased concomitantly to evidence of disease progression suggesting increase tumor recruitment of TEMs and subsequent release of IFNa . The 57% of the treated patients underwent a 2nd line treatment (either pharmacological or surgical) with an interim survival rate at 2-years of 28% (5 of 18 patients; 3 patients excluded as follow-up is below 12 months), which is higher than that reported in literature (15%). One out of the surviving patients was enrolled in a long-term follow-up study and survived up to 3 years after surgery without any 2nd-line therapy added for 2 years.

Conclusions These data provide initial evidence on Temferon potential to counteract disease progression and improve the survival of uMGMT GBM patients.

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