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A PHASE I-IIA STUDY OF GENETICALLY MODIFIED TIE-2 EXPRESSING MONOCYTES IN PATIENTS WITH GLIOBLASTOMA MULTIFORME (TEM-GBM STUDY)

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Background: Genetically modified cell-based therapies are relevant in immunooncology due to their potential for tumor specificity and potential durability. We developed a cell-based treatment, Temferon, relying on ex-vivo transduction of autologous hematopietic stem and progenitors cells (HSPCs) to express therapeutic payloads within the tumor microenvironment. Temferon targets IFNa to Tie-2 expressing macrophages (TEMs).

Aims: The aim of TEM-GBM study is to evaluate the safety and the efficacy of Temferon in up to 21 newly diagnosed patients with glioblastoma and unmethylated MGMT promoter.

Methods: TEM-GBM is an open-label, Phase I/IIa dose-escalation study. Autologous HSPCs are transduced *ex-vivo* with a lentiviral vector encoding for IFN-α. The transgene expression is confined to TEMs due to the Tie2 promoter and the posttranscriptional regulation by miRNA-126.

Results: As of January 17 2021, 15 patients have been enrolled; 9 received Temferon (D+0) with follow-up of 61 – 559 days. There was rapid engraftment and hematological recovery after the conditioning regimen. Median neutrophil and platelet engraftment occurred at D+13 and D+12, respectively. Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA of peripheral blood and bone marrow cells, were found within 14 days post treatment and persisted subsequently, albeit at lower levels (up to 18 months). We also detected very low concentrations of IFNa in the plasma (median 5pg/ml at D+30; baseline < LLOQ) and in the cerebrospinal fluid, suggesting tight regulation of transgene expression. Three deaths occurred: two at D+343 and +402 after Temferon administration due to disease progression, and one at D+60 due to complications following the conditioning regimen. Seven patients had progressive disease (PD; range D+27-239) as expected for this tumor type. SAEs include infections, venous thromboembolism, brain abscess, hemiparesis, GGT elevation and poor performance status compatible with autologous stem cell transplantation, concomitant medications and PD. Four patients underwent second surgery. These recurrent tumors had gene-marked cells present and increased expression of IFN-responsive gene signatures compared to diagnosis, indicative of local IFNa release by TEMs. In one patient a stable lesion (as defined by MRI) had a higher proportion of T cells and TEMs within the myeloid infiltrate and an increased IFN-response signature than in a progressing lesion. The T-cell immune repertoire changed with evidence for expansion of tumor-associated clones. Tumor microenvironment characterization by scRNA and TCR sequencing is ongoing.

Summary/Conclusion: Our interim results show that Temferon is well tolerated by patients, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon potential to modulate the TME of GBM patients, as predicted by preclinical studies.

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