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Treatment of advanced gastrointestinal cancer in a clinical phase I/II trial with genetically modified mesenchymal stem cells: A Phase-I clinical study

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Introduction: Targeting therapy to cancer and other diseases with high medical need has been a long held goal and a challenge. A large body of published literature, however, points to the unique ability of mesenchymal stem cells (MSCs) to actively home to tumors and areas of inflammation and tissue damage. Here, we describe the development of genetically modified MSCs that combine the inherent ability to target tumors with the expression of the desired therapeutic trans-gene *in situ*.

Materials & Methods: A Phase I/II clinical trial (TREAT-ME 1) was designed and commenced based on *in vivo* efficacy data and proof of concept previously described in mice. In the Phase I part of the trial (completed), six patients were treated, suffering from advanced-stage gastrointestinal adenocarcinomas (three colorectal, two pancreatic, and one cholangiocellular carcinoma). The treatment schedule was an administration of either a low (3 patients; 0.5 million cells/kg body weight/weekly infusion) or a high (3 patients; 1 million cells/kg body weight/weekly infusions) dose per week, for three weeks, each followed by ganciclovir administration on the 3rd, 4th and 5th day. All protocols were approved by a Data Safety Monitoring Board (DSMB), a local Ethics Committee (EC) and the Paul-Ehrlich Institute (PEI).

Results: The infusion of the genetically modified MSC and the treatment was safe and tolerable in all patients. No related Serious Adverse Events (SAEs) or other Adverse Events with CTC-AE Grade 3-5 toxicity were recorded. Close patient monitoring by laboratory parameters, cardiac monitoring and vital signs revealed no signs for clinically significant negative changes and trends. Preliminary results also indicate that elevated liver enzymes and cholestasis parameters due to the underlying liver involvement (G-GT, aP, Bilirubin, GPT, GOT) declined significantly in chronological correlation to the therapy (MSC+GCV). This effect was not sustained after end of treatment and might require repeated doses. According to RECIST (1.1) 4/6 patients showed stable disease at three months follow-up, 2/6 progressive disease. 1/6 was in sustained SD (>5 months). 2/6 patients had stable clinical condition.

Discussion: This is the first reported clinical trial with genetically modified MSCs and the first report that MSCs have been used in oncology. The data support the hypothesis that genetically modified MSCs are a viable, safe and promising therapeutic modality and are consistent with what was previously observed in mice, where recruitment of cells to the tumors, transgene expression and a significant decrease in tumor volume were seen. Based on the positive data and relevant regulatory approvals, the clinical trial has now progressed to the Phase II part.

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