CXCL12 inhibition in MGMT unmethylated glioblastoma – results of an early proof-of-concept assessment in the multicentric phase I/II GLORIA trial (NCT04121455).

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Background: Preclinical studies showed that CXCL12-mediated influx of highlyangiogenic monocytes/macrophages is a key driver of tumor re-vascularization andre-growth after radiotherapy (RT) of glioblastoma (GBM). We report findings from aphase I/II proof-of concept (PoC) study on CXCL12 inhibition during and after RT ofGBM.

Methods: Patients ≥18years with incompletely or unresected GBM without MGMTpromoter hypermethylation and ECOG≤2 were eligible to participate. Patientsreceived continuous (24/7) i.v. infusions of 200mg/week (n=3), 400mg/week (n=3) or600mg/week (n=3) of the CXCL12 inhibitor olaptesed pegol (OLA) for 26 weeksduring and after normo- or hypofractionated RT (60Gy/40.05Gy). The primaryendpoint was safety as per the incidence of treatment-related adverse events. Thestudy was accompanied by PoC-research including multiparametric MRI biomarkers (relative cerebral blood volume, rCBV; fractional tumor burden with high perfusion, FTBhigh; apparent diffusion coefficient, ADC) and of multiplexed immunofluorescenceimaging (CODEX®) of reference and patient samples. Initial results of theseanalyses are reported for the first six patients enrolled.

Results: Five of six (83%) patients assessed with advanced MRI showed responseunder OLA in rCBV/FTBhighand ADC. Maximum reduction in perfusion (rCBV) frombaseline was 55%, maximum reduction of FTBhigh was 55% and maximum increasein ADC was 77%. Furthermore, five of six (83%) patients analyzed showed reductionof enhancing tissue volumes in at least one scan under OLA therapy. In both onepatient and two reference samples CXCL12 co-localized with endothelial cells of themicrovascular proliferation zone. In a paired sample (before/during OLA) of onepatient, endothelial cells stained positive for CXCL12 before but not during treatmentand almost all GBM cells were negative in Ki67 staining in the sample obtainedunder OLA therapy.

Conclusions: Advanced MRI and multiplexed immunofluorescence suggest efficacyof combined radiotherapy and CXCL12 inhibition in unmethylated GBM.

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