Radiotherapy and Olaptesed pegol (NOX-A12) in partially resected or biopsy-only MGMT-unmethylated glioblastoma – interim data from the German multicenter phase 1/2 GLORIA trial.

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Background: Pre-clinical studies consistently demonstrate that inhibition of the CXCL12/CXCR4/CXCR7 axis abrogates recruitment of pro-vasculogenic bone marrow-derived cells after radiotherapy (RT) of glioblastoma (GBM) and promotes T cell exclusion from the tumor microenvironment (TME). The German multicenter phase 1/2 trial GLORIA (NCT04121455) assesses safety of RT plus escalating dose levels (DL) of the CXCL12-neutralizing RNA-Spiegelmer Olaptesed pegol (OLA; NOX-A12) in patients with chemotherapy-resistant GBM.

Methods: Until now, GLORIA enrolled 10 patients newly diagnosed with incompletely resected (n = 8) or biopsied (n = 2) GBM with ECOG≤2, age ≥18 and without MGMT promoter hypermethylation. All patients receive standard RT (60 Gy in 30 fractions or 40.05 Gy in 15 fractions) and continuous (24/7) i.v. infusions of either 200 mg (DL1; n = 3), 400 mg (DL2; n = 3) or 600 mg (DL3; n = 4) per week of OLA for 26 weeks. The primary endpoint (EP) is safety as per incidence of treatment-related adverse events (AE). Secondary EPs include radiographic response as per mRANO criteria, dynamic susceptibility contrast perfusion (DSC) and the fraction of highly-perfused tumor (FTB^{high}) as well as the apparent diffusion coefficient (ADC). Target lesions (TL) and non-target lesions (NTL, i.e. in-field satellite lesions) are analyzed separately. Tumor tissue is assessed by high-plex immunofluorescence imaging (co-detection by indexing; CODEX). Matched reference cohorts serve as controls for MRI (n = 14) and CODEX (n = 8) data.

Results: Combination of RT and OLA was well-tolerated and safe. Of all G≥2 AEs (n = 77), 3 (4%) were deemed to be solely OLA-related, including 1 grade 3 AE at DL3. There were no dose limiting toxicities and no treatment-related deaths. In total, eight of the nine patients (89%) with TLs at baseline showed a TL response during OLA therapy, with four (40%) reaching partial remission (PR) as per radiologic mRANO criteria (n = 2 at DL1 and n = 2 at DL3). All three patients treated at DL1 and all four of DL3 reached PR of one or more NTLs. In three cases (n = 2 at DL1; n = 1 at DL3), at least one NTL completely disappeared. Under OLA, radiographic responses of NTL were best at the highest DL (DL1 +49.5/DL2 +488.3/DL3 -59%), as was the increase in diffusion (mean ADC increase +46.4/+28.2/+56.7%) and the decrease in FTB^{high} (mean -33.5/-32.8/-47.7%). Matched pre-

/post-surgery CODEX of a confirmed pseudoprogression revealed intralesional clusters of proliferating cytotoxic T cells. Analysis of tissue from a non-responding patient showed T-cell encapsulation by M2-polarized macrophages in an immune-cell enriched TME. Additional follow-up is ongoing.

Conclusions: Interim data from the ongoing GLORIA trial demonstrates safety of RT plus OLA and suggests promising clinical efficacy of a new class of drugs targeting CXCL12 in GBM.