Abstract 6407

# Spatial remodeling of the immune tumor microenvironment after radiotherapy and CXCL12 inhibition in glioblastoma in the phase 1/2 GLORIA trial

Type: Abstract

Category: CNS tumours

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## Background

Radiotherapy (RT) causes upregulation of CXCL12, a chemokine facilitating recruitment of tumor-associated macrophage (TAM) precursors promoting neovasculogenesis and the formation of an immunosuppressive tumor microenvironment (TME). Here, we report an in-depth analysis of the immune TME (iTME) in patients of the multicentric phase 1/2 GLORIA trial (NCT04121455) which combines RT and CXCL12 inhibition with the RNA-Spiegelmer NOX-A12.

## Methods

We analyzed tumor tissue of 10 GLORIA patients with newly diagnosed, incompletely resected (n=8) or biopsied (n=2) GBM with ECOG≤2 lacking MGMT promoter methylation. All patients received standard RT and escalating dose levels of continuous (24/7) i.v. infusions of NOX-A12. Two patients underwent re-surgery, whereas one was diagnosed with pseudoprogression (PsP) and one with recurrence. To characterize the iTME, we used highly multiplexed immunofluorescence (mIF) imaging. As a comparison to the GLORIA cohort, we investigated the pre/post-therapeutic iTME of reference patients receiving standard-of-care (n=7) treatment.

## Results

In all samples analyzed, CXCL12 co-localized with endothelial cells. Unlike in the reference cohort, matched pre-/post-treatment tissue analysis of the patient with PsP revealed endothelial and gliomal CXCL12 depletion following treatment with NOX-A12, confirming the mode of action of the drug. Both post-treatment GLORIA samples showed intralesional clustering of activated $CD8^+$ T cells. In the non-responder diagnosed with recurrence, a pro-tumorigenic spatial rearrangement of the iTME was observed, characterized by a presence of M2-like TAMs in the proximity of the perivascular T cell clusters, confirmed by nearest neighbor analysis. None of the reference patients showed similar alterations of the iTME.

## Conclusions

mIF of matched pre-/post-therapy tissue samples from the ongoing GLORIA trial supports the proposed modes of action of RT and NOX-A12 counteracting vasculogenesis and modulating the iTME reflected through its spatial rearrangement. This opens up the question of a targetable, compartment-specific role of CXCL12 to be further assessed.

## Clinical trial identification

NCT04121455

## Editorial acknowledgement

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