640 **COMBINATORIAL CHEMOIMMUNOTHERAPY BASED ON THE ANTIBODY-CYTOKINE FUSION PROTEIN L19TNF UNLEASHES POTENT ANTI-TUMOR IMMUNITY AGAINST TREATMENT-REFRACTORY GLIOBLASTOMA**

[1]Thomas Look, [2]Emanuele Puca, [2]Riccardo Stucchi, [2]Roberto De Luca, [2]Dario Neri, [1]Michael Weller, [2]Teresa Hemmerle*, [1]Tobias Weiss. [1]*Universitätsspital Zürich, Zürich, Switzerland*; [2]*Philogen S.p.A., Otelfingen, Switzerland*

Background Glioblastoma is a poorly immunogenic brain tumor and treatment options at recurrence after standard of care chemoradiation are very limited. Several immunotherapeutic strategies, including immune checkpoint inhibition and peptide vaccination, have failed to improve the survival of patients. Except from potentially regorafenib, no other agent has demonstrated superior activity to the alkylating chemotherapeutic lomustine. Here, we investigate a new combination treatment based on lomustine and on the tumor-targeting antibody-cytokine fusion protein L19TNF in preclinical glioma models and in patients with recurrent glioblastoma.

Methods Orthotopic immunocompetent mouse glioma models were used to study the anti-tumor activity of L19TNF in combination with (i) anti-PD1 antibody, (ii) bevacizumab, (iii) L19IL2, or (iv) lomustine. Tumor growth was monitored by MRI as well as survival. Single-cell RNA-sequencing, Flow cytometry and microscopy were used to characterize tumor-infiltrating-immune cells. MHC immunoaffinity purification and mass spectrometry were used to investigate the MHC immunopeptidome. Genetic mouse models enabled to study immune-dependent effects. Subsequently, the most efficient treatment combination, L19TNF plus lomustine, was translated to patients with recurrent glioblastoma within a phase I/II clinical trial (NCT04573192). The study has been approved by the Swiss national authority (Swissmedic reference number 2020DR1125) and the ethic committee (BASEC number 2020-02413).

Results The combination treatment based on lomustine and L19TNF cured the majority of immunocompetent orthotopic glioma-bearing mice, whereas other mono- or combination therapies had only limited anti-glioma activity. The investigation of the mechanisms of action revealed that lomustine plus L19TNF led to intratumoral necrosis, DNA damage and triggered a strong local anti-tumor immune response with increased MHC-I expression, presentation of neoepitopes and increased abundance of tumor-infiltrating lymphoid cells. In the first patients treated within a phase I/II clinical trial, the treatment was well tolerated, and durable objective tumor responses as well as disease stabilizations could be observed, even in patients with unmethylated MGMT promoter.

Conclusions The combination of L19TNF and lomustine is demonstrating promising anti-glioma activity. Additional patients are currently being recruited within a phase I/II clinical trial for patients with glioblastoma at first progression.

Trial Registration NCT04573192

Ethics Approval The study was approved by the Swiss national authority (Swissmedic reference number 2020DR1125) and the ethic committee (BASEC number 2020-02413)

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0640

J Immunother Cancer: first published as 10.1136/jitc-2022-SITC2022.0640 on 7 November 2022. Downloaded from http://jitc.bmj.com/ on February 29, 2024 by guest. Protected by copyright.