638 CHARACTERISATION OF THE IMMUNE RESPONSE TO EO2401, A NEW IMMUNOTHERAPY APPROACH AGAINST CANCER, PLUS NIVOLUMAB IN RECURRENT GLIOBLASTOMA: THE EOGBM1–18/ROSALIE STUDY

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Background EO2401 is a novel generation of cancer immunotherapies designed to activate memory T cells that recognize commensal-derived peptides and cross-react with tumor-associated antigens (TAAs). EO2401 includes synthetically-produced HLA-A2 peptides with molecular mimicry to IL13RA2, BIRC5 and FOXM1, which are commonly upregulated in glioblastoma (GB), and the CD4 helper peptide UCP2. The study (NCT04116658) was approved by all participating institution's Ethics Boards.

Methods Patients with GB at first progression following standard treatment received EO2401 with nivolumab ± bevacizumab. Blood was collected at baseline, every two weeks during the first 5 months, then every month until progression. Immune response in cryopreserved PBMCs was investigated using tetramer staining, IFNγ ELISpot and intracellular cytokine staining (ICS) *ex vivo* and after *in vitro* stimulation (IVS).

Results The efficacy of commensal-derived peptides in generating immune responses against their homologous TAAs was studied *ex vivo*. Tetramer staining showed that commensal-specific T cells were observed in 93% of tested patients (n=55), with early responses (after 1 vaccine) seen in 42% of patients evaluated at this visit (n=24). The most immunogenic peptides were EO2317 and EO2318, with 90% (maximal response: 15.4% of $CD8^+$ T cells) and 85% (maximal response: 3.7%) of responding patients, respectively. Cross-reactivity against targeted-TAA (BIRC5 for EO2317, FOXM1 for EO2318) could be detected in most tested patients (100% and 48%, respectively). These results were supported by *ex-vivo* IFNg ELISpot, where 90% of patients (n=21) showed functional T cells against the pool of commensal-derived peptides, and 56% and 22% reacted against two or three of these peptides, respectively. 76% of the patients also showed *ex vivo* responses against UCP2. Importantly, generated antigen-specific $CD8^+$ T cells (>90%) were effector memory (T_{EM} and T_{EMRA}). Additionally, expression of the late activation marker CD57 increased throughout time. However, no increase in PD-1 or LAG-3 was observed, hinting that these cells do not become exhausted. Indeed, vaccine-specific T cells were strongly expanded and produced high levels of cytokines (ICS) after IVS and long-term analyses revealed a durable response of almost one year after first vaccination.

Conclusions EO2401 in combination with nivolumab can generate fast, strong and durable immune responses in patients. Expansion of commensal-specific $CD8^+$ T cells that cross-react with TAAs is a promising approach to create broad immune responses against tumors with low neoantigen expression and poor T cell priming, such as GB.Further phenotypic analyses of antigen-specific T cells and other immune subsets are ongoing and will be correlated with clinical outcome.

Ethics Approval All subjects gave their informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the faculty of medicine of Heidelberg - Germany (Ref: AFmu-511/2019); the Ethics Committee of Saint-Antoine Hospital - France (Ile-de-France V – ref: 54319); and the Ethics Committee of the Hospital Universitario 12 de Octubre – Spain (ref: 19/396) as well as by the Institutional Review Board from the Office of human research studies of the Dana-Farber Cancer Institute – USA (iRIS ref: 326446).

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