Presentation Number #185P

Interim Analysis Of The EOGBM1-18 Study: Strong Immune Response To Therapeutic Vaccination With EO2401 Microbiome Derived Therapeutic Vaccine + Nivolumab

ID261: ESMO Immuno-Oncology Congress 2022

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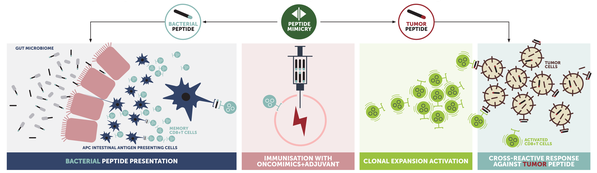
BACKGROUND

Recurrent glioblastoma (GB) has a poor prognosis and a limited number of treatment options, with an expected median survival around 8-9 months in trials with longer follow-up. EO2401, is investigated in a multicenter, Phase Ib/IIa, FIH study (EOGBM1-18 – Rosalie study) to assess the safety, tolerability, immunogenicity, and preliminary efficacy of EO2401 in patients with unequivocal evidence of progressive or first recurrent GB confirmed by MRI as defined by the Response Assessment in Neuro-Oncology (RANO) criteria.

EO2401 is designed to activate commensal specific T cells that are cross-reacting against validated tumor associated antigens (TAAs). EO2401 is composed of three high-affinity microbial-derived synthetically produced peptides mimicking CD8+ T cell HLA-A2 epitopes from the tumor associated antigens IL13Rα2, BIRC5/survivin, and FOXM1, and the helper CD4+ peptide UCP2.

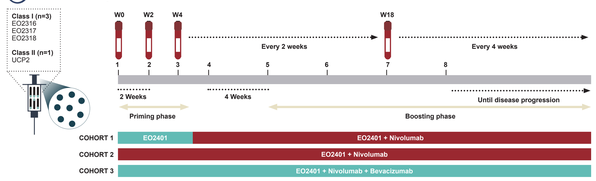
The microbiome-mimicry concept utilizing non-self-microbiome-derived peptides mimicking TAAs to expand pre-existing commensal memory T cells cross-reacting with the selected TAAs.



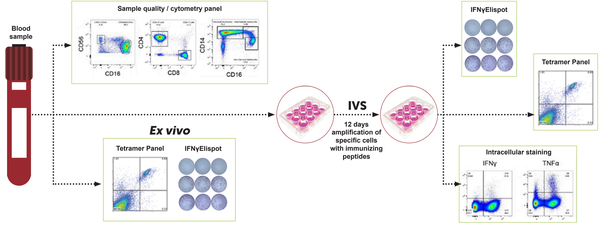
METHODS

Patients with glioblastoma at first progression after radiotherapy/temozolomide received EO2401 (300 µg/peptide, q2w x4 then q4w) with nivolumab (3 mg/kg q2w; EN), or EN with bevacizumab (10 mg/kg q2w; ENB) (NCT04116658). Nivolumab support T cell expansion and infiltration of tumor. Bevacizumab has anti-edema properties and can counteract immunosuppression by VEGF. Blood collection was performed at baseline and then every two or four weeks. Immunomonitoring investigations were performed on blood samples either *ex vivo* on cryopreserved PBMCs, or after 12 days *in vitro* stimulation (IVS), using four main readouts: Phenotyping of PBMCs, Intracellular staining of cytokines (ICS), quantification of antigen specific CD8 T cells with tetramer using flow cytometry assay and quantification of IFN-γ secretion using ELISpot assay.

Clinical trial protocol overview

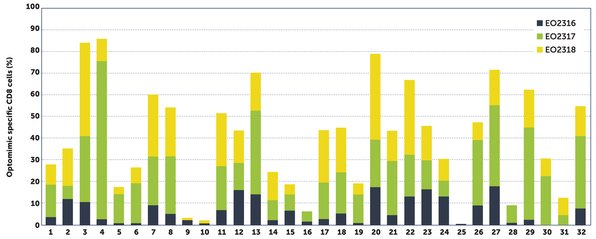


Immuno-monitoring overview



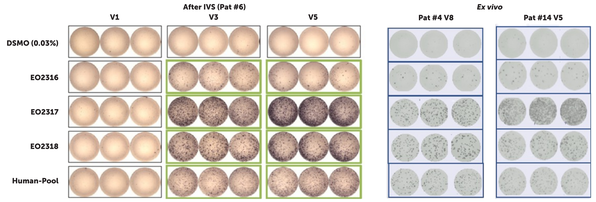
RESULTS

Immune monitoring in EO2401 treated patients demonstrates the ability of microbiome-derived peptides (Oncomimics) to induce CD8+ T cell response in 30/32 investigated patients, with extremely high frequency of Oncomimics specific T cells detected after IVS



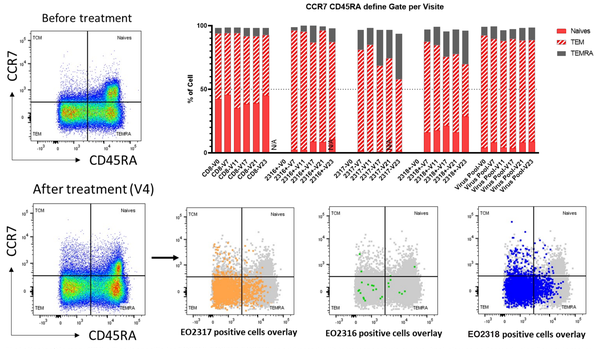
% of CD8 + T cells specific for EO2401 as assessed by tetramer analysis after IVS. Cumulative percentage of EO2316, EO2317 and EO2318 tetramer positive CD8 cells after 12 days *in vitro* stimulation with Oncomimics (best response observed for each peptide between V4 and V10). Data from all treated patients with immunomonitoring data available after Visit 3 (week 4) were shown, n=32.

Functional activity of T cells reacting against Oncomimics or cross-reacting against TAAs (Human pool) is validated using IFNγ ELISpot either after IVS or directly *Ex vivo*



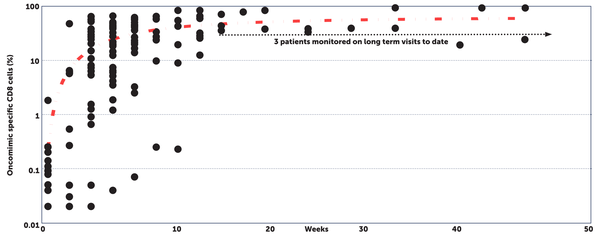
IFN-γ ELISpot assay performed directly *ex vivo*, or after 12 days *in vitro* stimulation with Oncomimics pool and restimulation with either EO2316, EO2317, EO2318 or human peptide pool (assessment of crossreactivity). Available data from representative patients. ELISpot were performed with 0.2 millions cells per well after IVS or 0.4 millions cells per well for *ex vivo*.

EO2401 efficacy is supported by the large proportion of effector memory T cells reacting against Oncomimics that could be detected soon after first administration



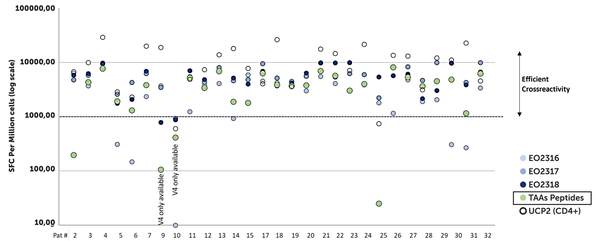
% of effector/Memory CD8 + T cells specific for EO2316, EO2317, EO2318, as addressed with tetramer analysis *ex vivo*. Analysis was performed using flow cytometry on CD8 positive cells and specific tetramers staining. Example given for one representative patient. TEM: T effector memory cells, TCM: T central memory, TEMRA: terminally differentiated effector memory T cells.

Immune response could be detected as soon as 2 weeks after first vaccination, reaching a plateau after 4 weeks in almost all patients with a long-lasting response in patients tested to date



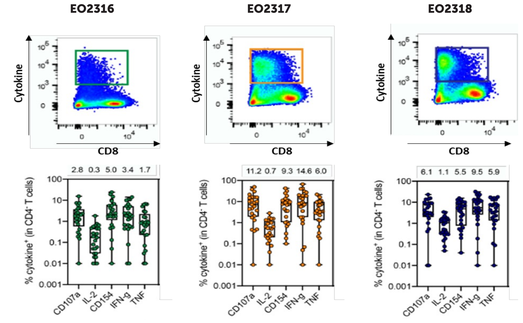
% of CD8 + T cells specific for EO2401 as assessed by tetramer analysis after IVS (Cumulative percentage of EO2316, EO2317 and EO2318 tetramer positive CD8 cells; Red curve: nonlinear curve fitting performed on whole dataset). Data from all treated patients with immunomonitoring data available after Visit 3 (week 4) were shown, n=32.

Functional crossreactive T cells reacting against Human Tumor Associated Antigens (TAAs peptides) could be detected with Elispot in 28/29 investigated patients



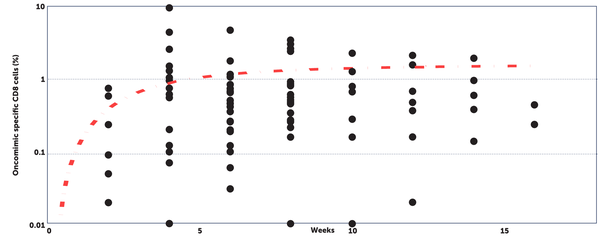
Number of positive spots forming colony (SFC) per 1.106 cells obtained with IFN-γ ELISpot assay after 12 days in vitro stimulation with bacterial peptide pool or UCP2 (helper peptide) and restimulation with either EO2316, EO2317, EO2318, human peptide pool (crossreactivity) or UCP2. Best response between V4 and V10 given for all patient with Elispot data available after Visit 3 (week 4).

Antigen-specific CD8+ T cells display high levels of activation markers



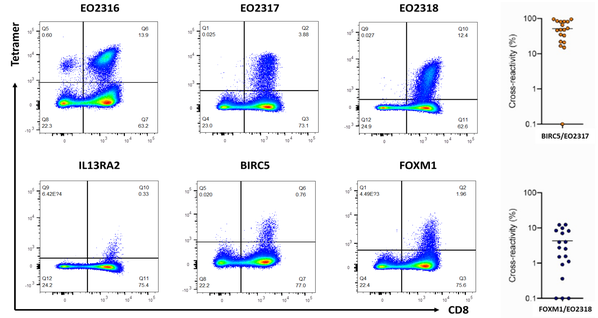
Detection of CD107a, IL-2, CD154, IFNγ and TNF after IVS in the presence of bacterial peptides. Representative dot plots for one cytokine (IFNγ) are shown after o/n stimulation with EO2316, EO2317 or EO2318. Quantification of the % of marker positive CD8+ T cells is shown

Ex vivo, significant high percentage of specific T cells reacting against oncomimics could be detected as early as two weeks after vaccination in peripheral blood of patients



% of CD8 + T cells specific for EO2401 as assessed by tetramer analysis *ex vivo* on all investigated available timepoint and patients' samples (Cumulative percentage of EO2316, EO2317 and EO2318 tetramer positive CD8 cells; Red curve: nonlinear curve fitting performed on whole dataset). Data from all treated patients with *ex vivo* immunomonitoring data available after Visit 3 (week 4) were shown, n=30.

Crossreactivity could be demonstrated using Tetramer staining with strong response for BIRC5 and FOXM1 antigens



Detection of cross-reactive T CD8 cells after vaccination. PBMCs from patients were stained with specific tetramers after 12 days *in vitro* amplification in the presence of bacterial peptides. CD8 cells specific for bacterial and human corresponding peptides were quantified using specific tetramers staining and flow cytometry. Graph shows the percentage of cross-reactivity for peptides pairs EO2317/BIRC5 and EO2318/FOXM1.

CONCLUSIONS

- EO2401 demonstrates ability to generate fast and durable immune responses in 30/32 patients treated with EO2401/ nivolumab +/- bevacizumab (ROSALIE STUDY)
- Memory specific CD8+ T cells response is detected as early as two weeks after the first vaccination and maintenance of a strong immune response could be detected for more than 10 months
- EO2401 demonstrates ability to generate large number of cross-reactive T cells against self Tumor Associated Antigens.

The best cross reactivity being observed against BIRC5 and FOXM1 in the patients

- CD8+ T cells effectors are polyfunctional with frequent expression of CD107a as well as IFN-γ and TNF-α production after stimulation
- Activation of specific T cells cross-reacting against non self commensal antigens and TAAs is thereby validated as an efficient approach to activate strong immune responses in a difficult to treat tumor.
- For clinical related data please check abstract #170P

For clinical related data please check poster presentation 170P - EO2401 microbiome derived therapeutic vaccine + nivolumab +/- bevacizumab, in neoadjuvant, adjuvant and non-surgery linked treatment of recurrent glioblastoma: phase 1-2 EOGBM1-18/ROSALIE study (ID 261)