Abstract 4395

EO2463 Peptide Immunotherapy in Patients with Newly Diagnosed Asymptomatic Follicular Lymphoma Results in Monotherapy Objective Clinical Responses Linked with Anti-Peptide Specific CD8 Memory T Cell Responses: EONHL1-20/SIDNEY

2024 ASH Annual Meeting, Dec 7-10, San Diego, California | Session 623. Mantle Cell, Follicular, Waldenstrom's, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological: Poster III | Monday, December 9, 2024; 6:00 PM - 8:00 PM

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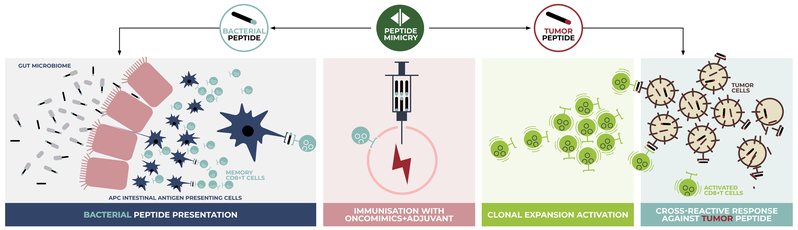
BACKGROUND

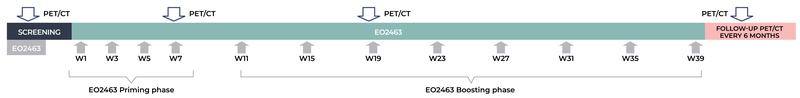
Follicular lymphoma (FL) is an indolent disease where a watch and wait strategy is standard in asymptomatic patients with a low tumor burden. Harnessing antitumor immunity through an anti-tumor immunization strategy at this stage may delay or avoid the subsequent need for more toxic and complex therapies.

EO2463 is a therapeutic vaccine designed from non-self protein sequences, derived from gut bacteria, including 4 HLA-A2 synthetically produced 9-mer CD8 cytotoxic T cell epitopes, exhibiting molecular mimicry with specific epitopes on the B cell markers CD20, CD22, CD37, and CD268 (BAFF-receptor). Additionally, EO2463 contains a CD4 helper epitope UCP2 derived from hTERT. The compound expands pre-existing memory CD8 T cells recognizing the non-self protein sequences from gut bacteria which can then cross-react with the selected B cell antigens on tumor cells.



METHODS

Cohort 2 of the ongoing study includes patients with newly diagnosed, previously untreated FL and marginal zone lymphoma (MZL), grade 1-3A, HLA-A2, and not in need of treatment. The current interim assessment incldued 15 patients of a planned 25. Main further eligibility criteria: ECOG 0-1, low tumor burden by GELF, and measurable disease



Immune responses are assayed by flow cytometry and peptide specific tetramers or by IFN-γ ELISPOT without any pre-stimulation (ex vivo), or with proceeding in vitro stimulation (IVS 12 days).

RESULTS

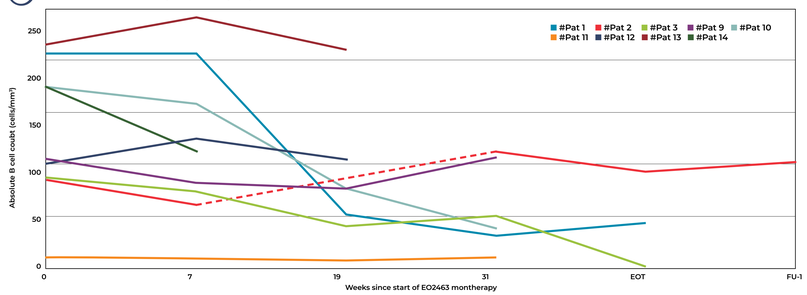
At time of data extract (2024-10-25), of the 15 patients, 9 are still ongoing, 2 completed treatment, 2 discontinued for disease progression, 1 withdrew consent, and 1 discontinued by PI decision. The median follow-up time was 30 weeks (range 19-44 weeks).

Baseline Characteristics / Cohort 2 (N=15)

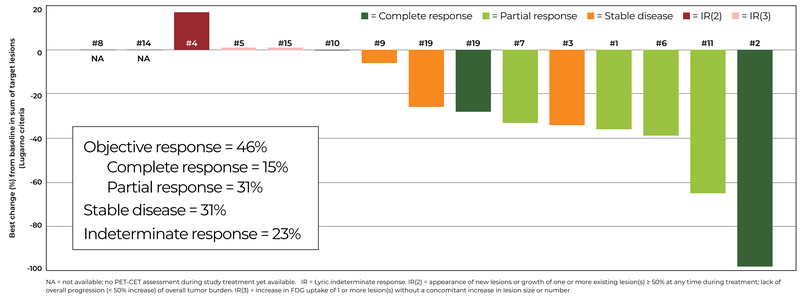
Age (years)	Median (Q1-Q3)	60.0 (50.0-66.0)
Gender [n (%)]	Male / Female	9 (60) / 6 (40)
Ethnicity [n (%)]	Not Hispanic or Latino	15 (100)
	White	15 (100)
	Other	0 (0)

ECOG Performance status [n (%)]	0 / 1	14 (93) / 1 (7)
Primary diagnosis [n (%)]	Follicular lymphona	15 (100)
Time since primary diagnosis [months]	Median (Q1-Q3)	5.5 (3.1-18.2)
Ann Arbor stage [n (%)]	I+II / III+IV	2 (13) / 13 (87)

Absolute B cell count (cells/mm3) in patients with baseline values available



Objective response according to Lugano criteria/LyRIC (n=13)



NA = not available; no PET-CET assessment during study treatment yet available. IR = Lyric indeterminate response. IR(2) = appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment; lack of overall progression (< 50% increase) of overall tumor burden. IR(3) = increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number

SAFETY

The most common related adverse events were local administration site reactions, including erythema, induration, pruritus, and pain in 13 of 15 patients; grade 1 (35 events), grade 2 (9 events). No grade ≥ 3 local administration site reactions occurred.

Other related events occurring in more than one patient were grade 1 and 2 fatigue (n=2), grade 1 headache (n=2) and grade 1 and 2 myalgia (n=2). Asthenia was the only reported grade 3 event considered related to EO2463, duration 2 days.

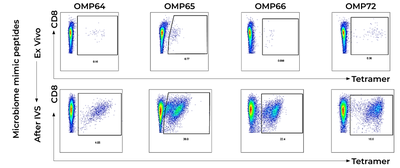
Infections were found in 7 patients with a total of 13 events: grade 1, 5 events in 2 patients, and grade 2, 8 events in 5 patients. Only grade 2 herpes zoster was considered related..

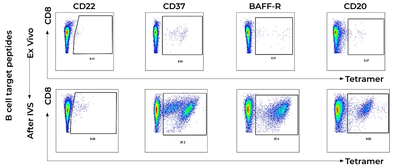
Absolute B cell counts during study treatment showed a decrease in 4 of 9 patients with baseline values available; no clear correlation to the seen low-grade infections. No clinically significant decreases in immunoglobulins (IgG, IgA, and IgM) were seen. No correlation between decrease of B cell counts and clinical outcome.

IMMUNE RESPONSE

Specific CD8 T cells detected ex vivo and after in vitro stimulation:

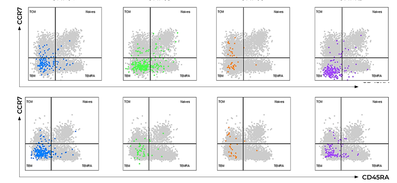
Example from patient #2 at 4 weeks.



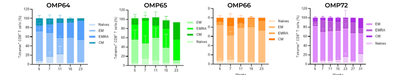


EO2463 administration leads to expansion of TEM and TEMRA specific CD8 T cells:

CD8 T cells specific for microbiome mimic peptides and corresponding B cell target peptides were quantified using specific tetramers staining and flow cytometry directly ex vivo on PBMCs from patients. Memory phenotype was determined using CCR7 and CD45RA staining of tetramer positive cells. TEMRA: effector; TCM T central memory; TEM T effector memory.



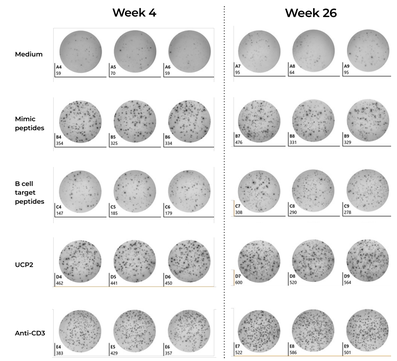
Above: Representative dot plots of memory cell staining for cells reactive to different microbiome mimic peptides. Upper row = patient #6 at week 7; lower row = patient #2 at week 5



Above: Quantification of microbiome mimic peptide specific memory T cells over time for available patients (n=6 patients for OMP64, n=5 patients for OMP65, n=7 patients for OMP66, and n=8 patients for OMP72).

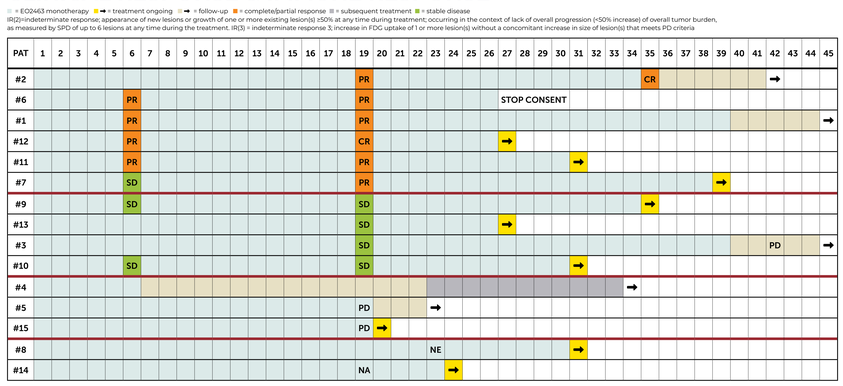
Long term function shown by specific T cell IFNγ production:

Functionality of T cells reacting against microbiome mimic peptides and B cell target peptides (cross-reactivity) demonstrated by ex vivo IFNγ ELIPOT assays, with detection of IFNγ secreting cells early after first administration (patient #1 at w4) and long-term maintenance (patient #1 at 26 weeks after start of EO2463). Representative IFN γ ELISPOT wells are shown, 0.4 million cells/well for microbiome mimic peptides, B cell target peptides, and UCP2 (CD4 helper peptide in EO2463), and 0.04 million cells/well for anti-CD3 positive control.



CLINICAL RESPONSE & IMMUNE RESPONSE

○ = EO2463 monotherapy ■➡ = treatment ongoing ○➡ = follow-up ■ = complete/partial response ■ = subsequent treatment ■ = stable disease
IR(2)=indeterminate response; appearance of new lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment. IR(3) = indeterminate response 3; increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in size of lesion(s) that meets PD criteria



Best OR	Max sum immune response w5-w15 % specific CD8 T cells IVS & tetramers*		Max sum immune response w5-w15 % specific CD8 T cells ex vivo & tetramers*	
	Mimic peptides in EO2463	B cell target peptides = cross-reactivity	Mimic peptides in EO2463	B cell target peptides = cross-reactivity
CR	84.55	72.98	1.39	1.20
PR	84.11	35.10	1.01	0.36
PR	49.01	44.76	0.85	0.50
CR	16.77	14.56	0.39	0.18
PR	0.02	0.14	0.00	0.00
PR	NOT YET AVAILABLE		NOT YET AVAILABLE	
SD	80.25	61.18	0.67	0.84
SD	41.92	16.53	1.02	0.43
SD	34.26	22.15	0.28	0.39
SD	4.84	6.62	0.62	0.67
IR(2)	0.28	0.37	0.21	0.00
IR(3)	NOT YET AVAILABLE		NOT YET AVAILABLE	
IR(3)	NOT YET AVAILABLE		NOT YET AVAILABLE	
NA	NOT YET AVAILABLE		NOT YET AVAILABLE	
NA	NOT YET AVAILABLE		NOT YET AVAILABLE	

*Green indicates positive immune response

CONCLUSIONS

- EO2463 monotherapy administered SC with an oil-in-water adjuvant has a benign safety profile including as main component mild-moderate (grade 1-2) local administration site reactions (e.g., erythema, induration), and in addition limited low grade constitutional symptoms in a minority of patients.
- B cell decreases are noted in approx. half of patients during EO2463 treatment, and no clinically significant impact on IgG/IgA/IgM-levels, or clear association with infections.
- Consistent with the preclinical hypothesis, expansion of CD8 memory T cells specific for the microbiome mimic peptides and the B cell targeted antigens (cross-reactivity) are seen in the majority of patients.
- EO2463 monotherapy objective response rate in patients fulfilling criteria for the watch-and-wait setting in this first early assessment is 46%.
- The EO2463 monotherapy safety profile and level of early efficacy seems to indicate the potential for a compound being a possible alternative to watchful waiting in patients with FL; the approach is under consideration for evaluation in a larger development context.
- Study EONHL1-20/SIDNEY also includes cohorts, not covered in this presentation, exploring EO2463 plus rituximab for 1st line FL/MZL, and EO2463 plus lenalidomide/rituximab in relapsed FL/MZL.
- For further correlative studies in relation to EO2463, see ASH session 622, publication number 1616:
  - EO2463 Peptide Immunotherapy in Patients with Indolent NHL: A Phase 1 Exploration of a Response Biomarker for EO2463 Monotherapy and EO2463 in Combination with Lenalidomide/ Rituximab

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