Abstract 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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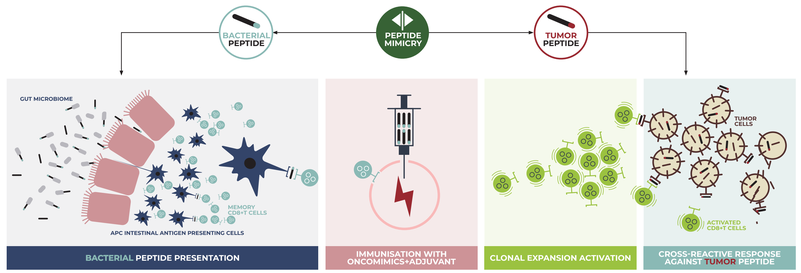
BACKGROUND

Follicular and marginal zone B cell lymphoma (FL; MZL) demonstrate an indolent course with heterogeneous outcomes and a potential for spontaneous remissions indicating immune system intervention.

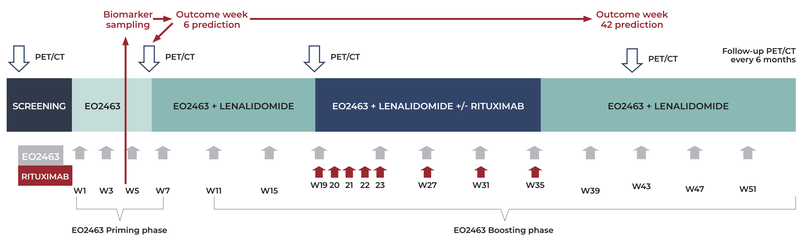
T cell-based therapeutic approaches are therefore an attractive proposition in FL and MZL. EO2463 peptide immunotherapy expands pre-existing memory CD8 T cells recognizing non-self-protein sequences from gut bacteria which cross-react with B cell antigens.

The EO2463 compound includes 4 HLA-A2 synthetically produced 9-mer peptides which exhibit molecular mimicry with protein sequences on the B cell markers CD20, CD22, CD37, and CD268 (BAFF-receptor), as well as the CD4 helper-epitope UCP2 derived from hTERT.

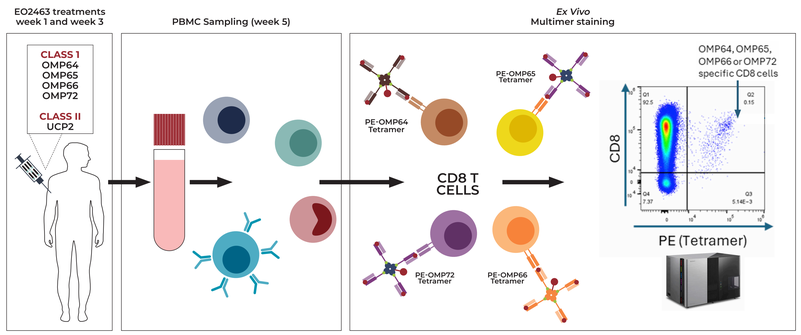


METHODS

The current report describes testing of a possible biomarker assessing the expansion of CD8 T cells targeting EO2463 mimic peptides as a predictive indicator of clinical response in the phase 1 portion of the ongoing EONHL1-20/SIDNEY trial (NCT04669171). This part of the trial (Cohort 1, safety lead-in) included patients (n=9) with relapsed (at least 1, no limit, prior treatment) FL and MZL, stage 1-3A, measurable disease, confirmed to be positive for HLA-A2.



To assess a possible biomarker, tetramers were used to specifically detect CD8 T cells recognizing the 4 mimic epitopes in the EO2463 compound (exhibiting molecular mimicry with the B cell markers CD20, CD22, CD37, and CD268). Results are presented as percentage of EO2463 specific CD8 T cells among all CD8 T cells in the peripheral blood of the patient.



SAFETY

- Nine patients started study treatment; 1 received EO2463 monotherapy only, 2 received EO2463/lenalidomide (EL), and 6 received EO2463/lenalidomide/rituximab (ER2). Five patients completed all planned study treatments (12 months); reasons for early stopping were PD (3) and SAE (1).

EO2463 monotherapy

- No related grade ≥3 event occurred.
- The most common events attributed to EO2463 only, were local administration site reactions (LASRs) (e.g., erythema, induration, and pain) in 6/9 patients (max grade 1 in 3 patients, and max grade 2 in 3 patients).
- The only other related event with EO2463 monotherapy was grade 1 headache (1/9).

EO2463 in combination with lenalidomide +/- rituximab

- The related events to either study drug were:
  - Hematology (in any patient of 9):
    - neutropenia max grade 2 (1 pat), grade 3 (1 pat) and max grade 4 (2 pts); anemia grade 3 (1 pat); thrombocytopenia grade 3 (1 pat)
  - Non-hematology (in >1 patient of 9):
    - headache grade 1 (2 pts); diarrhea grade 1 (2 pts); rash (2 pts grade 3; 1pt grade 1); rituximab infusion related reaction grade 2 (2 pts)
- One SAE of atrial fibrillation followed by heart failure was reported in a patient with baseline cardiac insufficiency; the event led to discontinuation of ER2 (patient at the time in CR).

EFFICACY AND BIOMARKER RESPONSE

Assessing the biomarker at samples collected week 5, i.e., after 2 administrations of EO2463 monotherapy, showed a positive biomarker response in 5/9 (56%) patients; percentage of CD8 T cells specific for the microbiome derived mimic peptides in EO2463 ranged from 0.16% - 2.13%. Thus, up to approx. 2% of all peripheral blood CD8 T cells were shown to be specific for the mimic peptides in EO2463 after only 2 administrations.

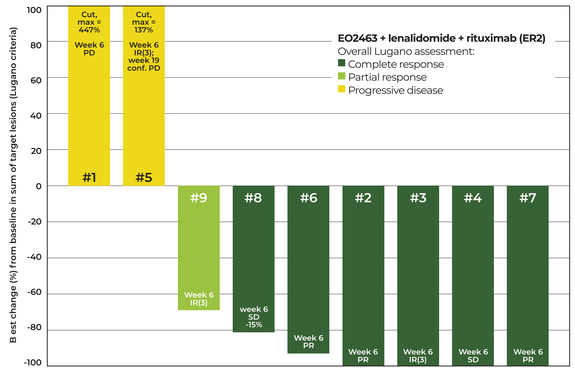
Baseline Characteristics - Biomarker Outcome Week 5 - Clinical Outcome Week 6 & Week 42

PAT	EO2463 Dose (ug/Pep)	Sex	Age	ECOG	Race	Ethnicity	Tumor	Ann Arbor Stage	GELF Score	FLIPI Score	FLIPI-2 Score	Prior Therapy RT	Prior Therapy Systemic	Biomarker At Week 5	Week 6 Response	Week 42 Response[3]
#1	150ug	M	80	1	White	Not Hispanic Or Latino	FL	III	0	2	2	1	1	Negative	PD	PD
#2	150ug	F	55	0	White	Not Hispanic Or Latino	FL	II	0	0	0	0	2	Positive	PR	CR
#3	150ug	F	73	0	White	Not Hispanic Or Latino	FL	IV	0	3	3	0	1	Positive	IR(3)	CR
#4	300ug	M	53	0	White	Hispanic Or Latino	FL	III	1	1	0*	0	2	Negative	SD	IR(2)
#5	300ug	M	63	0	White	Not Hispanic Or Latino	EMZL	IV	1	5	3	0	4^	Negative	IR(3)	PD
#6	300ug	M	54	0	White	Hispanic Or Latino	FL	IV	1	1	0	0	1	Positive	PR	CR
#7	300ug	F	66	0	White	Not Hispanic Or Latino	FL	II	0	2	1	1	1	Positive	PR	CR
#8	300ug	M	55	0	White	Not Hispanic Or Latino	NMZL	IV	1	1	0	2	2	Positive	SD	CR
#9	300ug	M	50	0	White	Not Hispanic Or Latino	FL	IV	0	1	0	0	4^	Negative	IR(2)	PR

* prior treatment including CART; ^ missing B2m-value; & Week 42 or earlier if PD and stop of study treatment

OBJECTIVE RESPONSE RATE

EO2463 + lenalidomide + rituximab (ER2) Overall Lugano assessment



ER2 combination response (n=9)

Overall best response:

- Objective response rate = 78%
  - Complete response = 67%
  - Partial response = 11%
- Progressive disease = 22%

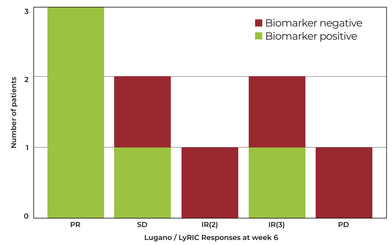
EO2463 monotherapy response (n=9)

Response at week 6:

- Partial response = 33%
- Stable disease = 22%
- Indeterminate response (3) = 33%
- Progressive disease = 11%

IR(3) = Lyric indeterminate response (3) = increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number

Predicting EO2463 monotherapy PET-CT objective response at week 6



Biomarker sensitivity, true positive rate of EO2463 monotherapy PET-CT objective response at week 6:

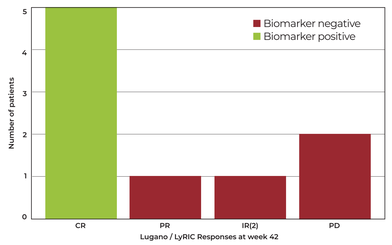
- Sensitivity = true positives (3) / [true positives (3) + false negatives (0)] = 100%

Biomarker specificity, true negative rate predicting lack of EO2463 monotherapy PET-CT objective response at week 6:

- Specificity = true negatives (4) / [true negatives (4) + false positives (2*)] = 67%

** One false positive patient had a SD with 15% tumor shrinkage at week 6 (i.e., too little response to qualify for an early criteria objective response, at week 19 however a PR, and at week 42 a CR), and the other an isolated increase in FDG-uptake at week 6, followed by a CR at week 19 (i.e., a pseudoprogression at week 6). Thus, both "false positive" patients have interesting positive outcomes later during treatment.*

Predicting EO2463 + lenalidomide + rituximab (ER2) combination therapy PET-CT complete response at week 42



Biomarker sensitivity, true positive rate of EO2463 + lenalidomide + rituximab combination therapy PET-CT complete remission at week 42:

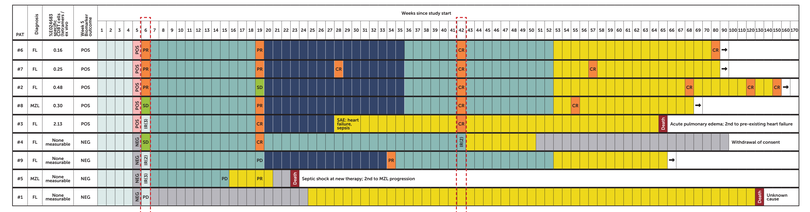
- Sensitivity = true positives (5) / [true positives (5) + false negatives (0)] = 100%

Biomarker specificity, true negative rate predicting lack of EO2463 + lenalidomide + rituximab combination therapy PET-CT complete remission at week 42:

- Specificity = true negatives (4) / [true negatives (4) + false negatives (0)] = 100%

CLINICAL & BIOMARKER OUTCOME

= EO2463 monotherapy = EO2463 + lenalidomide = EO2463 + lenalidomide + rituximab = follow-up → = follow-up ongoing = other anti-lymphoma treatment = complete/partial response = stable disease = Death IR(2)=indeterminate response; appearance of new lesions or growth of one of more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) or 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



CONCLUSIONS

- EO2463 monotherapy, and EO2463 in combination with lenalidomide (EL) and rituximab (ER2) are well tolerated in patients with relapsed/refractory FL and MZL.
- EO2463 monotherapy showed an objective response rate of 33% at week 6, and the overall objective response rate for EO2463 in combination with lenalidomide and rituximab was 78%, including a complete response rate of 67%.
- After 2 administrations of EO2463 monotherapy (sampling week 5) 56% of patients had expanded CD8 T cells specific for the microbiome derived mimic peptides in EO2463.
- The current assessment indicates that the biomarker as applied (measuring fast expansion of EO2463 specific CD8 T cells) can predict for clinical response, both for EO2463 monotherapy, and for EO2463 in combination with lenalidomide + rituximab.
- In the current limited size dataset, the biomarker can at week 5 predict complete remission at week 42 for ER2 with a sensitivity of 100% and specificity of 100%; obviously, these data needs to be validated in a larger dataset.
- The current plan include further investigation of the biomarker in the currently ongoing study cohorts of the trial; EO2463 monotherapy in the "watch & wait" setting, EO2463 + rituximab in 1st line FL/MZL, and ER² in relapsed FL/MZL.

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