Abstract 5377

EO2463 peptide immunotherapy in patients with newly diagnosed asymptomatic follicular lymphoma (FL) and marginal zone lymphoma (MZL): study EONHL1-20/SIDNEY (NCT04669171) primary endpoint Lugano objective response analysis

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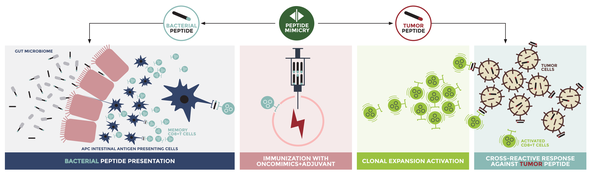
BACKGROUND

Watchful waiting is a common option for patients with asymptomatic FL/MZL. Anti-tumor immunization could delay or even avoid subsequent need for more toxic therapies. EO2463 is designed from non-self-protein sequences derived from gut bacteria, including 4 HLA-A2 CD8 T cell epitopes (synthetic mimic peptides), exhibiting molecular mimicry with specific epitopes on B cell markers (CD20, CD22, CD37, BAFF-receptor). EO2463 also contains a CD4 helper epitope UCP2. EO2463 expands pre-existing memory CD8 T cells recognizing non-self-epitopes from gut bacteria that cross-react with B cell antigens on tumor cells.

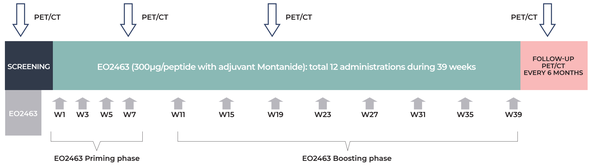


METHODS

Cohort 2 (planned 25 patients) of EONHL1-20/SIDNEY includes HLA-A2 positive (EO2463 peptide specificity) patients with ECOG 0-1, previously untreated FL/MZL (measurable disease) not in need of treatment.

Primary endpoint is objective response rate (ORR) per Lugano 2014. A pre-defined futility boundary was applied (ORR uninteresting = 5% / promising = 20%).

Finding at least 3 of 25 patients with ORR would meet criteria to continue development (chance of 13% and 90% for true ORR of 5% and 20%, respectively).

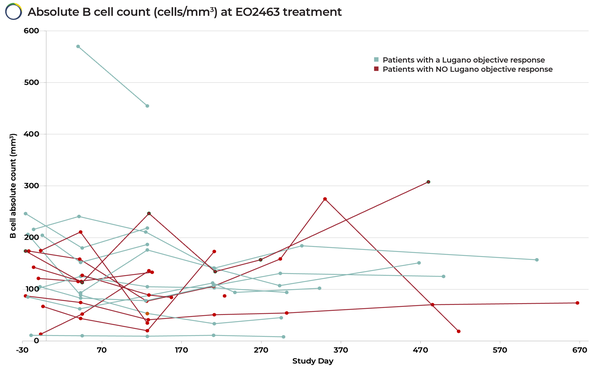


DURATION OF RESPONSE

10 patients with Lugano objective responses:

- Median time to response 18 weeks (range 5-41).
- 8 of 10 responders no PD event.
- 6 of 8 responders censored before 12 months.
- Current duration of response range 0.03-16.07 months.
- 2 Confirmed PD (surgery/biopsy 7.2/10.3 months after start response).
- 1 patient started R-CHOP due to transformation.
- Median follow-up for PFS (n=24) is 8.8 months, too early to assess PFS.

Absolute B cell count (cells/mm³) at EO2463 treatment



BASELINE CHARACTERISTICS

EONHL1-20/SIDNEY, Cohort 2 Baseline Characteristics		n = 24
Age (years)	Median (range)	59 (32-86)
Gender [n (%)]	Male / Female	14 (58%) / 10 (42%)
Ethnicity [n (%)]	Not Hispanic or Latino	24 (100%)
	White	24 (100%)
ECOG Performance status [n (%)]	0 / 1	21 (88%) / 3 (13%)
Primary diagnosis [n (%)]	FL/MZL	21 (88%) / 3 (13%)
Time since primary diagnosis [months]; [time intervals, n (%)]	Median (range) ≤ 6 months >6 to ≤ 12 months >12 to ≤ 24 months >24 months	4.9 (1.5-55.6) 16 (67%) 1 (4%) 2 (8%) 5 (21%)
Ann Arbor stage [n (%)]	I+II / III+IV	4 (17%) / 20 (83%)
Number of nodal sites	Median (range)	4 (1-8)
FLIPI [n (%)]	Low / intermediate / high risk	8 (33%) / 10 (42%) / 6 (25%)
FLIPI-2 [n (%)]	Low / intermediate / high risk	14 (58%) / 7 (29%) / 3 (13%)
GELF [n (%)]	Negative / positive*	21 (88%) / 3 (13%)

* 15 patients enrolled and starting treatment before protocol v3.0 when "GELF negative" not specified in eligibility.

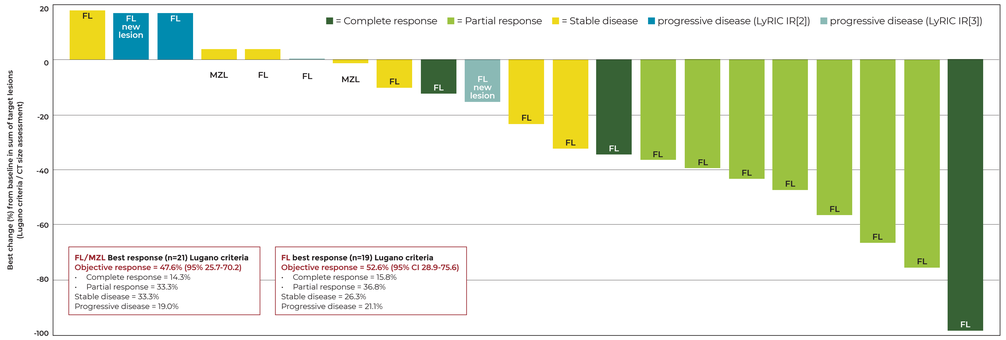
EXPOSURE AND SAFETY

- At data extract (2025-10-10 safety DB; 2025-10-18 efficacy DB), 24 patients had started EO2463; 10 completed planned treatment, 7 ongoing treatment, 4 discontinued for disease progression, 1 withdrew consent, and 2 discontinued by PI decision.
- Median treatment duration 29 weeks (range 1-39 weeks).
- 3 (14%) patients with ANY interruption of EO2463; 1 related Gr 2 LASR; 1 non-related Gr 2 diverticulitis; 1 non-related Gr 1 flat-effect / left visual field disturbance.
- No AE leading to withdrawal of EO2463.

EONHL1-20/SIDNEY, Cohort 2 Safety (DB 2025-10-10), n = 22	Irrespective of relationship to treatment	Related to EO2463
Any grade treatment emergent adverse events (TEAEs)	**Any grade ≥10%; or corresponding to related**	**Any grade ≥5%**
Local administration site reaction (LASR)*	19 (86%)	19 (86%)
Fatigue	8 (36%)	4 (18%)
Headache	5 (23%)	3 (14%)
Myalgia	3 (14%)	2 (9%)
Diarrhea	3 (14%)	0 (0%)
Cough	3 (14%)	0 (0%)
Urinary tract infection	3 (14%)	0 (0%)
Chills	2 (9%)	2 (9%)
Asthenia	2 (9%)	2 (9%)
Grade 3 TEAEs no grade 4 or 5 (death) events	**All Grade 3 events**	**All Grade 3 events**
Asthenia	1 (4.5%)	1 (4.5%)
Gastroenteritis	1 (4.5%)	0 (0%)
Syncope	1 (4.5%)	0 (0%)
Left inguinal hernia	1 (4.5%)	0 (0%)
GI-hemorrhage (only SAE reported)	1 (4.5%)	0 (0%)

* LASR including injection site reaction LINS, induration, erythema, pain, pruritus. Frequency by event 83% Grade 1, 17% Grade 2, no Grade 3. Median time to first event 2.1 weeks (range 0.1-26.9).

Best objective response per Lugano criteria (n=21) at EO2463 treatment



PSEUDOPROGRESSION / ATYPICAL RESPONSE PATTERN

Initial progression (indeterminate response per LyRIC) assessed with a follow-up scan or biopsy/surgery in 11 patients:

- Confirmed progression at follow-up scan or biopsy/surgery in 6 patients (55%).
- **Non-confirmed progression at follow-up scan in 5 patients = 45% rate of pseudoprogression.**

Characteristics of patients with pseudoprogression:

- 5 of 5 have finalized EO2463 treatment without stop due to progression,
- 4 of 5 have objective responses per Lugano (5th has SD with 32% decrease of target lesions),
- 1 of 5 has a confirmed progression (week 96),
- 5 of 5 have not started any new systemic anti-lymphoma treatment, and
- current follow-up is 67-101 weeks.
- If LyRIC response criteria had not been applied 3 of 5 would have stopped EO2463 at week 6-7; however, the phenomenon of pseudoprogression during treatment with EO2463 is not only happening early but can also appear late (week 42-45) = progression must be confirmed whenever appearing during/after EO2463 therapy!

CONCLUSIONS

- EO2463 monotherapy in the "watch-and-wait" setting in patients with follicular and marginal zone lymphoma has a favourable safety profile and is associated with a Lugano criteria objective response rate of 48% exceeding the study prespecified boundary for promising activity.
- Expansion of CD8 memory T cells specific for the EO2463-mimic peptides and the B cell targeted antigens (cross-reactivity versus epitopes on CD20, CD22, CD37, and BAFF-R) are seen in more than 80% of patients.
- The EO2463 induced expansion of specific CD8 T cells is rapid, strong, and sustained, with the expanded cells being memory phenotype dominated by effector memory cells (EM).
- The immune response characteristic of patients with an objective Lugano criteria response is a fast and robust expansion of specific CD8 T cells already after 1-2 administrations of EO2463 (week 3-5), while patients without an objective response (who might still benefit from EO2463-treatment by e.g., long-lasting stabilization of disease) have a more gradual expansion of specific CD8 T cells.
- There is no correlation between Lugano criteria response and peripheral blood B cell decreases at treatment with EO2463, and decreases are generally rare and do not seem to correlate with infections.
- EO2463 monotherapy seems to be a possible alternative to watchful waiting in patients with follicular lymphoma; the approach is under consideration for evaluation in a larger development context.

IMMUNE RESPONSE

Twenty-one (21) patients were tested for immune responses during EO2463 treatment utilizing specific tetramers/ex vivo:

- EO2463-mimic peptide specific CD8 T cell expansion in 18 (86%) of tested patients.
- B cell target peptide specific CD8 T cell expansion in 17 (81%) of tested patients.

EO2463-expanded specific CD8 T cells present a memory phenotype dominated by effector memory CD8 T cells (TEM).

The level of expansion of CD8 T cells specific for both EO2463-mimic and B cell target peptides correlates with Lugano criteria objective response.

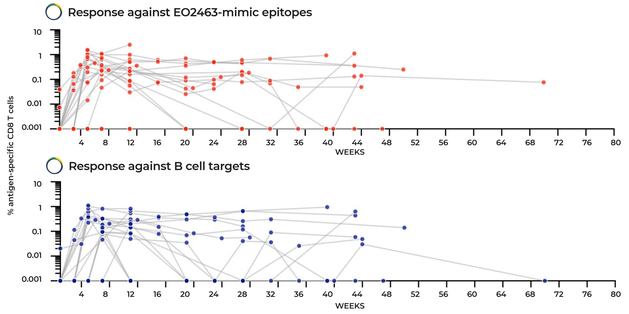
The level of expansion of specific CD8 T cells in patients with pseudoprogression (n=5) was significantly higher vs in patients without such a phenomenon (n=16) (Mann-Whitney, 2-sided):

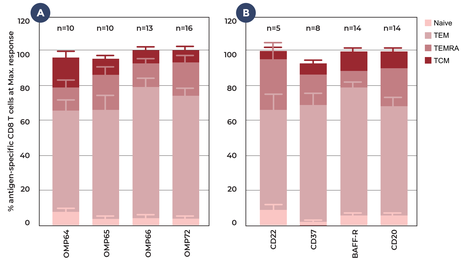
- EO2463-mimic responses: week 3-5, p=0.011; week 3-8, p=0.039; any time, p=0.098
- B cell target responses: week 3-5, p=0.008; week 3-8, p=0.007; any time, p=0.035

Anti-CD3 expansion (IFN-γ ELISPOT, ex vivo) of T cells indicating T cell intrinsic activation potential did not correlate with objective clinical response:

- Patients with OR [n=6] vs no-OR response [n=7], 2-sided Mann-Whitney, p=1.055 for max anti-CD3 response any time; p=0.818 for max anti-CD3 week 3-8; p=0.876 for baseline anti-CD3 response.

EO2463 induced immune response
CD8 T cells from PBMCs were stained ex vivo with tetramers at the indicated weeks to assess specific responses against EO2463-mimic (top) or B cell target (bottom) peptides. Zero values were set to 0.001 for logarithmic representation.

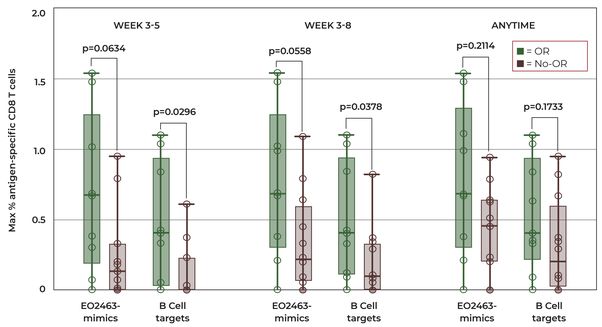




Phenotype of EO2463 induced immune response
CD8 T cells specific for EO2463-mimic (A; OMP64, OMP65, OMP66, OMP72) and B cell target peptides (B; epitopes on CD22, CD37, BAFF-R, CD20) were quantified using tetramers/flow cytometry ex vivo on PBMCs from patients. Memory phenotype was determined using CCR7 and CD45RA analyses within tetramer-positive populations. TEMRA: terminally differentiated effector memory cells; TCM T central memory; TEM T effector memory.

Fast expansion of EO2463-mimic and B cell target specific CD8 T cells correlates with objective response

EO2463-mimic and B cell target peptides specific CD8 T cells assayed by tetramers: max pooled specific responses against the 4 EO2463- or 4 B cell target-peptides at a single timepoint within the time intervals indicated. The results are expressed as percentage specific CD8 T cells among all CD8 T cells in peripheral blood (ex vivo analyses). P-values by 2-sided Mann-Whitney testing.



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