Abstract PF938

EO2463 an off-the-shelf multi-target peptide immunotherapy: in vivo CD8 T cell expansion kinetics correlates with efficacy in patients with follicular (FL) and marginal zone (MZL) lymphoma. Study EONHL1-20/SIDNEY (NCT04669171).

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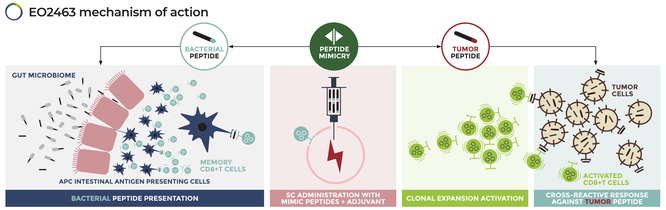
EO2463 COMPOSITION AND MECHANISM OF ACTION

EO2463 is an off-the-shelf peptide immunotherapy designed to expand in vivo pre-existing memory CD8 T cells recognizing non-self-protein sequences from gut bacteria cross-reacting with B cell antigens. EO2463 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.

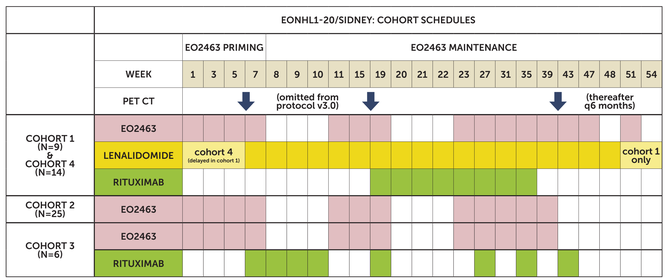
EO2463 mechanism of action



PATIENT TREATMENT SCHEDULES

Study EONHL1-20/SIDNEY is a multi-cohort first-in-human study of EO2463 (SC 300 µg/peptide, except 3 initial patients at half-dose, with adjuvant Montanide ISA 51 VG), including patients who are HLA-A2 (EO2463 peptide specificity) with FL/MZL:

- Cohort 1 (safety lead-in) + Cohort 4 (expansion): previously treated relapsed/refractory disease; EO2463 plus lenalidomide (oral, 20 mg/day for 21/28 days for 12 cycles) and rituximab (IV, 375 mg/m² for 8 doses).
- Cohort 2 (expansion): previously untreated, low-tumor burden, patients suitable for watchful waiting; EO2463 monotherapy.
- Cohort 3 (expansion): previously untreated, low-tumor burden, patients in need of treatment; EO2463 plus rituximab (IV, 375 mg/m² for 8 doses).



PATIENT BASELINE CHARACTERISTICS

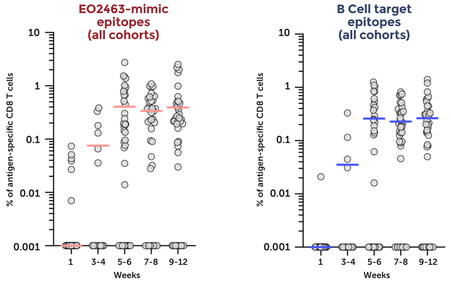
Baseline Characteristics	COHORT 2 (N=25) previously untreated, not in need of SOC treatment EO2463 monotherapy	COHORT 3 (N=6) previously untreated, in need of treatment EO2463 + rituximab	COHORT 1 + 4 (N=23) relapsed/refractory disease EO2463 + lenalidomide + rituximab
Age (years); median (range)	58 (20-86)	66 (46-73)	61 (40 - 80)
Gender [n (%)]; male / female	14 (56%) / 11 (44%)	4 (67%) / 2 (33%)	18 (78%) / 5 (22%)
ECOG Performance status [n (%)]; 0/1	22 (88%) / 3 (12%)	6 (100%) / 0 (0%)	18 (78%) / 5 (22%)
Primary diagnosis [n (%)]; FL/MZL	22 (88%) / 3 (12%)	6 (100%) / 0 (0%)	18 (78%) / 5 (22%)
Time since primary diagnosis (months); median (range)	4.5 (1.5-55.6)	12.2 (1.1-83.0)	68.1 (24.9-264.9)
Number of prior systemic treatments; median (range)	NA	NA	1 (1-4)
Ann Arbor stage [n (%)]; I+II / III+IV	4 (16%) / 21 (84%)	0 (0%) / 6 (100%)	5 (22%) / 18 (78%)
Number of nodal sites; median (range)	3 (1-8)	3 (0^^-6)	5 (0^^-16)
FLIPI [n (%)]; low / intermediate / high risk	9 (36%) / 10 (40%) / 6 (24%)	2 (33%) / 2 (33%) / 2 (33%)	6 (26%) / 9 (39%) / 8 (35%)
FLIPI-2 [n (%)]; low / intermediate / high risk	12 (50%) / 8 (33%) / 4 (17%) ^	2 (33%) / 4 (67%) / 0 (0%)	7 (30%) / 12 (52%) / 4 (17%)
FLIPI24***; low / intermediate / high risk	14 (58%) / 9 (38%) / 1 (4%) ^	3 (50%) / 3 (50%) / 0 (0%)	NA
GELF [n (%)]; negative / positive	22 (88%) / 3 (12%)*	6 (100%) / 0 (0%)	15 (65%) / 8 (35%)
POD24** [n(%)]: no / yes	NA	NA	17 (74%) / 6 (26%)
PFS on 1st line systemic (months); median (range)	NA	NA	30.4 (9.2-150.6)

^ one patient missing β2m; ^^ 0 nodal sites in two patients with bone lesions and BM involvement.
* 15 patients enrolled and starting treatment before protocol v3.0 when "GELF negative" not specified in eligibility.
** POD24 per Blood 2022, 139, 1684; *** FLIPI24 per JCO 2025, 44, 117

IN VIVO CD8 T CELL EXPANSION KINETICS

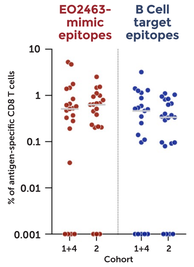
Immune responses were rapid with a plateau during the EO2463 priming phase

Immunomonitoring in 48/54 patients; 43 (90%) positive immune response in tetramer or ELISPOT IFN-γ assays against EO2463-mimic or B cell target peptides. Ex vivo tetramer assessments demonstrated rapid induction of responses (week 5-6) in most patients. Relative frequencies (median max % of total CD8 T cells at any time) were 0.52% for EO2463-mimic and 0.35% for B cell target specific CD8 T cells. At response-peak, specific CD8 T cells displayed predominantly an effector memory phenotype suggesting pro-inflammatory features and cytotoxic potential. Durable specific responses detectable up to 34 months after last EO2463-administration. Lack of correlation between common pathogen-derived epitopes (CEFSX) or anti-CD3 stimulation with EO2463-mimic responses argues specificity of EO2463 responses.



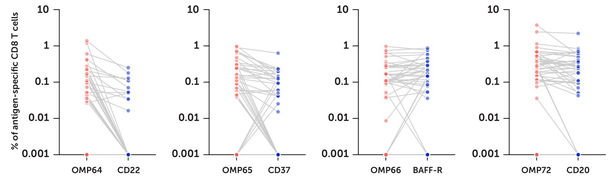
Immune responses similar for EO2463 monotherapy and EO2463 in combination with lenalidomide/rituximab

The number of EO2463-mimic positive patients was in Cohort 1+4 17/21 (81%), and in Cohort 2 18/21 (86%); B cell target positivity was in Cohort 1+4 16/21 (76%) and in Cohort 2 17/21 (81%). Figure shows ex vivo tetramer staining, dots representing the highest observed value for each patient across all visits. EO2463-mimic and B cell target-specific responses correspond to cumulative % of CD8 T cells specific for the 4 EO2463-mimic or B cell target peptides. Grey lines indicate median values. Zero values were set to 0.001 for log scale representation.

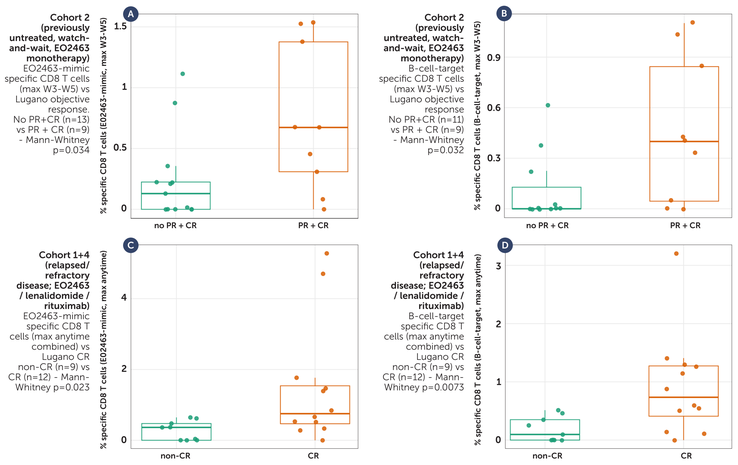


Robust immune responses against all components of EO2463 translating into cross-reactive immune responses against the B cell targets

Maximal immune responses to individual EO2463-mimic and B cell target peptides assessed by ex vivo tetramer staining; cross-reactive responses depicted for the indicated EO2463-mimic peptide and the B cell target pairs. Zero values were set to 0.001 for logarithmic representation.



EFFICACY & CD8 T CELL EXPANSION CORRELATES



Cohort 2

High level of early expansion (after 1-2 EO2463 administrations) of EO2463-mimic and B cell target peptide specific CD8 T cells is associated with Lugano objective tumor response on EO2463 monotherapy. Two no-PR/CR immune response outliers (two highest values): i) pat with SD at 9.7 mo ongoing FU, and ii) pat with new lesions at 10.6 mo, start R-Benda at 14.2 mo.

Cohort 1+4

High level of expansion of EO2463-mimic and B cell target peptide specific CD8 T cells (any time during treatment) is associated with Lugano complete tumor response on EO2463 + lenalidomide + rituximab therapy.

Methods

Sum of tetramer ex vivo responses at one single timepoint for the 4 tetramers specific for the EO2463-mimic peptides or B cell target peptides using 4 separate fluorochromes, and in addition for EO2463-mimic peptides a single fluorochrome for all 4 tetramers. Mann-Whitney, two-tailed tests.

EO2463 clinical efficacy across treatment settings

Database 2026-APR-24	COHORT 2 (N=25) previously untreated, not in need of SOC treatment EO2463 monotherapy	COHORT 3 (N=6) previously untreated, in need of treatment EO2463 + rituximab	COHORT 1 + 4 (N=23) relapsed/refractory disease EO2463 + lenalidomide + rituximab
Lugano criteria* objective (PR+CR) response rate (95% CIs)	41% (20.7-63.6) ^	100% (54.1-100)	74% (51.6-89.8)
Lugano criteria* complete response rate (95% CIs)	14% (2.9-34.9) ^	83% (35.9-99.6)	61% (38.5-80.3)
Time to objective response; median (range)	17.1 (5.3-41.1) weeks	17.1 (6.0-18.0) weeks	17.1 (5.0-71.7) weeks
Duration of objective response; median (95% CIs)	NR (7.2-NR) months	NR (16.8-NR) months	35.2 (8.8-NR) months
Median follow-up of progression-free survival	9.7 months	19.1 months	16.5 months
Progression-free survival; median (95% CIs)	too short follow-up to assess	NR (20.5-NR) months	19.2 (14.6-NR) months

* Lugano criteria (J Clin Oncol 2014, 32, 3059) taking LyRIC criteria (Blood 2016,128, 2489) into account for possible continuation of treatment to detect pseudoprogression.
^ 22 patients evaluable for tumor response; 3 too early, have not reached week 19 tumor assessment.
NR = not reached; Clopper–Pearson exact 95% CIs for Lugano response/progression; Brookmeyer–Crowley 95% CIs for DOR

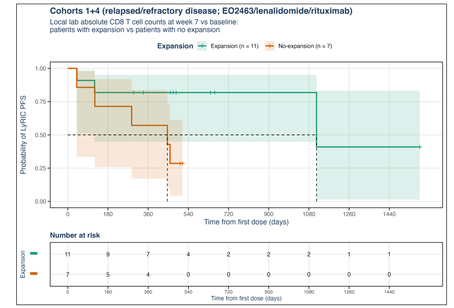
ABSOLUTE CD8 COUNT AS A BIOMARKER FOR EO2463 EFFICACY

Absolute CD8 T cell counts (local lab) showing a CD8 T cell expansion at week 7 (after 3 EO2463 administrations) vs baseline seems associated with extended progression-free survival

Absolute CD8 T cell counts
CD8 expansion vs no-expansion

- HR = 0.26 (95% CI 0.05-1.07)
- Log-rank p = 0.052

The possible impact seen for absolute CD8 T cell expansion at week 7 on PFS outcome, does not seem to be present for absolute CD4 T cell expansion; CD4 expansion vs no-expansion HR = 0.44 (95% CI 0.10-1.81), log-rank p = 0.249. Note, the CI is too wide to formally rule out a CD4 effect, but the result is compatible with no CD4 effect under low power.



Cohorts 1+4	Median follow-up for PFS (months	Median PFS (95% CIs) (months)
Whole group (n=23)	16.4	19.2 (14.6-NR)
Pts with CD8 expansion (n=11)	15.9	36.5 (3.9-NR)
Pts without CD8 expansion (n=7)	16.7	14.6 (1.3-NR)
Pts without CD8 data (n=5)	14.4	18.5 (1.2-NR)

Patients with a CD8 T cell expansion at week 7 have a similar PFS on EO2463 + lenalidomide + rituximab as on the same patients first-line treatment indicating avoidance of the usual by line attrition in PFS

Stratified HR for PFS on 1st line treatment (PFS1) vs PFS on EO2463:

- HR = 0.33 (95% CI 0.03-3.20)
- Log-rank p (stratified) = 0.32

First-line treatments compared to EO2463/ lenalidomide/rituximab given as 2nd (7 pts), 3rd (2 pts), 4th (1 pat), and 5th (1 pat) line treatment included:

- 6 pts = rituximab or obinutuzumab + CHOP; 4 pts with maintenance R/O, 1 pat with initial RTX + bendamustine, and 1 pat with added ibrutinib
- 2 pts = rituximab + bendamustine followed by rituximab maintenance
- 3 pts = rituximab or obinutuzumab monotherapy

CONCLUSIONS

- EO2463 monotherapy and the combinations (with R and R²) are well tolerated with EO2463 only adding local administration site reactions to the well-known R/R² safety profiles:
  - EO2463 safety described in Hematological Oncology, 43, e92_70093; Blood 2025, 146 (Supplement 1), 5377; Blood 2025, 146 (Supplement 1), 3594.
- EO2463 rapidly induces extensive multi-targeted in vivo expansions of EO2463-mimic and B cell target peptide specific mainly effector memory CD8 T cells that are long lasting.
- EO2463 shows monotherapy activity.
- Combinations are promising:
  - Data suggests a potentially higher-than-expected CR-rate with EO2463 + R² over R² alone in R/R FL [J Clin Oncol 2019, 37, 1188; Blood 2024, 144 (Supplement 2), LBA-1; Lancet 2026, 407, 161].
  - EO2463 + R in low-tumor burden FL is feasible and has a promising response profile.
- EO2463-induced CD8 T cell expansions with specificity for EO2463-mimic and B cell target peptides are associated with clinical outcomes, a potential for a predictive biomarker.
- A local laboratory biomarker, absolute CD8 T cell expansion at week 7 of EO2463 + lenalidomide + rituximab, is associated with PFS.
- EO2463 warrants further study as monotherapy and in combination with other anti-lymphoma therapies.

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