EO2463 an off-the-shelf multi-targeted 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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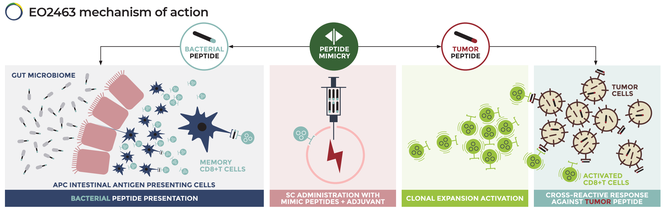
Authors: Stephen D. Smith[1], Jose Villasboas[2], Danielle Wallace[3], Reid Merryman[4], Francesc Bosch[5], Carlos Grande[6], Antonio Pinto[7], Luca Arcaini[8,9], Jean-Pierre Marolleau[10], Norma Gutiérrez[11], Brian Till[1], Carla Casulo[3], Cristina García Hercé[5], Maria Rocío Figueroa Mora[6], Sara Rattotti[9], Pierre Morrel[10], Philippe Rinaudo[12], Karlijn Kroon[12], Jean-Marie Carpier[12], Pier Luigi Zinzani[13], Philippe Armand[4], Stephen Ansell[2]

1 Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA; 2 Mayo Clinic, Rochester, MN, USA; 3 University of Rochester, Rochester, NY, USA; 4 Dana-Farber Cancer Institute, Boston, MA, USA; 5 University Hospital Vall d'Hebron, Barcelona, Spain; 6 Universidad de Navarra, Pamplona, Spain; 7 Fondazione 'G. Pascale', IRCCS, Naples, Italy; 8 Department of Molecular Medicine, University of Pavia, Pavia, Italy; 9 Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 10 Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; 11 Hospital Universitario De Salamanca, IBSAL, Salamanca, Spain; 12 Enterome, Paris, France; 13 University of Bologna, Bologna, Italy.

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.

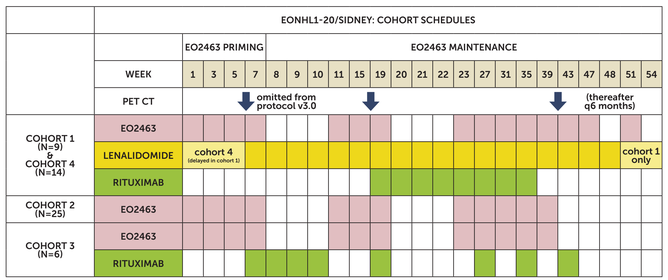
EO2463 mechanism of action



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/m^2 for 8 doses).



PATIENT BASELINE CHARACTERISTICS

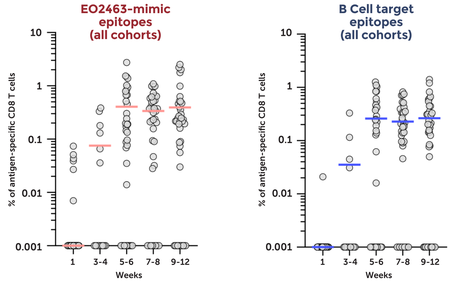
Baseline Characteristics	COHORT 2 (N=25) previously untreated, not in need of SOC treatment EO2463 monotherapy	COHORT 3 (N=6) previously untreated, in need of treatment EO2463 + rituximab	COHORT 1 + 4 (N=23) relapsed/refractory disease EO2463 + lenalidomide + rituximab
Age (years); median (range)	58 (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

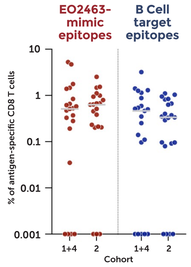
Immune responses were rapid with a plateau during the EO2463 priming phase

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 supports specificity of EO2463 responses.



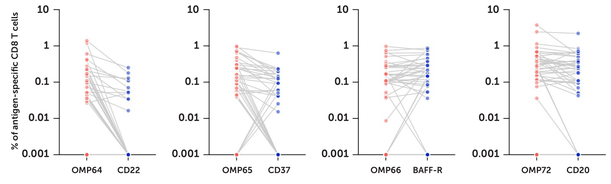
Immune responses similar for EO2463 monotherapy and EO2463 in combination with lenalidomide/rituximab

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.

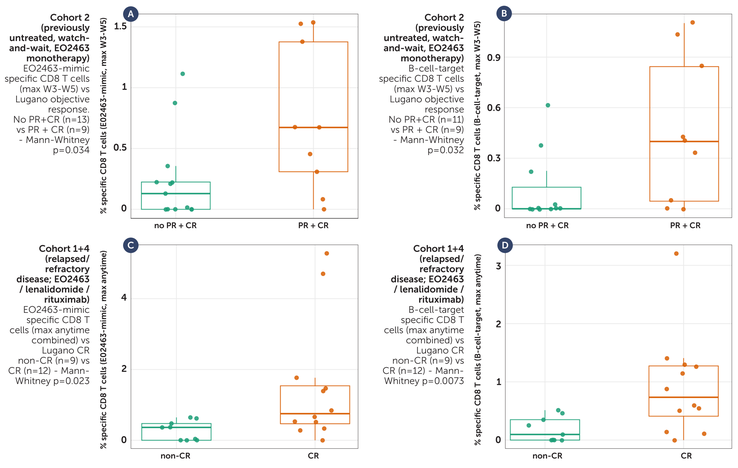


Robust immune responses against all components of EO2463 translating into cross-reactive immune responses against the B cell targets

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

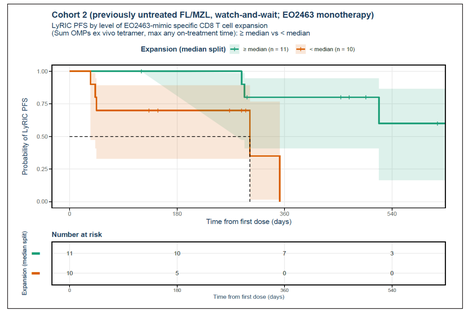
Sum of tetramer ex vivo responses at one single timepoint for the 4 tetramers specific for the EO2463-mimic peptides or B cell target peptides using 4 separate fluorochromes, and alternatively for EO2463-mimic peptides a single fluorochrome for all 4 tetramers. Mann-Whitney, two-tailed tests.

EO2463 clinical efficacy across treatment settings

Database 2026-MAY-18	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)	36% (18-57)	100% (54-100)	73% (50-89) ^
Lugano criteria* complete response rate (95% CIs)	12% (3-31)	83% (36-100)	64% (41-83) ^
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 (8.3-NR) months	NR (16.8-NR) months	35.2 (8.8-NR) month
Median follow-up of progression-free survival	9.7 months	18.5 months	16.8 months
Progression-free survival; median (95% CIs)	17.0 (9.6-NR) months	NR (20.5-NR) months	18.5 (4.0-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; 1 no on study tumor assessment.
NR = not reached; Clopper–Pearson exact 95% CIs for Lugano response/progression; Brookmeyer–Crowley 95% CIs for DOR

PROGRESSION-FREE SURVIVAL ON EO2463 MONOTHERAPY IN THE "WATCH-AND-WAIT" SETTING IS ASSOCIATED WITH LEVEL OF EXPANSION OF CD8 T CELLS SPECIFIC FOR EO2463-MIMIC PEPTIDES



Level of expansion of CD8 T cells specific for EO2463-mimic peptides (max for an individual patient at any time during treatment; ex vivo tetramer assays) is associated with extended progression-free survival on EO2463 monotherapy.

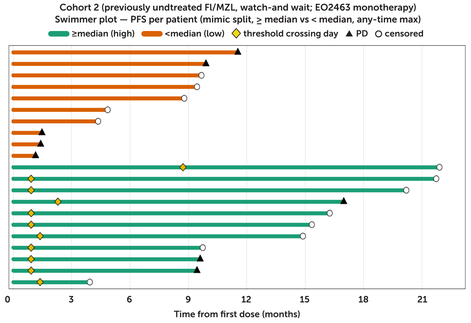
Progression-free survival

- patients with ≥ median level of expansion of CD8 T cells specific for EO2463-mimic peptides vs patients with < median expansion
- HR = 0.18 (95% CI 0.03-0.82)
- Log-rank p = 0.020

Cohorts 2 EO2463 monotherapy	Median follow-up for PFS [months]	Median PFS (95% CIs) [months]
Whole group (n=25)	9.7	17.0 (9.6-NR)
Pts ≥ median expansion of EO2463-mimic specific CD8 T cells (n=11)	16.3	NR (9.4-NR)
Pts < median expansion of EO2463-mimic specific CD8 T cells (n=10)	9.4	9.9 (1.1-NR)
Pts currently without immune testing data (n=4)	Recently started patients, censored for PFS 2x d 1 and 2x d 127-129	

EONHL1-20/SIDNEY, COHORT 2

- Gold diamonds show the day of crossing median value of EO2463-mimic peptide ex vivo tetramer measured specific CD8 T cell expansion.
- Only one patient in the "≥ median" group passes the median somewhat late (week 39/month 9). Excluding this patient the log-rank stays significant (p = 0.031).
- None of the patients in the "< median group" passes the median during treatment/follow-up).



CONCLUSIONS

- EO2463 monotherapy and the combinations (with R and R^2) are well tolerated with EO2463 only adding local administration site reactions to the well-known R/R^2 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 suggest a potentially higher-than-expected CR-rate with EO2463 + R^2 over R^2 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 Lugano objective response.
- A high level of expansion of EO2463-mimic peptide specific CD8 T cells is associated with progression-free survival on EO2463 monotherapy.
- EO2463 induced expansions of specific CD8 T cells might be developed into a predictive biomarker.
- EO2463 warrants further study as monotherapy and in combination with other anti-lymphoma therapies.

Contact info: Enterome (medicalmonitoring-hem@enterome.com) / Stephen D. Smith (ssmith50@fredhutch.org)