Abstract 7058

Phase 1/2 of EO2463 immunotherapy as monotherapy and in combination with lenalidomide and/or rituximab in indolent NHL EONHL1-20/SIDNEY

2024 ASCO Annual Meeting, May 31 – June 4, Chicago, Illinois
Poster Session Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
June 3, 9:00 AM-12:00 PM CDT

Phase 1/2 EONHL1-20/SIDNEY

AUTHORS

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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.

Therapeutic immunization is therefore an attractive approach but new antigens that evoke a strong immune response are needed.

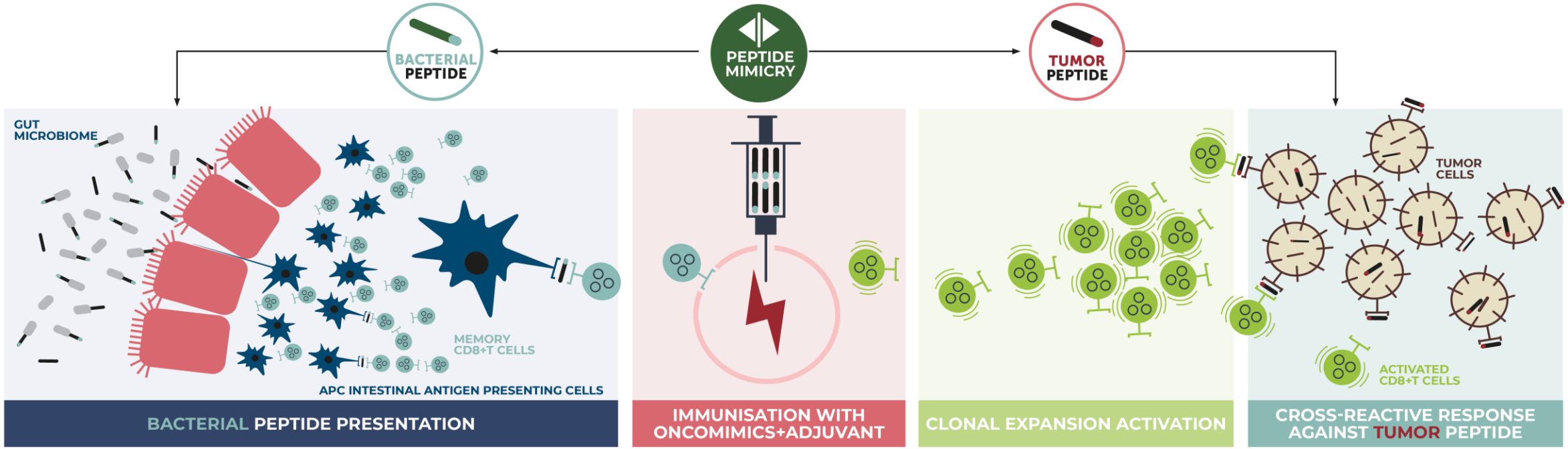
EO2463 expands pre-existing memory CD8+ T cells recognizing non-self protein sequences from gut bacteria which cross-react with B cell antigens (OncoMimics) and can kill HLA-A2 restricted lymphoblastoid cells.

EO2463 includes 4 HLA-A2 synthetically produced epitopes which exhibit molecular mimicry with the B cell markers CD20, CD22, CD37, and CD268 (BAFF-receptor), as well as a CD4 helper-epitope UCP2 derived from hTERT.

EO2463 is being used to drive anti-tumor activity against B cell malignancies.

Phase 1/2 EONHL1-20/SIDNEY

BACKGROUND



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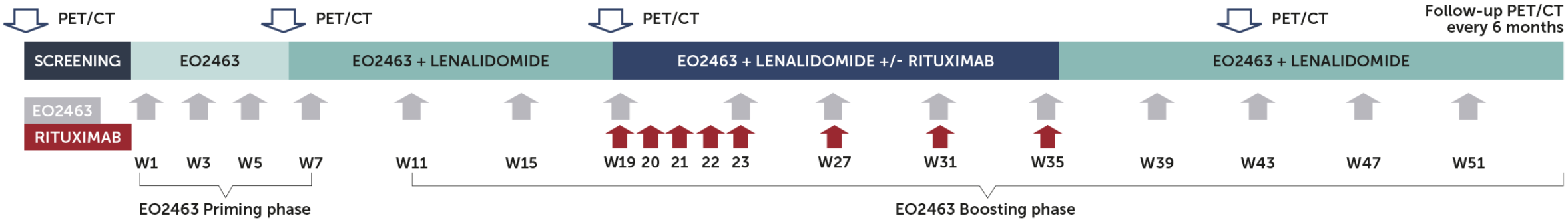
METHODS

This dose-finding safety lead-in phase 1 part of the ongoing phase 1/2 trial included patients with relapsed/refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL) and investigated EO2463 + lenalidomide + rituximab in patients with Grade 1-3A FL or MZL, who received ≥ 1 line of prior systemic therapy. Patients are HLA-A2 with ECOG PS 0-2, no contraindications and measurable disease.

Patients received EO2463 q2 weeks x4, then every 4 weeks; administered SC with adjuvant Montanide ISA 51 VG up to 15 doses. After 6 weeks of EO2463 monotherapy, oral lenalidomide (20 mg/day for 21/28 days up to 12 cycles) was added, and if no complete remission (CR) at week 19, rituximab (375 mg/m^2 IV, weekly x 4, followed by q4 w infusions x 4) was also added.

The peptide-dose was evaluated in a 3-by-3 safety design, starting at 150 µg/peptide, with a max escalation to 300 µg/peptide. Treatment was given until treatment completion, toxicity, or tumor progression.

The primary objective of the phase 1 part of the trial was to define the recommended phase 2 dose (RP2D) for EO2463 monotherapy, and to confirm the safety of EO2463 at the monotherapy RP2D in combination with lenalidomide (EL) and rituximab (ER^2).



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IMMUNOMONITORING

For the secondary objective, immunogenicity (quantification of T cells specific for the OncoMimics used for immunization, i.e., OMP72, OMP64, OMP65, OMP66, and their B cell antigen counterparts, i.e., CD20, CD22, CD37, and CD268 (BAFF-receptor)), blood collection was performed at baseline and then every two to four weeks. Immunomonitoring was performed on blood samples (initially cryopreserved PBMCs) either ex vivo, or after 12 days in vitro stimulation (IVS), using quantification of antigen specific CD8+ T cells with either peptide specific tetramers/flow cytometry, or IFN-γ secretion/ELISpot after peptide stimulation.

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SAFETY

Exposure

- 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 grade ≥3 related events occurred.
- Events attributed to EO2463 only, were local administration site reactions (LASRs) (injection site pain, erythema, induration, inflammation, edema, and swelling) in 6/9 patients (3 G2, and 3 G1).
- The only other related event with EO2463 monotherapy was G1 headache (1/9).
- EO2463 administration was delayed with one week for one patient due to LASR. No further dose/schedule modifications occurred.

EO2463 in combination with lenalidomide +/- rituximab

- The related events to either study drug were:
  - Hematology (in any patient of 9):
    - neutropenia G2 (1 pat), G3 (1 pat) and G4 (2 pts); anemia G3 (1 pat); thrombocytopenia G3 (1 pat)
  - Non-hematology (in >1 patient of 9):
    - Diarrhea G1 (2 pts); rash G3 (2 pts); rituximab infusion related reaction G2 (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).

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IMMUNE RESPONSE

Patients exhibited a rapid and robust immune response against both OncoMimics and the corresponding B cell antigens (Figure 1).

Immune monitoring demonstrated the ability of EO2463 to expand specific CD8+ T cells with cross-reactivity against the targeted B cell antigens in a significant portion of patients (Table 1), with up to 5.3% of all peripheral blood CD8+ T cells being specific for OncoMimics.

Specific CD8+ T cells could be detected ex vivo early, and in long-term follow-up, currently until 94 weeks after study treatment start (Figure 2). Functionality of EO2463 specific CD8 T cells could be demonstrated by direct cytotoxic activity against lymphoblastic cell lines (Figure 3), also after long-term EO2463 treatment.

The specific CD8+ T cells expanded by EO2463 have a memory phenotype (Figure 4) and remains polyfunctional long-term (Figure 5).

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IMMUNE RESPONSE

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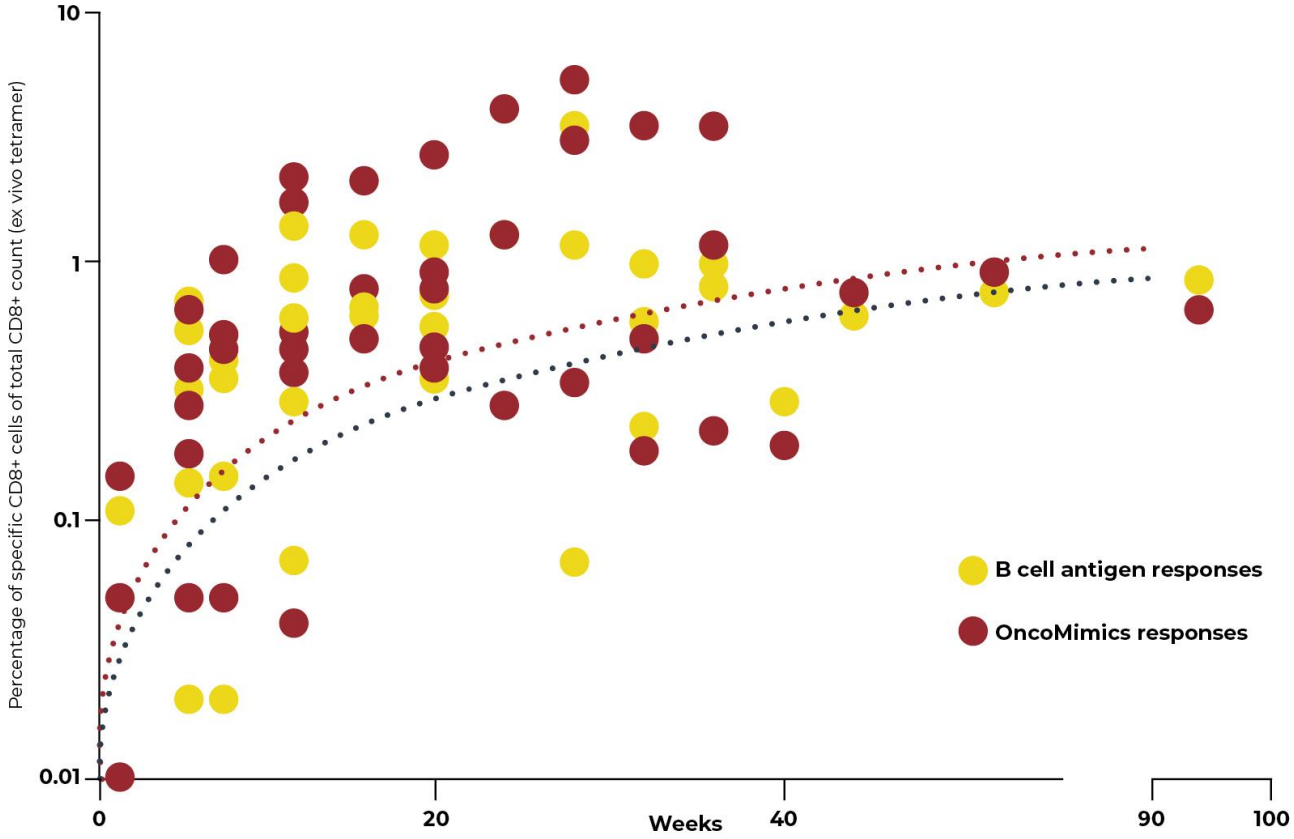
FIGURE 1: Percentage of CD8+ T cells specific for EO2463 and B cell antigens as assessed by tetramer analysis ex vivo.



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IMMUNE RESPONSE

TABLE 1: Summary of EO2463 OncoMimics and B cells antigen specific CD8+ T cells.

	OMP72	OMP64	OMP65	OMP66	OncoMimics sum (%)
Pat #1	nd	0	0	nd	**0.00**
Pat #2	0.14	0.21	0.65	0.46	**1.46**
Pat #3	2.44	1.39	0.48	0.98	**5.29**
Pat #4	0.72	0.16	0.35	0.63	**1.86**
Pat #5	0.01	0.04	0.01	0.01	**0.07**
Pat #6	0.22	0.21	0.10	0.16	**0.69**
Pat #7	0.25	0.27	0.06	0.11	**0.69**
Pat #8	1.50	0.37	0.63	0.23	**2.73**
Pat #9	0.47 (bk)	0.05	0.04	0.02	**0.11**

CD20	CD22	CD37	BAFF-R	B cell antigen sum (%)
nd	0	0	nd	**0.00**
0.34	0.12	0.24	0.34	**1.04**
2.21	0.18	0.11	0.76	**3.26**
0.52	0.02	0.34	0.65	**1.53**
0.02	0.03	0.01	0.02	**0.07**
0.33	0.07	0.04	0.21	**0.65**
0.77	0.11	0.06	0.34	**1.28**
0.24	0.13	0.07	0.26	**0.70**
0.37 (bk)	0.02	0.02	0.18 (bk)	**0.04**

Peptides were quantified using specific tetramers and flow cytometry ex vivo (percentage of tetramer positive cells from total CD8 count); best immune response any time during study. Numbers highlighted in green are showing significant specific CD8+ T cell responses as assessed vs controls. bk = high background, not positive.

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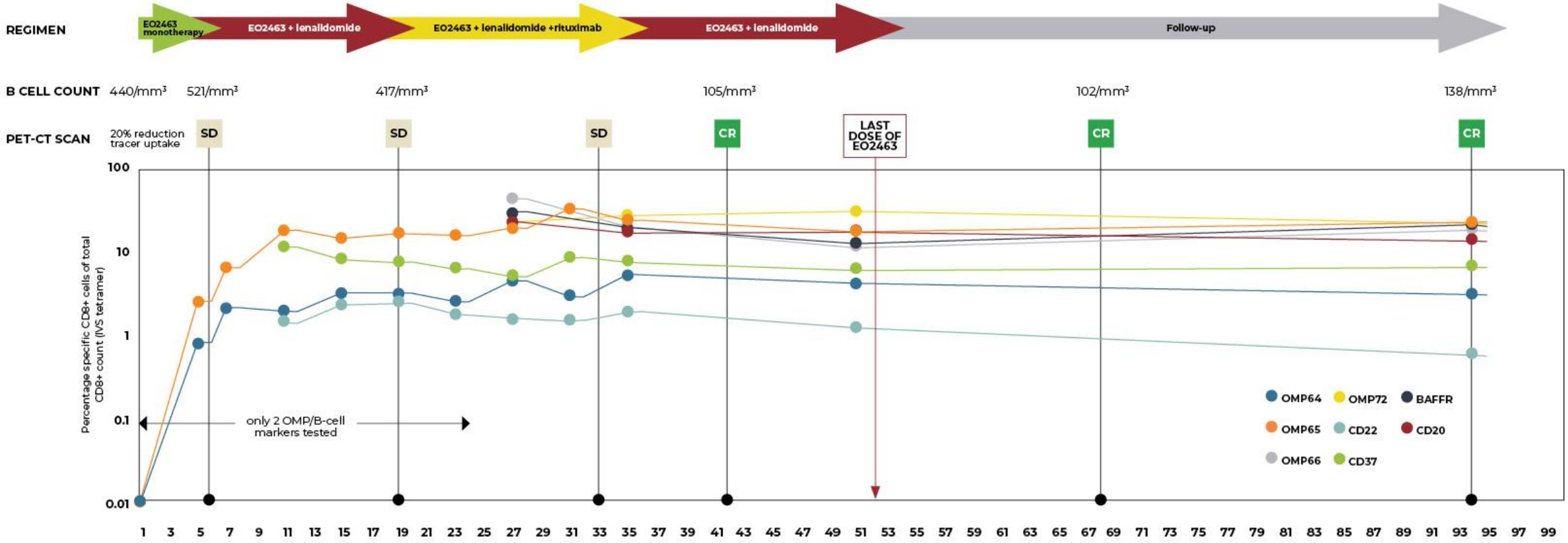
IMMUNE RESPONSE

FIGURE 2: Long-term detection of cross-reactive CD8+ T cells after EO2463 administration.



CD8+ T cells specific for OncoMimics and the corresponding B cell antigen peptides were quantified using specific tetramers staining and flow cytometry after 12 days In Vitro Stimulation (IVS) of PBMCs from patient #2.

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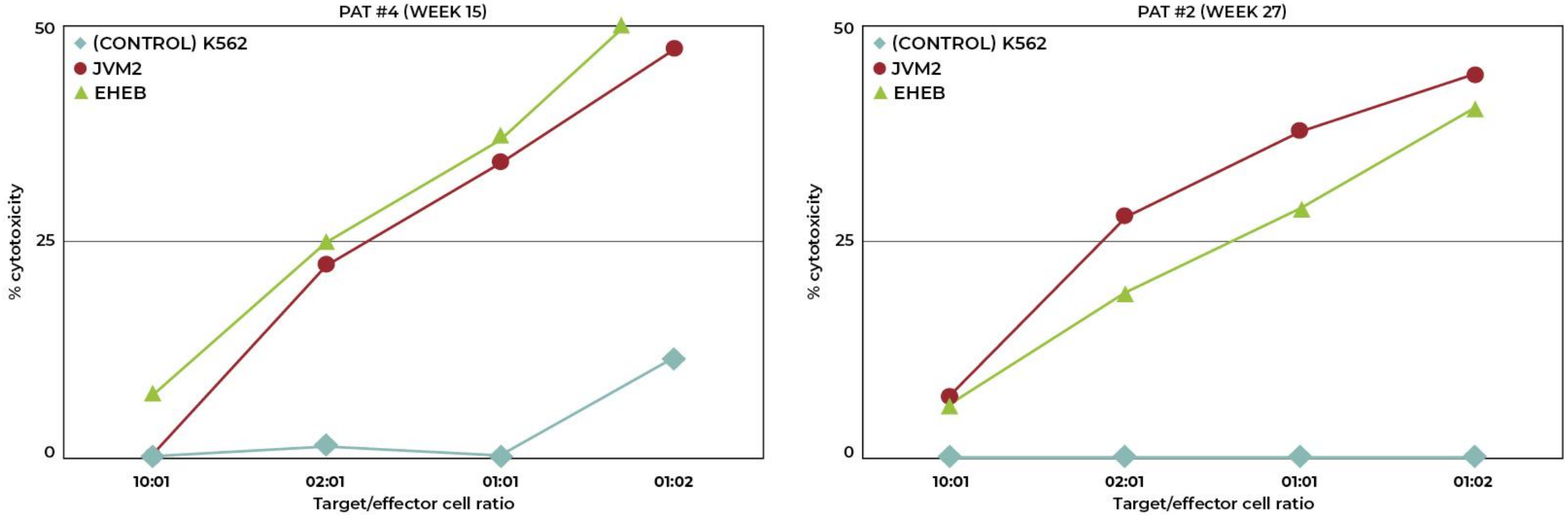
IMMUNE RESPONSE

FIGURE 3: Cytotoxicity against HLA-A2 cell lines.



CD8+ T cells were expanded from patient PBMCs ≥ 12 days by pool of 4 OncoMimic peptides, and then assessed for cytotoxicity against two B cell target-expressing HLA-A2 lymphoblastic cell lines (JVM2 and EHEB) and an MHC class I deficient cell line (K562 cells) at different target/effector cells ratio. Killing was evaluated using cytometry and cell death marker.

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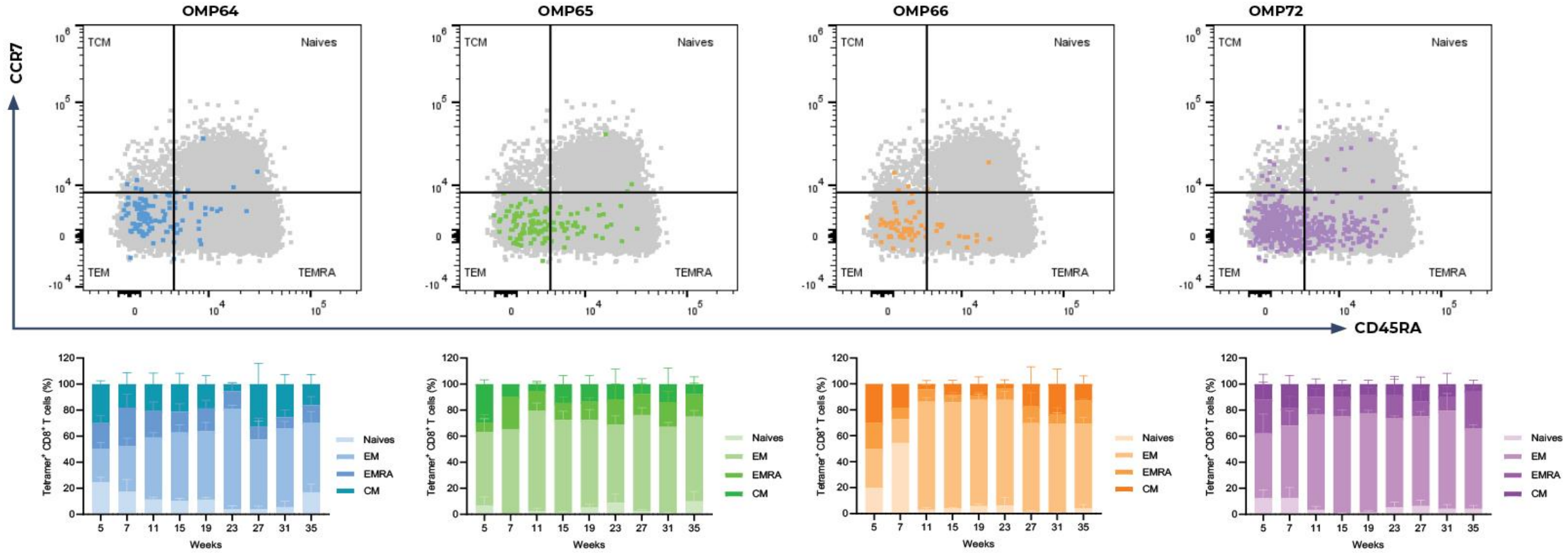
IMMUNE RESPONSE

FIGURE 4: EO2463 expanded CD8+ T cells have a memory phenotype.



CD8+ T cells specific for OncoMimics were quantified using specific tetramers staining and flow cytometry ex vivo, from one patient (upper part, patient #8, week 35), and from multiple timepoints (lower part, n=1-5 patients per timepoint). CM = central memory; EM = effector memory; EMRA = effector memory cells re-expressing CD45RA

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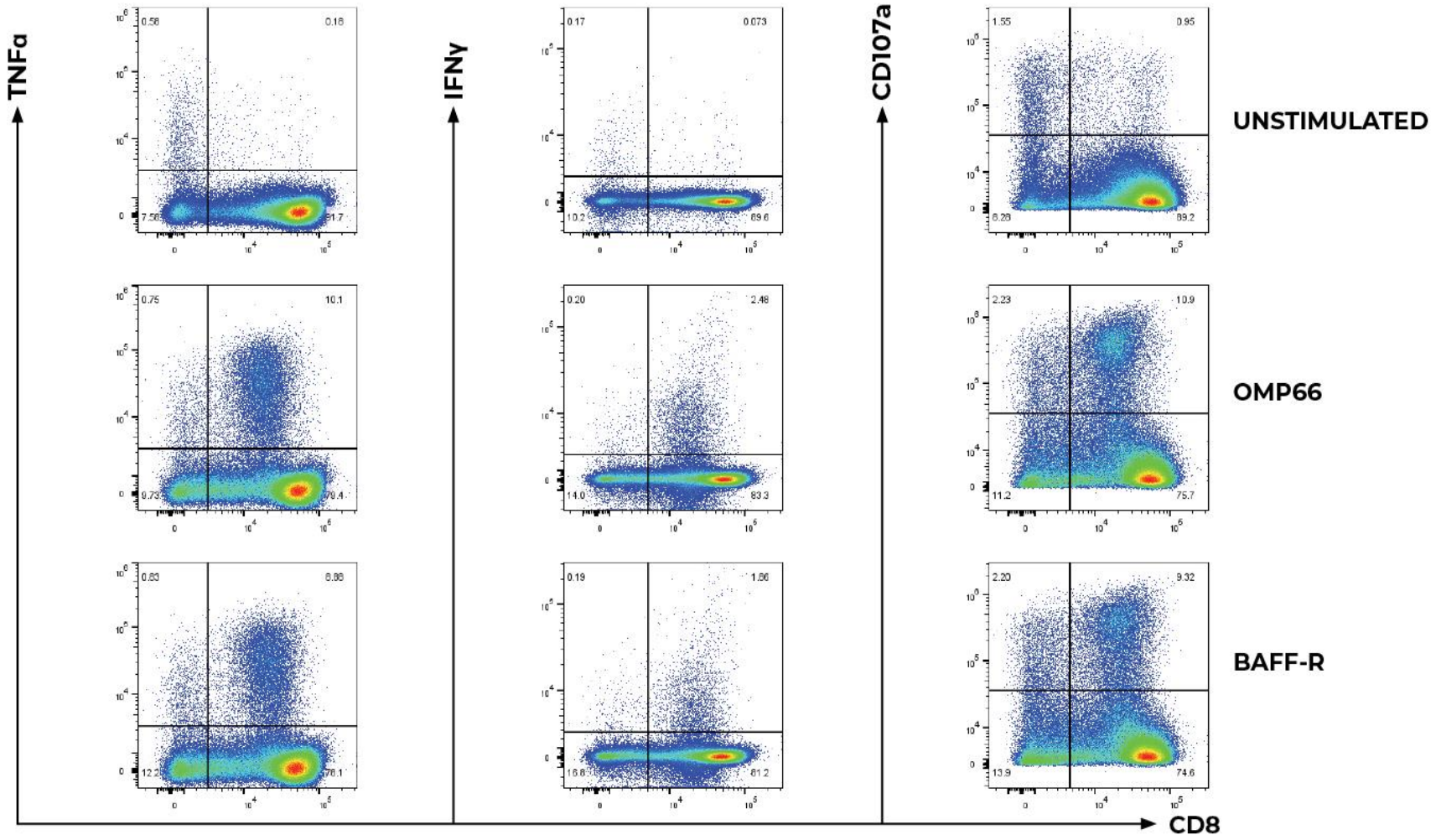
IMMUNE RESPONSE

FIGURE 5: Polyfunctionality of OncoMimics and B cell antigen specific CD8+ T cells (after IVS) from patient #2.

PBMC drawn 3 months after last study treatment. Polyfunctionality was assessed using intracellular cytokine staining and CD107 expression on CD3+ T cells.

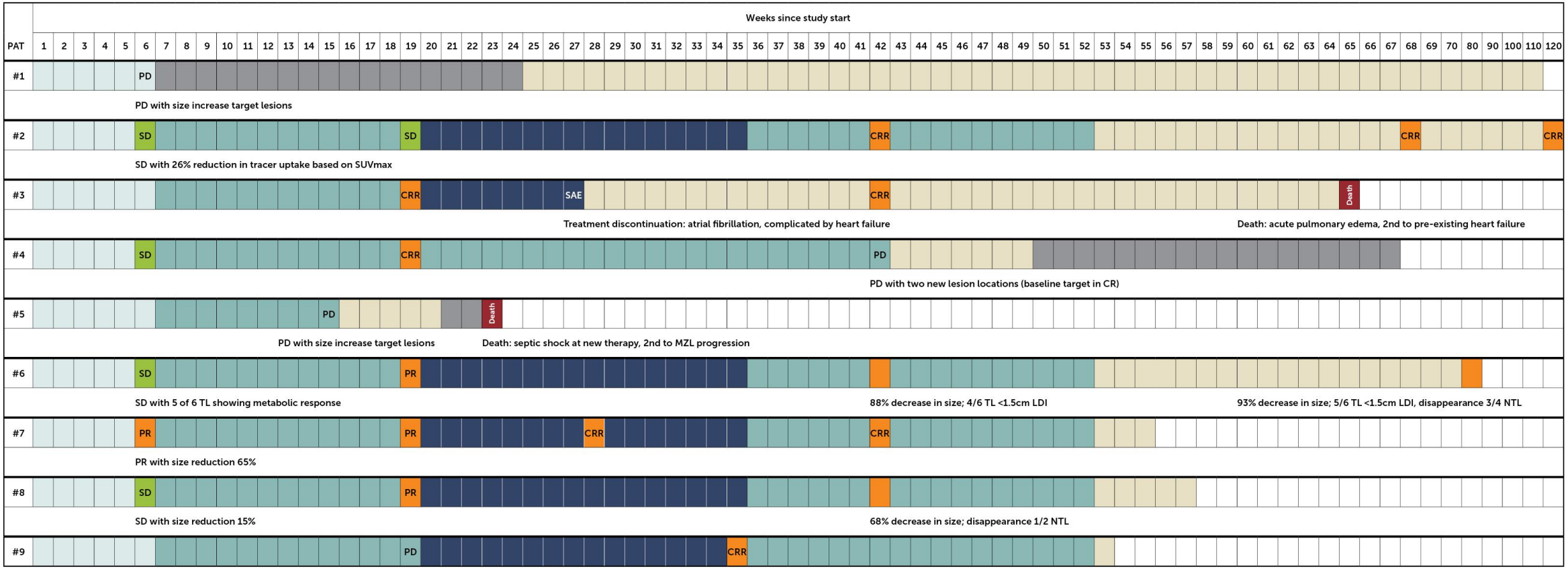


Phase 1/2 EONHL1-20/SIDNEY

CLINICAL OUTCOME

= EO2463 monotherapy = EO2463 + lenalidomide = EO2463 + lenalidomide + rituximab = follow-up = other anti-lymphoma treatment = complete/partial response = stable disease = Death

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



Response assessment per Lugano (2014) and Lyric Classification (2016) CMR = complete metabolic response; CRR = complete radiologic response; NTL = non-target lesion; TL = target lesion

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CLINICAL OUTCOME

TABLE 2: Baseline characteristics, EO2463 peptide dose, and response outcomes

Patient	Sex	Age	Tumor	Prior Therapy		EO2463 µg/pep	Best objective response		Baseline B-cell count	Immune response
				RT	Systemic		EO2463 mono	EL or ER[2] combo		
#1	M	80	FL	1	1	150ug	PD	NA	39	No
#2	F	55	FL	0	2	150ug	SD[a]	CRR (ER[2])	441	Yes
#3	F	73	FL	0	1	150ug	IR(3)	CRR (EL)	0	Yes
#4	M	53	FL	0	2	300ug	SD	CRR (EL)	0	Yes
#5	M	63	EMZL	0	4^	300ug	IR(3)	PD (EL)	1	No
#6	M	54	FL	0	1	300ug	SD[a]	CMR (ER[2])	10	Yes
#7	F	66	FL	1	1	300ug	PR[a]	CRR (ER[2])	ND	Yes
#8	M	55	NMZL	2	2	300ug	SD[a]	CMR (ER[2])	107	Yes
#9	M	50	FL	0	4^	300ug	IR(3)	CRR (ER[2])	0	No

^ prior therapy incl. CAR-T; a. metabolic/size reduction EO2463 monotherapy activity; b. see Table 1; CMR=complete metabolic response; CRR=complete radiologic response

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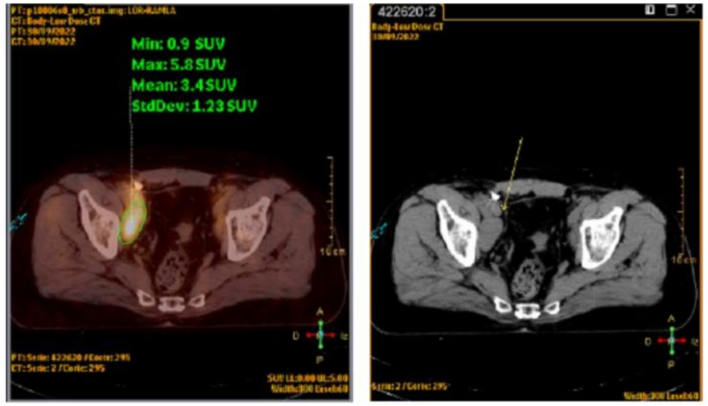
CLINICAL OUTCOME

PATIENT #6: Target lesion (TL) right iliac mass*

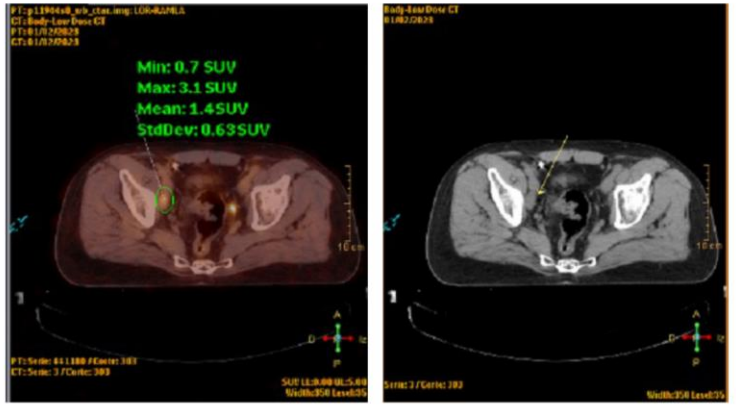
Baseline



Overall, 6 TL (43.91 cm2): BL 5PS=6x5

Right iliac TL: 4.5*2.6=11.70 / 5PS=5

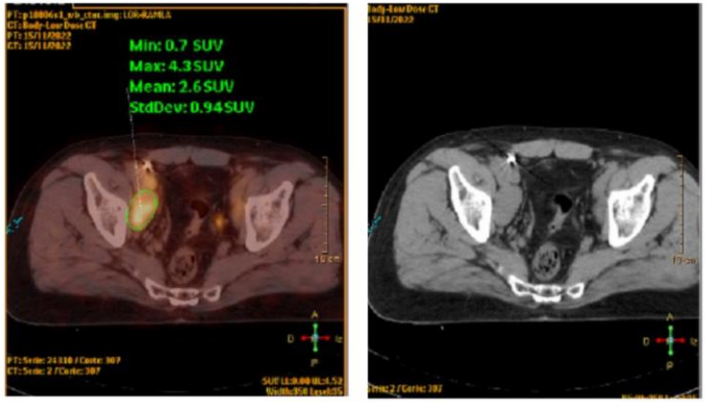
Week 19



Overall radiologic PR (-62%); 6/6 TLs metabolic response (5PS=4x1 / 1x2 / 1x4)

Right iliac TL: 2.4*1.3=3.12 / 5PS=4

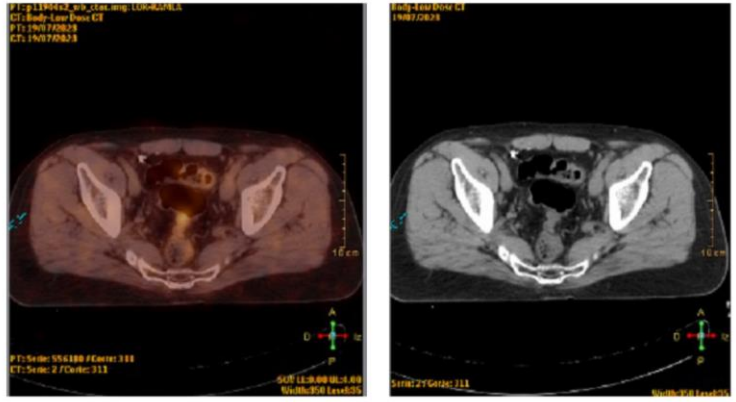
Week 6



Overall radiologic SD (0%); 5/6 TLs metabolic response (5PS=2x2 / 3x4 / 1x5)

Right iliac TL: 4.7*2.9=13.63 / 5PS=5

Week 42



Overall radiologic PR (-88%, 4 of 6 TL <1.5 cm LDi); 6/6 TLs metabolic response (5PS=6x1)

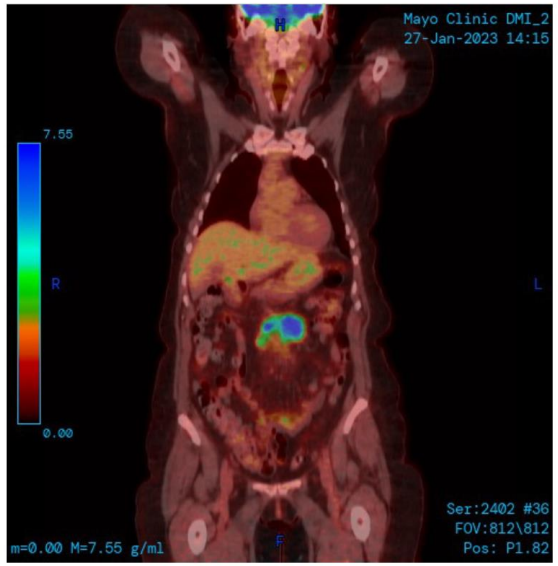
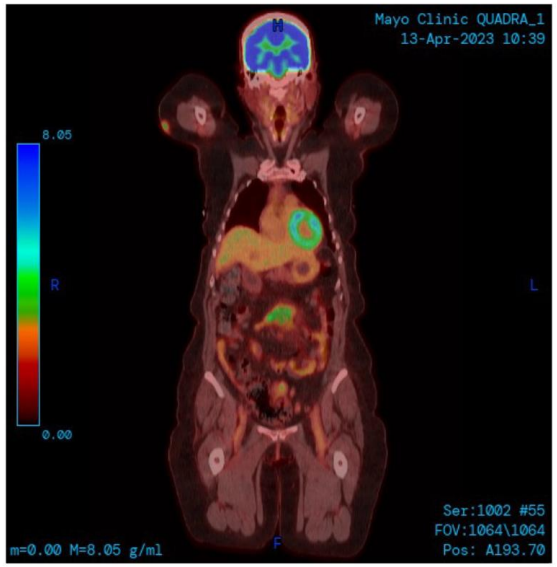
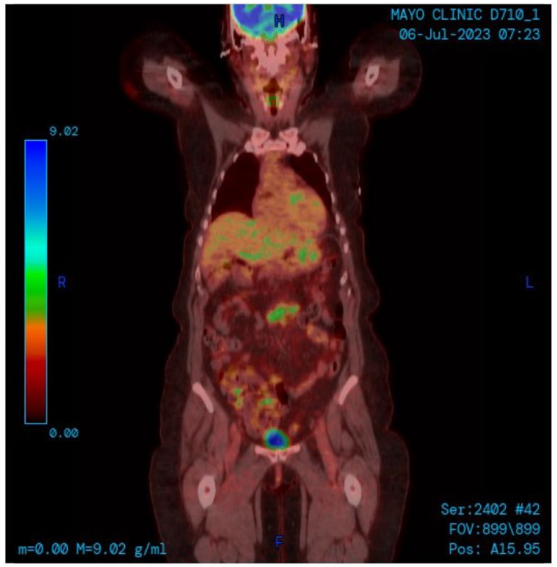
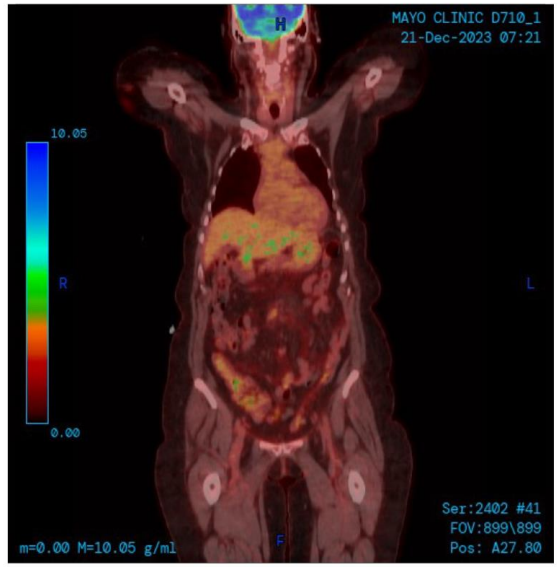
Right iliac TL: 1.4*0.7=0.98 / 5PS=1

* In addition, five further target lesions (axillary, interaortic, paracaval, mesenteric, obturator), and 4 non-target lesions.

Phase 1/2 EONHL1-20/SIDNEY

CLINICAL OUTCOME

PATIENT #7: Target lesions (TL) two mesenteric masses

Baseline	Week 6	Week 19	Week 42
			
Overall, 2 TL (12.78 cm^2), 5PS=2x4	Overall radiologic PR (-65%); 5PS=2x4	Overall radiologic PR (-67%); 5PS=2x4	Overall radiologic CR (-100%); 5PS=2x1

Phase 1/2 EONHL1-20/SIDNEY

CONCLUSIONS

- **EO2463 (300 µg/peptide) monotherapy, EL, and ER2 are well tolerated in patients with relapsed/refractory FL and MZL**
- **EO2463 generated fast, strong, and durable on-target immune activation with expansion of specific cytotoxic T cells with the ability to kill malignant HLA-A2 B cell lines in vitro**
- **Encouraging early clinical activity with EO2463 monotherapy; metabolic/size reduction in 4 of 9 (44%) patients already at 6 weeks**
- **At subsequent combination therapy (EL/ER2) 7 of 9 (78%) patients had a complete response (including 5 of 9 radiologic CR; 56%)**

- **Expansion cohorts are now investigating:**
  - EO2463 monotherapy; patients with newly diagnosed, previously untreated, FL/MZL not in need of standard available therapy (watch-and-wait setting)
  - EO2463 + rituximab (from w7-); patients with newly diagnosed, previously untreated, FL/MZL and low tumor burden, in need of therapy
  - EO2463 + lenalidomide (from w1-) + rituximab (from w19-); patients with relapsed/refractory FL/MZL, at least one prior treatment (no upper limit)

Thank you!

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For open sites see clinicaltrials.gov NCT04669171.