FPN: 162P

EO4010 (EO) + nivolumab (N) +/- bevacizumab (B) in patients (pts) with microsatellite stable (MSS) metastatic colorectal carcinoma (mCRC) EOCRC2-22/AUDREY

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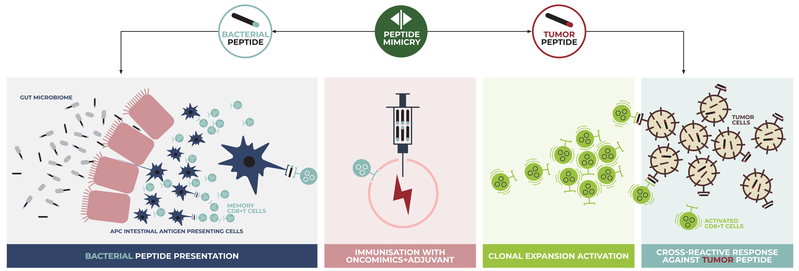
BACKGROUND

Immunotherapies display poor activity in mismatch repair proficient and microsatellite stable (pMMR/MSS) mCRC. Thus, novel therapeutic approaches are needed to enhance the treatment outcomes for patients with such disease types. EO4010 is designed to expand pre-existing memory CD8 T cells recognizing non-self protein sequences from gut bacteria which cross-react with tumor associated antigens (TAAs).
EO4010 is composed of five HLA-A2 synthetically produced epitopes which exhibit molecular mimicry with the TAAs BIRC5, FOXM1, UBE2C, CDC20 and KIF2C, upregulated in CRC, as well as a CD4 helper-epitope UCP2 derived from hTERT.



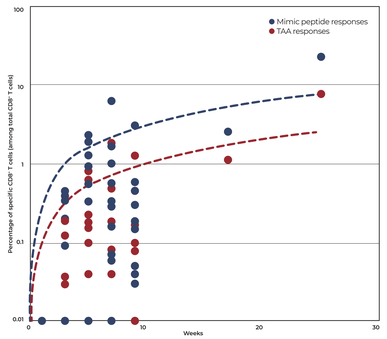
IMMUNE RESPONSE

Immune response against mimic peptides with sequences from gut bacteria was observed in 12 of 13 tested patients with cross-reactivity against at least one TAA demonstrated in the 12 positive patients.

Antigen-specific CD8+ T cells were effector memory with more than 80% of cells being either TEM or TEMRA, after week 5 of study treatment; EM = effector memory; EMRA = effector memory cells re-expressing CD45RA.

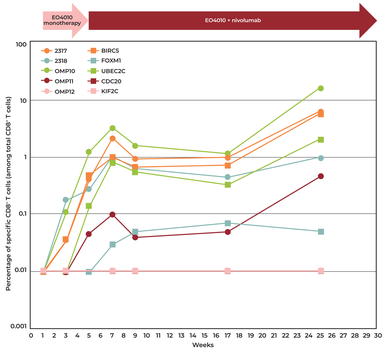
Functional activity of mimic and TAA specific CD8+ T cells was confirmed using IFNγ ELISPOT both ex vivo and after IVS at early (week 3) and late timepoints (week 25).

Figure 1. Percentage of specific CD8+ T cells for EO4010 peptides and tumor associated antigens assessed by ex vivo tetramer analysis.



All investigated available timepoints and patients' samples shown, sum of tetramer positive response for mimic peptides and TAA peptides, respectively. Note, only significative values are plotted on day 0, all other negative or non-significant value were set to 0.01, n=13 patients.

Figure 2. Long-term detection of specific CD8+ T cells after EO4010 administration.



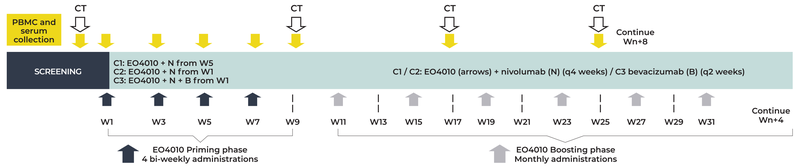
CD8+ T cells specific for mimic peptides and the corresponding TAA peptides were quantified using specific tetramers staining and flow cytometry after 12 days In Vitro Stimulation (IVS) of PBMCs from patient #3 treated in cohort 1.

METHODS

This is a phase 1/2 trial (NCT05589597) investigating EO4010 in patients with unresectable, pMMR/MSS mCRC, previously treated with, or not considered for, oxaliplatin, irinotecan, fluoropyrimidines and targeted therapies, and naïve to TAS-102 and regorafenib.

In Cohort 1 (safety lead-in) followed by expansion Cohort 2, patients received EO4010 (300 µg/peptide in Montanide ISA 51 VG subcutaneously; q2 weeks (w) x4 then q4w) + nivolumab (240 mg q2w x3 then 480 mg q4w; in Cohort 1 first 2 doses of nivolumab were omitted). In Cohort 3 bevacizumab 5mg/kg q2w was added to EO4010 + nivolumab. Treatment was given until toxicity, or tumor progression. The primary objective of the trial is to evaluate safety and tolerability of EO4010 in combination with nivolumab +/- bevacizumab in patients.

For the secondary objective, immunogenicity (quantification of CD8 T cells specific for the mimic peptides included in EO4010, i.e., EO2317, EO2318, OMP10, OMP11, and OMP12, and their TAA counterparts, i.e., BIRC5, KIF2C, FOXM1, UBE2C and CDC20), testing was performed on blood samples (initially cryopreserved PBMCs) either ex vivo, or after 12 days in vitro stimulation (IVS), using either peptide specific tetramers/flow cytometry, or IFN-γ secretion/ELISPOT after peptide stimulation.



EFFICACY

Cohort 2 (n=17):

- 1 partial response (PR) (**pat #15:** treatment ongoing > 36 weeks; mets liver -46%, mets lung -34%; CEA normalized)
- 2 stable disease (SD) (**pat #9:** treatment until week 11, stopped due to non-related myocardial infarction, death due to further conservatively treated infarctions, mets lung -7%, CEA -68%, CA19-9 -36%; **pat #16:** treatment 11 weeks before consent withdrawn (CW) for treatment, then later lost to follow-up)
- 14 progressive disease (PD), **including 6 patients (35% of cohort) with SD in target lesions but unequivocal progression in non-target lesions leading to termination of study treatment** (2 of the 6 patients had decreased CEA values; -16% and -19%)

Cohort 3 (n=5):

- 3 SD (**pat #3:** treatment ongoing >24 weeks; mets lung +8%, CEA normalized; **pat #2:** treatment 13 weeks; **pat #1:** treatment 8 weeks)
- 2 PD, both with progression in target lesions, i.e., **no patient with progression only in non-target lesions**

Figure 3. Cohort 2: patient #9

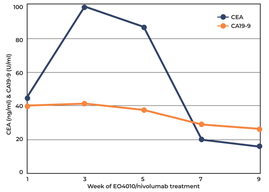
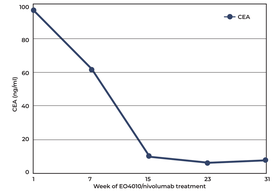
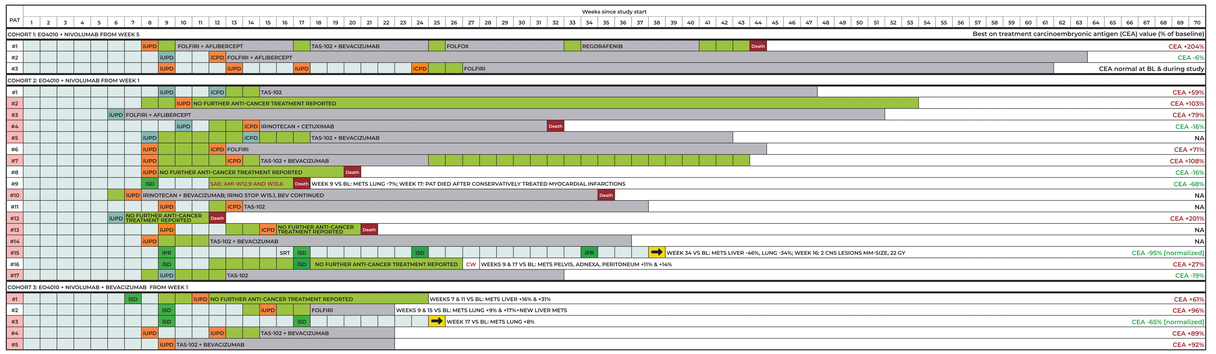


Figure 4. Cohort 2: patient #15



= Treatment = Follow-up = disease control = iUPD/iCPD ➡ = Treatment ongoing = Unequivocal PD non-target lesions = Baseline liver metastases = New anti cancer treatment = Death
CEA = Carcinoembryonic antigen; CW = consent withdrawal; SAE = serious adverse event; AMI = acute myocardial infarction; NA = not available; SRT = stereotactic radiotherapy



SAFETY

- Twenty-five patients (C1=3, C2=17, C3=5) started study treatment, and 2 patients have still ongoing treatment. Discontinuations of study treatment were due to progressive disease (PD; 21 patients), one death due to non-related myocardial infarction, and one withdrawn consent.
- Median treatment duration was 6 weeks (range 4-36); Median follow-up was 35 weeks (range 11-63)
- Most common (≥10% in total population) treatment emergent adverse events (TEAEs) irrespective of relationship were local administration site reaction (LASR) in 20 (80%), asthenia in 7 (28%), anemia in 6 (24%), fatigue in 5 (20%), transaminase elevations in 4 (16%), and diarrhea in 4 (16%) patients.
- Most common (≥10% in total population) TEAEs related to study treatment were local administration site reaction in 20 (80%), asthenia in 5 (20%), and fatigue in 3 (12%) patients.
- Seventeen (17) TEAEs Grade ≥ 3 were reported in 11 (44%) patients, among them 2 patients had 2 Grade ≥ 3 AEs (LASRs) related to study treatment. One patient died in a context of acute myocardial infarction, not related to study treatment. No further Grade ≥ 4 event was reported.

BASELINE CHARACTERISTICS

Baseline characteristics (n=25)		
Age [years]	median (min-max)	57.0 (38-80)
Gender [n(%)]	female / male	14 (56) / 11 (44)
ECOG [n(%)]	0 / 1 performance status	17 (68) / 8 (32)
Time since primary diagnosis [years]	median (min-max)	2.7 (0.9-7.8)
Primary tumor location [n(%)]	proximal / distal / rectum	7 (28) / 7 (28) / 11 (44)
Number of organs with metastases [n(%)]	1 / 2 / 3 organs	15 (60) / 7 (28) / 3 (12)
Liver metastases [n(%)]	present	15 (60)
Mismatch repair status [n(%)]	proficient	25 (100)
Microsatellite [n(%)]	stable / instable low	23 (92) / 2 (8)
KRAS [n(%)]	wildtype / mutation / unknown	9 (36) / 15 (60) / 1 (4)
NRAS [n(%)]	wildtype / mutation / unknown	15 (60) / 3 (12) / 7 (28)
HRAS [n(%)]	wildtype / mutation / unknown	12 (48) / 0 (0) / 13 (52)
Number of prior systemic lines of treatment for mCRC	median (min-max)	3 (1-5)
	1 line 2 lines 3 lines [n(%)] 4 lines 5 lines	2 (8) 9 (36) 7 (28) 4 (16) 3 (12

Note: patients #13 and #14 have mismatch repair proficient & microsatellite instable low status, all other patients have mismatch repair proficient & microsatellite stable status

CONCLUSIONS

- EO4010 + nivolumab +/- bevacizumab is well tolerated in patients with metastatic colorectal cancer.
- EO4010 generated rapid and robust expansions of mimic peptide and TAA specific memory CD8+ T cells detectable in peripheral blood after a single dose of EO4010 (week 3), and during prolonged time (currently tested until week 25 after start of treatment).
- Interesting preliminary efficacy seen on EO4010 + nivolumab treatment; including RECIST 1.1 objective response in liver metastases of mismatch repair proficient and microsatellite stable previously treated colorectal carcinoma.
- Adding bevacizumab to EO4010 + nivolumab might improve efficacy; further patient treatment and follow-up is needed.

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