Evaluation of safety, immunogenicity and preliminary efficacy of PolyPEPI1018 vaccine in subjects with metastatic colorectal cancer (mCRC) with a predictive biomarker

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Abstract

Background
This study evaluated the safety, tolerability, immunogenicity and initial efficacy of PolyPEPI1018 as an add-on to maintenance therapy in subjects with mCRC. PolyPEPI1018 peptide vaccine contains 12 unique epitopes derived from 7 conserved cancer antigens frequently expressed in mCRC. The predictive value of the novel *Personal EPItopes (PEPI)* test was also explored.

Methods
mCRC patients in first line setting received up to 3 doses of PolyPEPI1018 vaccine (0.2 mg/peptide) 12 weeks apart, just after the transition to maintenance therapy with fluoropyrimidine and bevacizumab. Vaccine-specific T cell responses were first predicted by PEPI test (using the patient's complete HLA genotype) then measured by ELISpot and Intracellular Cytokine Staining (ICS) after one cycle of vaccination. Tumor responses were evaluated by RECIST.

Results
Eleven patients were vaccinated with PolyPEPI1018. The vaccine was well tolerated; common adverse events were transient skin reactions and flu-like syndrome. No grade 3+ adverse events related to the vaccine occurred. Initial analysis of 8 patients after a single dose demonstrated that 100% of patients had CD4+ T cell response and 75% had CD8+ T cell responses against at least 3 antigens. Both CD8+ and CD4+ T cells were polyfunctional based on the secretion of multiple cytokines determined by *ex vivo* ICS. PEPI test correctly predicted ELISpot-measured CD8+ T cell responses (PPV = 65%, p = 0.049). Of the 5 patients who received at least 2 doses of the vaccine, 3 experienced Stable disease and 2 had unexpected tumor size reduction. Patients experiencing tumor shrinkage had higher number of predicted antigens than those without tumor response.

Conclusions
PolyPEPI1018 was safe, well-tolerated and induced unprecedented broad polyfunctional CRC-specific T cell responses, similar to personalized neoantigen vaccines. The candidate biomarker demonstrated high accuracy for the prediction of subject's vaccine-specific CD8+ T cell responses and indicated patient's clinical responses. Based on these encouraging results further development of the PolyPEPI1018 vaccine with companion diagnostic is planned.

PolyPEPI1018 Vaccine

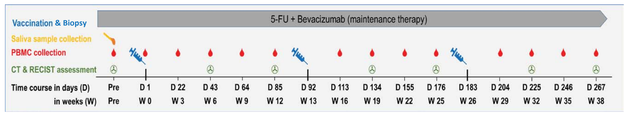
Vaccine:	6 long peptides containing 12 immunogenic "hot-spots" (PEPIs) of 7 Tumor-specific Antigens selected based on the HLA-genotype of subjects from a Model population*
Adjuvant:	Montanide ISA 51VG
Administration:	subcutaneous injection into 2 arms and 2 thighs
Dose:	0.2 mg / peptide

OBERTO-101 Trial Design: maintenance therapy + PolyPEPI1018

OBERTO-101 *(NCT 03391232)*
N=11

Part A
N=5
Single dose
12 weeks follow up
Safety, Tolerability, Immunogenicity

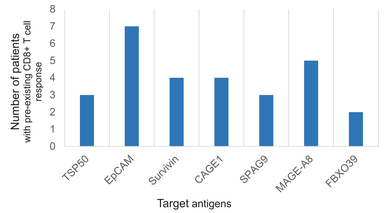
Part B
N=6
Multiple doses Q12W
38 weeks follow up
Safety, Tolerability, Immunogenicity, Preliminary efficacy



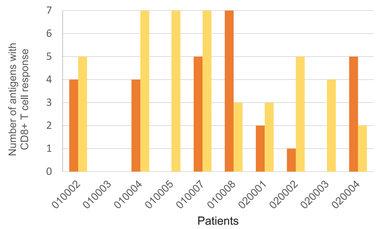
Treatment was safe and well tolerated. Transient local erythema and edema at the site of vaccination were observed as expected, as well as a flu-like syndrome with minor fever and fatigue. One SAE "possibly related" to the vaccine was recorded.

Broad CRC-specific T cell responses were elicited after vaccination

Patients with immunological responses	Percentage (n)
CD4+ T cell responses	100% (10/10)
CD8+ T cell responses	90% (9/10)
CD8+ T cell responses against **≥3 antigens**	80% (8/10)
Both CD8+ and CD4+ T cell responses	90% (9/10)
Ex vivo detected CD8+ T cell responses	89% (8/9)
Ex vivo detected CD4+ T cell responses	89% (8/9)



Pre-existing immune responses were detected against the vaccine antigens confirming the presence of the target antigen on the tumor surface (supporting the vaccine design).



PolyPEPI1018 vaccination restored (boosted) pre-existing immunity as well as induced *de novo* antigen-specific T cell responses against multiple antigens.

Agreement between predicted and measured immune responses

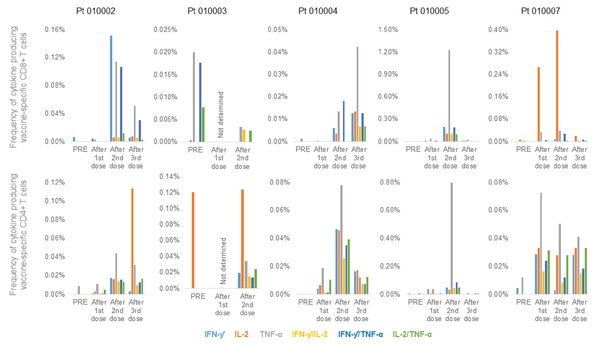
Patients' HLA class I genotype was determined from their saliva sample and served as input data for the prediction of PEPI-specific immune responses for each patient.

Immune responses by ELISpot were measured using 9mer test peptides of the 12 PEPIs.

PEPIs	10002 M	10002 P	10003 M	10003 P	10004 M	10004 P	10005 M	10005 P	10007 M	10007 P	10008 M	10008 P	20001 M	20001 P	20002 M	20002 P	20003 M	20003 P	20004 M	20004 P
Peptide 1A	-	-	-	-	-	-	-	-	+	-	+	+	+	+	+	-	-	-	+	+
Peptide 1B	-	-	-	-	+	-	-	-	+	+	+	-	-	-	+	-	+	+	+	-
Peptide 2A	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+
Peptide 2B	-	+	-	-	+	+	-	-	+	-	+	-	-	-	+	-	-	-	-	-
Peptide 3A	+	-	-	-	+	-	-	-	-	-	+	-	+	-	-	-	+	-	-	-
Peptide 3B	+	-	-	-	-	-	-	-	+	-	+	+	+	-	+	-	-	-	+	+
Peptide 6A	+	+	-	-	+	+	-	+	+	-	+	-	-	+	-	+	-	-	-	+
Peptide 6B	+	-	-	-	+	-	-	-	+	-	+	-	-	-	+	-	+	-	+	-
Peptide 7A	+	+	-	-	-	+	-	-	-	-	+	+	+	+	-	-	-	-	-	+
Peptide 7B	-	-	-	+	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	+
Peptide 8A	-	+	-	+	-	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+
Peptide 8B	-	-	-	+	-	-	-	-	+	+	+	-	-	-	+	+	-	+	+	-

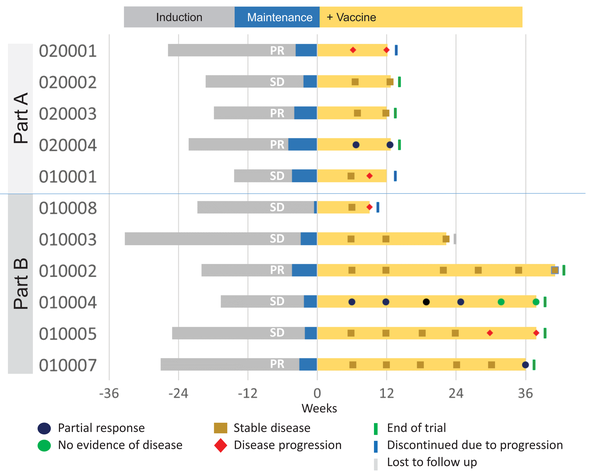
Positive Predictive Value: 68% **P<0.01 (Fisher exact test)** *M: measured, P: predicted*

Increased frequencies of circulating vaccine-specific T cells were detected in patients' blood, *ex vivo*



Durable treatment responses observed for MSS mCRC patients on maintenance therapy

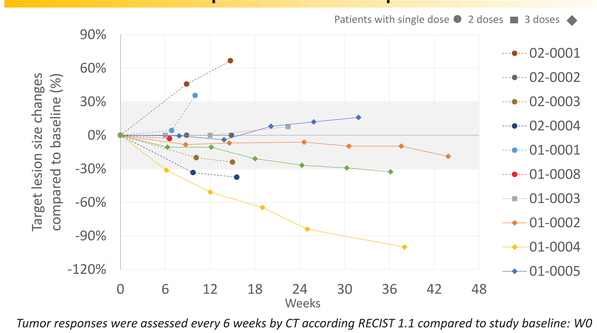
11 MSS mCRC patients were vaccinated with PolyPEPI1018 just after their transition to maintenance therapy with fluoropyrimidine and Bevacizumab.



Study	Dose(s)	ORR	DCR
Part A+B (n=11)	≥ 1	27%	72%
Part B (n=6)	≥ 2	33%	67%

ORR: Objective Response Rate; DCR: Disease Control Rate

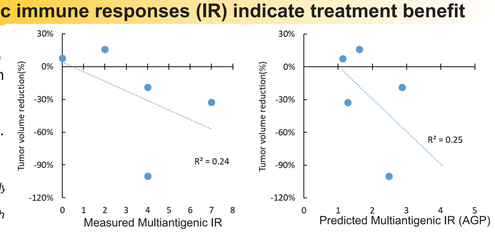
Continuous tumor responses observed upon vaccination



Tumor responses were assessed every 6 weeks by CT according RECIST 1.1 compared to study baseline: W0

Multiantigenic immune responses (IR) indicate treatment benefit

Tumor volume reduction tends to correlate with both predicted and measured multiantigenic IRs.



AGP = number of expressed antigens likely hit by antigen-specific immune responses on th patients' tumor.

Summary

Safe & Well tolerated

Shared tumor antigen-based vaccine is proven to be at least as immunogenic as mutated Neoantigen Vaccines – without tumor biopsy

- 100% of the tumor antigens targeted by the vaccine were expressed in the patients' tumor
- PolyPEPI1018 vaccination restored (boosted) pre-existing immunity as well as induced *de novo* antigen-specific T cell responses
- Multiantigenic immune responses exceed the ones observed with personalized neoantigen vaccines[#] (with CD8+ T cell responses against ≥3 antigens in 80% of patients)
- High frequencies of polyfunctional vaccine-specific T cells of both CD8+ and CD4+ type were detected *ex vivo*
- Patient-specific immune responses were correctly predicted - confirming previous findings that PEPI Test is able to predict subjects' antigen-specific immune responses*

Durable tumor responses indicate initial clinical efficacy in MSS mCRC patients

- Of the 11 vaccinated patients on maintenance therapy, 4 had progressed disease (PD), 4 had stable disease (SD) and 3 experienced unexpected partial tumor remission (PR)
- 3 out of 6 patients (Part B) control their disease for at least 10 months ➔ delay second line treatment
- patients experiencing tumor shrinkage had predicted and measured immune responses against higher number of vaccine antigens (candidate CDx)

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References: *Tőke et al. J Clin Oncol 37, 2019 (suppl; abstr e14295); *Lőrincz et al. J Clin Oncol 37, 2019 (suppl; abstr e14298) #Ott et al. Nat 547 (7662): 217-221, 2017; #Sahin et al. Nat 547 (7662): 222-226, 2017.

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