PolyPEPI1018 off-the shelf vaccine as add-on to maintenance therapy achieved durable treatment responses in patients with microsatellite-stable metastatic colorectal cancer patients

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Background

PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine against CRC, containing 12 immunogenic epitopes derived from 7 conserved cancer antigens frequently expressed in mCRC based on the analysis of 2,931 biopsies. Here we report the results of the phase I study of PolyPEPI1018 vaccine as an add-on to maintenance therapy in MSS mCRC patients.

Methods

11 patients with MSS mCRC in the first-line setting were vaccinated with PolyPEPI1018 just after the transition to maintenance therapy with a fluoropyrimidine and a targeted agent (bevacizumab). (Part A: n= 5, single dose, 12 weeks follow-up; Part B: n= 6, 3 doses, Q12W). Primary endpoints were safety and immunogenicity. Multiple analysis of vaccine-induced immune responses in blood and tumor were performed. Both immune response and clinical benefit were predicted using the autologous HLA-genotype determined from patient's saliva sample.

Results

The vaccine was well tolerated; most common side effects were transient skin reactions and flu-like syndrome. No vaccine-related SAE occurred. 90% of patients had vaccine-specific CD8+ T-cell responses of memory-effector type against at least 2 of the 7 vaccine antigens, 5 on average. Vaccine specific CD4+ T-cell responses were detected in all patients. Ex vivo CD8+ T cell responses of effector type were detected in 71% of patients, as well as increased fractions of CRC-reactive, polyfunctional, circulating CD8+ and CD4+ T cells in patient's PBMC after vaccination. Among the 11 patients 3 patients had objective tumor response according to RECIST v1.1, one of them received a single dose and 2 of them received 3 doses. For the Part B of the study, the Objective Response Rate (ORR) was 33% (2/6) and the Disease Control Rate (DCR) was 67% (4/6). Notably, one patient experienced complete tumor shrinkage on 2 of 3 target lesions and partial response on 1 lesion after 25 weeks of treatment, qualifying for curative surgery. Median duration of disease control was 9 months (95%CI 6.3-11.5) (mPFS not reached during the study). The 10 month PFS was 50% (3/6). Predicted vaccine antigen-specific CD8+ T cell responses were confirmed in vitro with a PPV of 79% (p=0.01). Predicted multiantigenic immune responses tend to correlate with both PFS and tumor volume reduction.

Conclusions

Treatment with PolyPEPI1018 vaccine and maintenance therapy was safe, well-tolerated, and demonstrated evidence of immunological and clinical activity in MSS mCRC tumors. In addition predicted multiantigenic immune responses indicated treatment benefit, which supports further development of a companion diagnostic together with the vaccine.

DESIGN OF THE POLYPEPI1018 VACCINE

- Target antigen selection based on expression frequency database of 2,391 CRC biopsies
- 7 cancer testis antigens (CTAs) were chosen that are tumor-specific and most frequently expressed
- Six 30aa long peptides, each contains two immunogenic 15mer fragments (2 immunogenic hotspots predicted for an HLA-genotyped Model Population)

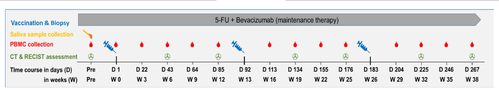
CTAs	Expression frequency based on 2,391 CRC biopsies
TSP50	89%
EpCAM	88%
Survivin	87%
CAGE1	74%
SPAG9	74%
MAGE-A8	44%
FBXO39	39%

OBERTO-101 TRIAL DESIGN

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



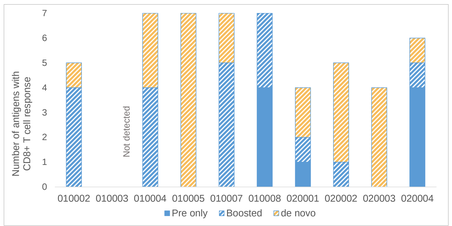
RESULTS: SAFETY AND IMMUNOGENICITY OF POLYPEPI1018 VACCINE

Vaccination was safe and well-tolerated

Patients were vaccinated with PolyPEPI1018 subcutaneously just after their transition to maintenance therapy with fluoropyrimidine and Bevacizumab. 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.

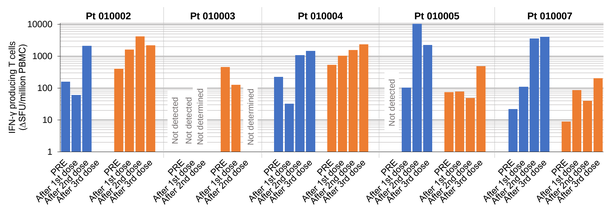
Patient	SAE	Relatedness
010001	Disease progression	Unrelated
010004	Embolism	Unlikely Related
010004	Abdominal pain	Unrelated
010007	Bowel Obstruction	Unrelated
020004	Non-Infectious Acute Encephalitis	Possibly Related

Peripheral immune responses: Broad and polyfunctional vaccine-induced circulating T cell responses in majority of patients

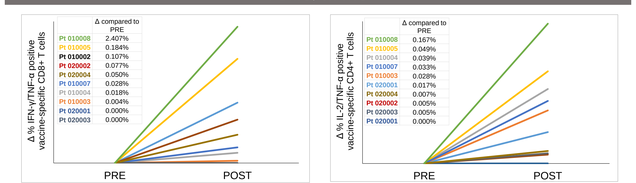


PolyPEPI1018 vaccination restored (boosted) pre-existing immunity as well as induced *de novo* antigen-specific T cell responses against multiple antigens

Repeated vaccinations increased the magnitude of immune responses



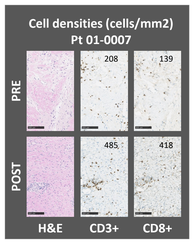
Increased frequencies of circulating vaccine-specific T cells were detected in patients' PBMC, ex vivo



Polyfunctional T cell responses of effector type were detected by both *Ex vivo* Intracellular Cytokine Staining and ELISpot assays

Ex vivo IFN-γ ELISpot	Percentage (n)
CD8+ T cell responses	89% (8/9)
CD4+ T cell responses	89% (8/9)

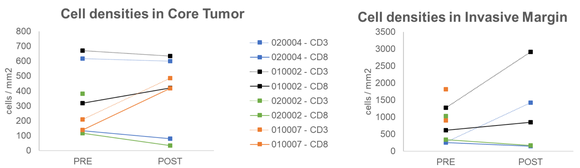
Immune responses at the tumor level
Accumulation of Cytotoxic T cells In the tumor following vaccination



HalioDx proprietary assay Immunoscore® CR TL (CD3/CD8) was performed for 4 patients' metastatic Liver biopsies to determine T cells infiltration in tumor (Core Tumor and Invasive Margin).

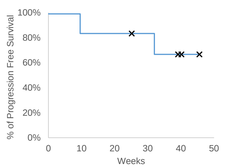
- Vaccination induced recruitment of tumor infiltrating lymphocytes (TILs) to the Invasive Margin and Core Tumor area for 3 out of 4 patients' tested.
- CD8+ cytotoxic T cells accumulated in the Core Tumor, for 2 patients experiencing clinical benefit post vaccination.

PRE: Tumor biopsy at baseline (except for Patient 010002, it is W12 sample)
POST: Tumor biopsy at W12 (Pt 020002 and 020004) or W38 (PT 010002 and 010007)



CLINICAL RESPONSES DETECTED AFTER 38 WEEKS FOLLOW-UP

Maintenance therapy combined with PolyPEPI1018 vaccine led to improved PFS for mCRC (MSS) patients



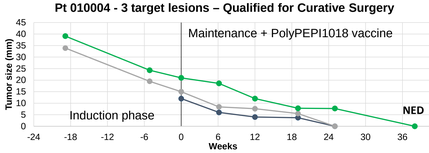
In the Part B of the study:

- 2 patients had progressed disease (PD),
- 2 patients had stable disease (SD) and
- 2 patients experienced partial tumor remission (PR) according to RECIST 1.1 criteria.
- 3 out of 6 patients control their disease for at least 10 months (end of study/censored data)
- 1 patient qualified for surgery

Study	OBERTO (Part B) Fluoropyrimidine + Bevacizumab + PolyPEPI1018
N=	6
Median PFS (m)	9 (95%CI 6.3-11.5) (Not reached)
10 Months PFS	50%
ORR (Objective Response Rate)	33%
DCR (Disease Control Rate)	67%

PFS = the time from the date of initiating maintenance therapy (study entry) to the date of first progression of disease (RECIST v1.1)

Pt 010004 - 3 target lesions – Qualified for Curative Surgery



Complete tumor shrinkage on 2 of 3 target lesions (Liver and Omentum) and partial response on 1 lesion after 25 weeks of treatment – removed by surgery.

NED = No Evidence of Disease

CORRELATION STUDIES

Patients' complete HLA-set predicts antigen-specific immune responses

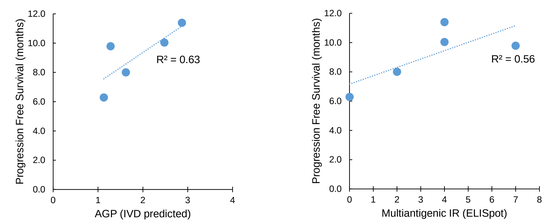
Patients' HLA class I genotype were determined from their saliva sample and served as input data for the prediction of vaccine antigen-specific immune responses for each patient.

Patient/AG	010002		010003		010004		010005		010007		010008		020001		020002		020003		020004	
	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred	Mea.	Pred
TSP50	-	-	-	-	+	-	-	-	+	+	+	+	+	+	+	-	+	+	+	+
EpCAM	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+
Survivin	+	+	-	-	+	+	-	-	+	-	+	-	-	-	+	-	+	-	+	-
MAGE-A8	+	-	-	-	-	-	-	-	+	-	+	+	+	-	+	-	-	-	+	+
CAGE1	+	+	-	-	+	+	-	+	+	-	+	+	+	+	-	+	-	-	-	+
SPAG9	-	-	-	+	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	+
FBXO39	-	+	-	+	-	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+
PPV	**79%**																			
NPV	**51%**																			
OPA	**64% (p=0.01)**																			

Mea: Measured by ELISpot using 9mer test peptides of the Personal epitopes (PEPIs);
Pred: PEPIs predicted for the specific vaccine antigen

Predicted tumor-directed multiantigenic immune responses indicate treatment benefit – candidate CDx

Both, higher predicted and measured multiantigenic immune response anticipated longer progression-free survival (not significant due to small sample size)



Tumor-directed immune response (predicted multiantigenic immune responses against likely expressed antigens)

CONCLUSIONS

- Vaccination was safe and well-tolerated
- Extensive analysis provided the complete chain of evidence for the vaccine's biologic activity *in vivo*:
  - antigen-specific immune responses are determined by the autologous HLA alleles,
  - peripheral immunogenicity revealed the antigen-specific T cell activation and the cytotoxic functionality for increased frequencies of circulating antigen-specific T cells
  - cytotoxic and helper T cells are recruited and are capable to enter the core tumor
  - increased densities of intratumoral and peritumoral CD3+ and CD8+ T cells transform the tumor into an inflamed, "hot" one
  - increased densities of TILs observed for patients with clinical benefit (tumor regression and longer PFS)
  - in contrast to chemotherapy, as we expected, vaccination had a slow but continuous anti-tumor activity which led to durable treatment effect (observed for patient's receiving multiple doses)
- Based on these encouraging results, the trial is being amended to enroll additional patients

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TREOS CANCER VACCINE TECHNOLOGY
www.treosbio.com

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