# #4048: Evaluation of safety, immunogenicity and preliminary efficacy of PolyPEPI1018 off-the-shelf vaccine with fluoropyrimidine/bevacizumab maintenance therapy in metastatic colorectal cancer (mCRC) patients

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## Background:

Colorectal cancer (CRC) is the 3rd leading cancer worldwide. Microsatellite stable (MSS) mCRC ("cold tumor") accounts for 96% of mCRC where checkpoint inhibitors (single agent/combination) have no meaningful activity.

PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine derived from 7 cancer testis antigens (CTAs) frequently expressed in patients with mCRC and administered with Montanide ISA51VG adjuvant. Six immunogenic peptide fragments were selected based on CTA–expression profile of 2,391 CRC biopsies, as well as shared personal epitopes (PEPIs) of subjects with different ethnicities in a Model Population.[1] Here we report the final results of the phase Ib study of PolyPEPI1018 vaccine as add-on to maintenance therapy in MSS mCRC.

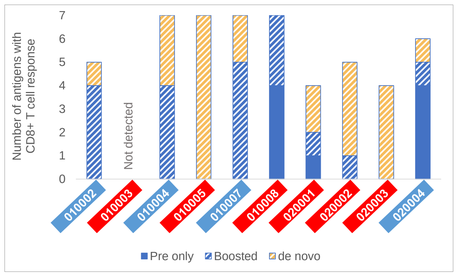
## Methods:

11 patients with MSS mCRC were vaccinated subcutaneously with PolyPEPI1018 just after their transition to maintenance therapy with fluoropyrimidine/bevacizumab after first-line combo chemotherapy and bevacizumab. Part A: n= 5, single dose; Part B: n= 6, 3 doses, Q12W. Primary endpoint was safety. Immunomonitoring was performed at both blood and tumor levels, as well as prospectively predicted. Objective responses were assessed by RECIST v1.1.

| Patient ID | BASELINE | | STUDY | | SAFETY | CLINICAL RESPONSE | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Disease | BOR at induction | Protocol | Doses received | Adverse Events (possibly or definitely related) | Objective response (RECIST v1.1) | Change in average tumor volume (vs baseline) | Weeks observed in trial | Weeks from maintenance (post-trial follow-up) |
| 010001 | BRAFwt/MSS | SD | Part A | 1 | - | PD | 36% | 12 | 13 |
| 020001 | BRAFwt/MSS | PR | | 1 | BURNING FEELING (G1) | PD | 67% | 12 | 9 |
| 020002 | BRAFwt/RASwt/MSS | SD | | 1 | BURNING FEELING (G1) | SD | 0% | 13 | 30 |
| 020003 | BRAFwt/KRASmut/MSS | PR | | 1 | - | SD | -24% | 12 | 33 |
| 020004 | BRAFwt/KRASG12D/MSS | PR | | 1 | NON-INFECTIOUS ACUTE ENCEPHALITIS (G3) Possibly related SAE | PR | -38% | 13 | 26 |
| 010002 | BRAFwt/KRASmut/MSS | PR | Part B | 3 | INJECTION SITE REACTION-SUBCUTANEOUS NODULES (G1); MYALGIA (G1) | SD | -19% | 41 | 53 |
| 010003 | BRAFwt/MSS | SD | | 2 | INJECTION SITE REACTION-RAISED ERYTHEMATOUS PATCHES (G1) | SD | 8% | 22 | 25 |
| 010004 | BRAFwt/KRASmut/pMMR | SD | | 3 | ANEMIA (G1); INJECTION SITE REACTION (G1) | PR | -84% | 38 | 55 |
| 010005 | BRAFwt/MSS | SD | | 3 | CONSTIPATION (G2); ARTHRALGIA (G1) | PD | 16% | 38 | 32 |
| 010007 | BRAFwt/RASwt/MSS | PR | | 3 | VOMITING (G1); SUPERFICIAL THROMBOPHLEBITIS (G2) | PR | -33% | 36 | >78 |
| 010008 | BRAFwt/MSS | SD | | 1 | ERYTHEMA (G2); FATIGUE (G2); ERYTHEMA MULTIFORME (G2) | PD | -3% | 9 | 9 |

**Patients with Durable Clinical Benefit (DCB):** **Patients achieving objective response and/or durable (>50 weeks) clinical benefit (n=4)**

## Robust immune responses against multiple tumor antigens




- 90% of patients had CD8+ T cell responses; 80% against at least 3 CRC-specific antigens. All patients had vaccine induced CD4+ T cell responses
- Repeated vaccinations increased the magnitude of T cell responses
- Patients' complete HLA-set correctly predicted antigen-specific immune responses (PPV=79%)[2]
- Increased frequencies of circulating vaccine-specific T cells were detected in patients' PBMC, *ex vivo*[2]

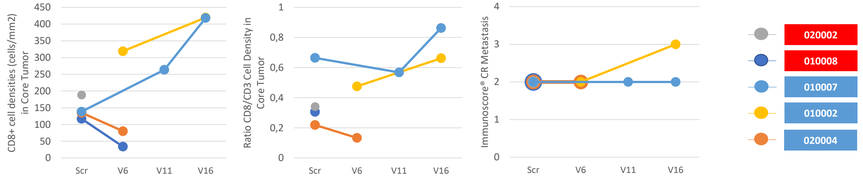
PolyPEPI1018 vaccination:

- ✓ restored (boosted) pre-existing immunity for 7/7 patients
- ✓ induced de novo antigen-specific T-cell responses against multiple antigens for 8/10 patients

Boost: mean number of spots after vaccination is at least 2 times higher compared to pre-vaccination, De novo: response is detected only after vaccination

## Turning immunologically "cold" tumor into "hot"

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

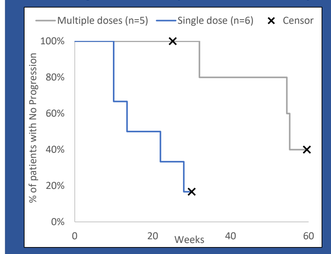



- Multiple doses of PolyPEPI1018 promotes infiltration of cytotoxic CD8+ TILs into the Core tumor (CT)
- Ratio of CD8/CD3+ T cells increases upon vaccination approaching almost 1
- High Immunoscore®CR* is obtained upon vaccination for 1 patient with clinical benefit; *High Immunoscore®CR describes a "hot" tumor, associated with response to immunotherapies[3]

References

[1]Hubbard et al. *J Clin Oncol* 2019; 37(15_suppl): 3557; [2]Hubbard et al. *J ImmunoTher Cancer* 2019; 7(1): 282.; [3]Galon&Bruni *Nat Rev Drug Discov* 2019; 18(3): 197-218.; [4]Ott et al. *Nat* 2017; 547(7662): 217-21.; [5]Sahin et al. *Nat* 2017; 547(7662): 222-6.; [6]Grothey et al. *Annal Oncol* 2018; 29(suppl_8).

## Maintenance therapy combined with multiple doses of PolyPEPI1018 led to objective responses and improved PFS for mCRC (MSS) patients




| Doses | ORR | DCR |
|---|---|---|
| 1 | 17% | 50% |
| ≥ 2 | 40% | 80% |
| Any | 27% | 64% |

ORR: Objective response rate; DCR: Disease control rate

HR: 0.23 [0.050, 1.094]
P=0.03
(not censored for curative surgery)

## Conclusions:

- Vaccination with PolyPEPI1018 was safe and well tolerated
- For 7 out of the 10 immune evaluable patients we found pre-existing immune responses against vaccine antigens confirming the expression of target CTAs on the surface of the tumors
- Patients with durable clinical benefit had low level but broad pre-existing anticancer immunity successfully boosted by PolyPEPI1018 at both peripheral and tumor level
- Anticancer immunity demonstrated to be HLA-genotype dependent – predicting also treatment benefit - AGP may be developed as CDx
- Multiantigenic CD8+ T cell responses detected for 80% of patients exceed immune response rates reported for personalized neoantigen vaccines[4,5]
- Three patients control their disease for at least 12 months delaying second line treatment; mPFS = 12.5 compares favorably to historical data obtained from MODUL trial with a recent relevant large cohort (n=148) (mPFS =7.39 months)[6]. Importantly, in this study, checkpoint inhibitor combined with the maintenance therapy did not improve mPFS, as well.

## Future directions:

Based on these encouraging results, PolyPEPI1018 with CDx is planned to be tested:

- In the same patient population in a randomized controlled study
- In late-stage patients as add-on to third-line therapy
- Given the boosting effect on the pre-existing immunity, there is a strong rational for combination of PolyPEPI1018 with checkpoint inhibitors

Acknowledgements

We would like to acknowledge the work of the clinical staff performing the study. We would also like to thank the contribution of patients and their families who participated in the study.

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## Correlative studies – Unleashing HLA-dependent anticancer immunity

Immune responses induced by PolyPEPI1018 at both peripheral and tumor level indicate tumor response

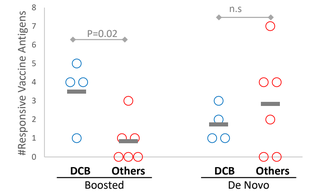
At peripheral level:

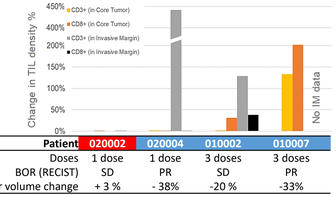
Patients with durable clinical benefit (DCB) had T cell responses boosted against higher number of tumor antigens.

At tumor level:

3/3 Patients with clinical benefit had increased T cell infiltration post-treatment

**Measured**



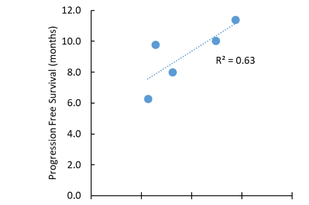



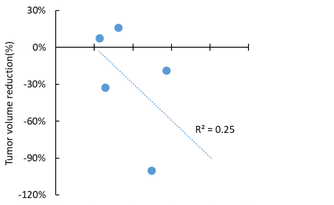

| Patient | 020002 | 020004 | 010002 | 010007 |
|---|---|---|---|---|
| Doses | 1 dose | 1 dose | 3 doses | 3 doses |
| BOR (RECIST) | SD | PR | SD | PR |
| Tumor volume change | + 3 % | - 38% | -20 % | -33% |

Boost: mean number of spots after vaccination is at least 2 times higher compared to pre-vaccination, De novo: response is detected only after vaccination

Patients with durable clinical benefit (DCB) had **HLA-predicted T cell responses against higher number of tumor antigens likely expressed on patients tumor (AGP).**

**Predicted**




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

## Clinical benefit – curative surgery:

2 patients qualified for curative surgery, 1 of them 27 weeks and the other 53 weeks after the first vaccination

| | Patient 010004 | Patient 010007 |
|---|---|---|
| **Disease** | adenocarcinoma of the cecum pMMR, KRAS mutant, BRAF wild type, mets to liver & omentum, mesentery | rectosigmoid adenocarcinoma, RAS/BRAF wild type, MSS, mets to liver, with lymphadenopathy – supraclavicular, axilla, mediastinum, hilum |
| **Induction** | FOLFOX, AVASTIN, CAPECITABINE, AVASTIN | FOLFOX + CETUXIMAB (ADDED AT CYCLE 2) |
| **BOR at induction** | SD | PR |
| **Doses received** | 3 | 3 |
| **Target lesions** | Liver, 2xOmentum (L Lateral Abdo&Anterior Abdo) | Liver |
| **BOR Maintenance+Vaccine** | **PR (2/3 lesions resolved to CR)** | **PR** |
| **Curative surgery: Pathological report** | Peritoneum active; Liver, mesentery negative for tumor; 8/29 lymph nodes are positive | Peritoneum, Liver, Mesentery, Sigmoid colon, Omentum are negative for tumor; 27/27 lymph nodes are negative |
| **Follow-up** | Recurrence approx. 6 months after last dose /surgery | No sign of recurrence as of today (2020 May), 78 weeks after first dose |