A Phase II, multicenter, open-label study of PolyPEPI1018 in combination with atezolizumab in participants with relapsed or refractory microsatellite-stable metastatic colorectal (MSS mCRC) cancer (Oberto-301): initial results

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Abstract

Background: The efficacy of checkpoint inhibitor immunotherapy in MSI-H mCRC has not been replicated in MSS mCRC. Therefore, additional interventions are needed to convert immunologically "cold" MSS CRC to "hot" tumors resembling MSI-H tumors. PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine containing 12 immunogenic epitopes derived from 7 cancer testis antigens which demonstrated early evidence of clinical activity, in first-line MSS mCRC[1].

Methods: Patients with MSS mCRC who have progressed on 2-3 lines of prior chemotherapy regimen received PolyPEPI1018 (1.2 mg, sc) and atezolizumab (1,200 mg, iv) Q3W. The primary endpoint was safety. A Simon 2-stage design was applied; data from the stage 1 of the study will be presented.

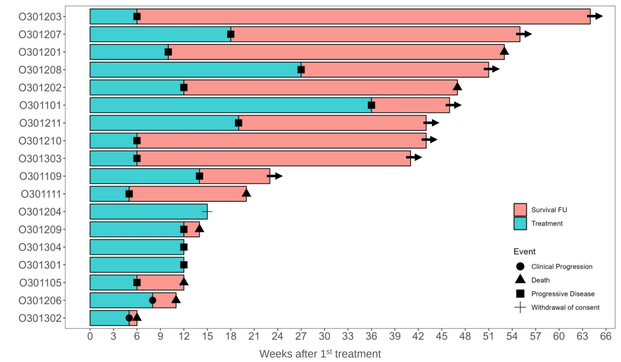
Results: 18 patients (77% female) were enrolled for stage 1 of the study. At baseline, median age was 55 years (range 38–79), 50% had liver metastases and 61% received at least 3 lines of prior therapies. PD-L1 expression was <1% for 85% of patients. The median number of doses received was 4 (range 2-10).

A formal review of safety was performed after the initial 6 participants received 2 cycles of study therapy. The combination was well-tolerated; most common side effect related to treatment was Grade (Gr) 1-2 local skin reaction (n=12). Gr 3 events (n=2) at least possibly related to treatment were nausea and vomiting. There were no Gr 4-5 events or study discontinuation due to treatment AE.

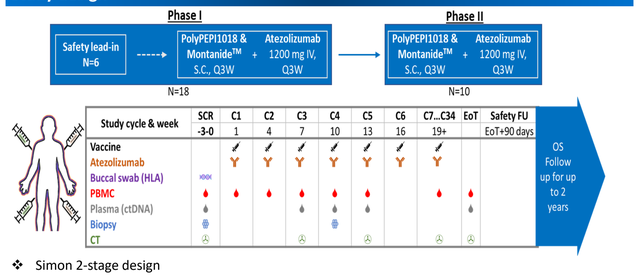
The ORR was 0% and the DCR was 68% (n=18). Post-treatment, vaccine-specific T cell responses were detected in the PBMC of 3/4 subjects tested and 3/5 patients had increased density of CD3+ and CD8+ TILs by up to 10-fold. The average PD-L1 expression (IC %) increased significantly after treatment (n=5; p=0.04), consequently 2/5 patients' tumor converted to high Immunoscore (Veracyte).

Conclusion: PolyPEPI1018 in combination with atezolizumab has a manageable safety profile. PolyPEPI1018 induced immunological responses at both peripheral and tumor level, converted "cold" tumor into "hot", although to date no responses per RECIST have been noted. The study is on-going.

Study status (N=18)



Study design



- Simon 2-stage design
- Vaccine administration to 4 anatomical sites (each dose)
- Continuous dosing until second confirmed PD

Key inclusion criteria

- Measureable MSS mCRC
- At least 2-3 prior lines of therapy for advanced or metastatic CRC
- Documented radiographic progression after the last regimen
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
- Adequate organ functions
- Has no major existing comorbidities

Primary Objectives

- Safety and tolerability of the combination

Secondary Objectives

- ORR per RECIST 1.1
- PFS
- OS
- Immune-related markers
- Change in TILs and PD-L1 in pre/post biopsies
- Clinical-marker correlations with HLA status

Progression Free Survival

Vaccine-specific peripheral T cell responses

***Ex vivo* IFN-γ FluoroSpot identified**

- 13/17 subjects with robust CD8+ and/or CD4+ T cell responses
- 7/15 subjects with CD8+ T cell responses detected with short 9mer peptide pools
- Spontaneous, pre-treatment responses

Polyfunctional T cell responses

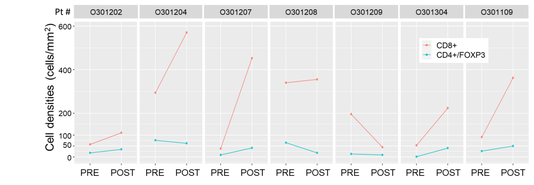
T cell responses were polyfunctional as detected by vaccine-specific IFN-γ, TNF-α and Granzyme B (GrB) cytokines produced, post-treatment

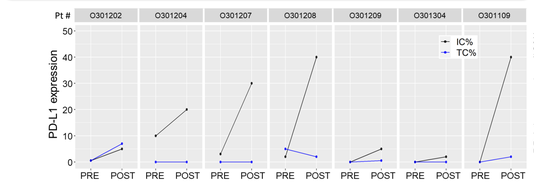
Number of subjects with responses		
CD8+	Cytokine	CD4+
7	IFN-γ+	11
5	GrB+	9
9	TNF-α+	4
5	IFN-γ+ & GrB+	8
7	IFN-γ+ & TNF-α+	3
5	GrB+ & TNF-α+	2
5	IFN-γ+ & GrB+ & TNF-α+	2

Turning Cold tumor to Hot

Immunogenicity at tumor level (pre- and post-treatment biopsies, IHC)

Significant increase of tumor- infiltrated CD8+ T cell density (IHC & Immunoscore)





Significant increase of expressed PD-L1 levels (IHC, Ventana SP263)

Conclusions

- Study did not proceed to Stage 2 - No objective responses by RECIST detected
- Treatment was safe and well-tolerated; no SAE related to treatment; most frequent side effects reported were local injection site reactions
- Vaccination induced robust immunological responses in majority of subjects-detected *ex vivo* in the patients' blood
- PolyPEPI1018 demonstrated activity at tumor level in turning "cold" tumor to "hot" evidenced by:
  - Significant increase in infiltrated CD8+ T cell levels for almost all patients
  - Significant increase in PD-L1 (IC%) levels for each patient (less in TC%)
  - Limited/no-change in CD4+/FOXP3+ T cell levels
  - Immune activity at tumor level confirmed also by Immunoscore CR & TL
- Consistent immune activity of PolyPEPI1018 observed across 3 clinical studies[1,2]
- Study is on-going for the collection of OS data

Baseline disease characteristics and demographics (N=18)

Anatomical Location n(%)	
Left Colon	2 (11.1)
Right Colon	1 (5.6)
Transverse Colon	3 (16.7)
Other	11 (61.1)
Missing	1 (5.6)
Mutation Type n(%)	
BRAF	3 (16.7)
KRAS	10 (55.6)
NRAS	2 (11.1)
RAS/RAF	1 (5.6)
WILD-TYPE	2 (11.1)
ECOG PS n(%)	
0	10 (55.6)
1	8 (44.4)

Baseline Lesions n(%)	
Abdomen	6 (33.3)
Groin	1 (5.6)
Left Ovarian Mass	1 (5.6)
Left Ovary	1 (5.6)
Left Pelvic Peritoneal	1 (5.6)
Liver	7 (38.9)
Lung	8 (44.4)
Lymph Node	4 (22.2)
Muscle/ Soft Tissue	1 (5.6)
Peritoneum	1 (5.6)
Presacral Nodes	1 (5.6)
Rectum	1 (5.6)
Stomach	1 (5.6)
Vaginal Cuff	1 (5.6)

MSI status n(%)	
Stable	18 (100.0)
Age at Screening (years)	
Mean (SD)	55.7 (11.40)
Median	54
Min, Max	38, 79
Sex at Birth n(%)	
Male	6 (33.3)
Female	12 (66.7)
Race n(%)	
Asian	1 (5.6)
African American	2 (11.1)
White	11 (61.1)
Other	2 (11.1)
Unknown	2 (11.1)

Adverse events related to treatment (N=18)

System Organ Class & Preferred Term	n (%)
Number of Participants with a TEAE	17 (94.4)
General disorders & administration site	16 (88.9)
Injection site reaction	12 (66.7)
Fatigue	8 (44.4)
Pyrexia	5 (27.8)
Chills	2 (11.1)
Chest pain	1 (5.6)
Influenza like illness	1 (5.6)
Injection site pain	1 (5.6)
Injection site rash	1 (5.6)
Oedema peripheral	1 (5.6)
Investigations: chemistry	4 (22.2)
Aspartate aminotransferase increase	2 (11.1)
Blood alkaline phosphatase increase	2 (11.1)
Lymphocyte count decreased	1 (5.6)
Metabolism & nutrition disorders	3 (16.7)
Decreased appetite	2 (11.1)
Hypokalaemia	1 (5.6)

System Organ Class & Preferred Term	n (%)
Gastrointestinal disorders	3 (16.7)
Nausea	3 (16.7)
Vomiting	3 (16.7)
Constipation	1 (5.6)
Skin & subcutaneous tissue disorders	3 (16.7)
Pruritus	1 (5.6)
Skin induration	1 (5.6)
Skin mass	1 (5.6)
Musculoskeletal & connective tissue	2 (11.1)
Pain in extremity	2 (11.1)
Nervous system disorders	2 (11.1)
Headache	2 (11.1)
Respiratory, thoracic & mediastinal dis.	2 (11.1)
Dyspnoea	2 (11.1)
Blood and lymphatic system disorders	1 (5.6)
Anaemia	1 (5.6)
Vascular disorders	1 (5.6)
Hot flush	1 (5.6)

Radiologic Tumor Responses (BOR)

ORR = 0%; DCR=61%

References

[1]Hubbard JM. CCR (2022) 28 (13); [2] Hubbard JM, ASCO 2023

DOI of the presenting author

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Collaborators and partners

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