#3595: PolyPEPI1018 vaccine in combination with TAS-102 in participants with late-stage microsatellite-stable metastatic colorectal cancer (MSS mCRC): A phase Ib study to evaluate safety, tolerability, immunogenicity and efficacy (OBERTO-201)

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BACKGROUND

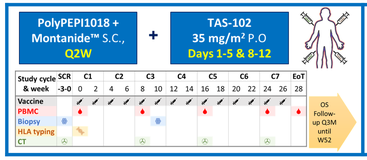
- MSS mCRC subjects do not benefit from checkpoint inhibitor immunotherapy; TAS-102 in combination with Nivolumab resulted in no improvement of PFS[1]
- PolyPEPI1018 is an off-the-shelf, multi-peptide vaccine containing 6 immunogenic peptides (30mers) derived from 7 tumor associated antigens frequently expressed in patients with CRC, administered with Montanide ISA51 VG adjuvant
- PolyPEPI1018 successfully induced anticancer immunity and triggered recruitment and infiltration of cytotoxic T cells into the tumor of MSS mCRC subjects demonstrating also early evidence of clinical activity, in first-line mCRC[2]
- Here we report the final results of the phase Ib study of PolyPEPI1018 vaccine plus TAS-102 in late-stage MSS mCRC patients.

Patient baseline characteristics (N=15)

RAS Status		***Primary Cancer Site***	
KRAS Mutant	11 (73.3%)	Colon, sigmoid	6 (40.0%)
NRAS Mutant	1 (6.7%)	Rectum	5 (33.3%)
Wildtype	2 (13.3%)	Other	2 (13.3%)
Unknown	1 (6.7%)	***Prior Treatment Regimens***	
BRAF Status		1	1 (6.7%)
Wildtype	14 (93.3%)	2	14 (93.3%)
Unknown	1 (6.7%)	***Liver Metastasis***	
Sex (F/M)	33% / 67%	No (NLM)	4 (26.7%)
Age (median)	*55 [31-71]*	Yes (LM)	11 (73.3%)
		***GPC / PPC**[4]*	6 (40.0%) / 9 (60.0%)

STUDY DESIGN

PolyPEPI1018 + Montanide™ S.C., Q2W + **TAS-102 35 mg/m² P.O Days 1-5 & 8-12**



- Metastatic CRC that is MSS (non-MSI-H)
- 2 prior lines of therapy for advanced/mCRC
- Measurable disease
- ECOG PS 0-1
- No Active Brain Mets

•Primary endpoint:
- Safety

•Secondary endpoints:
- PFS, ORR (per RECIST 1.1), OS
- Immune-related markers
- Change in TILs in pre/post biopsies
- Clinical-marker correlations with HLA status

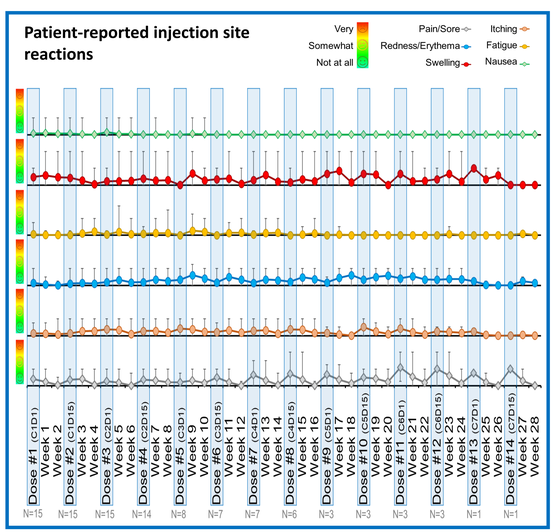
RESULTS

Safety and Tolerability

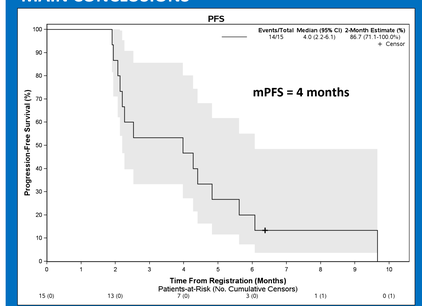
No SAEs leading to treatment interruption were noted; Frequent dosing of PolyPEPI1018 did not significantly increase the frequency of local reactions. Patient diaries of daily reported data support that vaccine administrations had in overall mild and transient reactions.

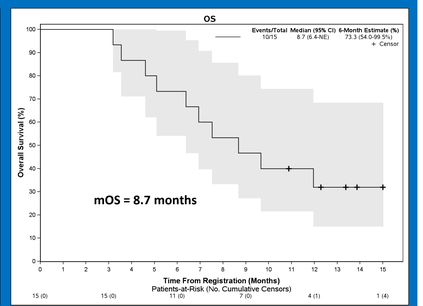
Adverse Events (at least possibly related to treatment)	Grade 2		Grade 3	
	N	%	N	%
Fatigue	5	33.3	3	20.0
Neutrophil count decreased	4	26.7	3	20.0
White blood cell decreased	5	33.3	1	6.7
Anemia	5	33.3		
Lymphocyte count decreased	1	6.7	3	20.0
Nausea	3	20.0	1	6.7
Diarrhea			2	13.3
Dysgeusia	2	13.3		
Anorexia	1	6.7		
Chills	1	6.7		
Dyspnea	1	6.7		
Fever	1	6.7		
Myalgia			1	6.7
Rash maculo-papular			1	6.7

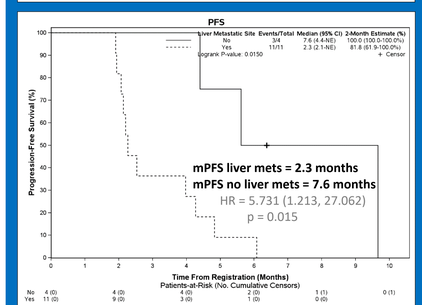
Patient-reported injection site reactions

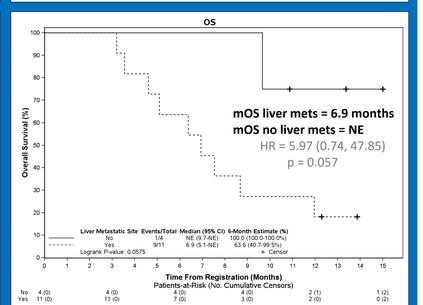


MAIN CONCLUSIONS





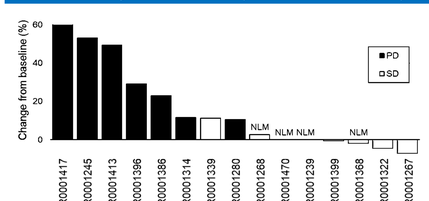




OBERTO-201:

- First study with promising results for TAS-102 in combination with an immunotherapy, in MSS mCRC
- Safe and tolerable combination
- Improved PFS and OS compared to TAS-102 alone historical data[3]
- Consistent immunological and clinical efficacy data
- Enhanced signal in patients without liver metastases, consistent with other IO data
- Despite small sample size, majority of the subjects in the study had factors indicative of poor prognosis (KRASmut and PPC*)
- PolyPEPI1018 activity in this study is consistent with previous clinical data[2]
- Combination warrants further testing, potentially supplemented also with bevacizumab (in light of recent SUNLIGHT and our Oberto-101 study data)[2,5]

**PPC - Poor Prognostic Characteristics for TAS-102 treatment, as defined by Tabernero et al[4]*



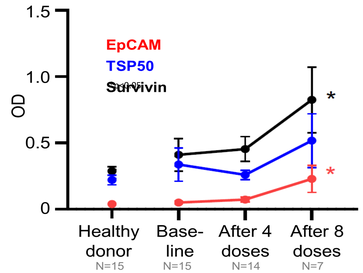
Response by RECIST v1.1 (BOR)	No liver mets (NLM) N=4	Liver mets N=11	All patients N=15
ORR	0%	0%	0%
DCR	100%	36%	53.3%

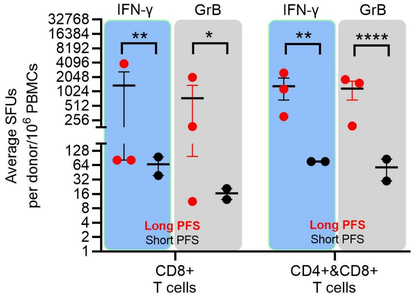
ORR: Objective Response Rate
DCR: Disease Control Rate
BOR: Best Overall Response

Patients with longer PFS had more robust vaccine-specific humoral and T cell responses

PolyPEPI1018 vaccination induced:

- Both CD8+ and CD4+ T cells in each patient as detected by *ex vivo* IFN-γ /GrB FluoroSpot (n=5)
- IgG antibody responses against 3 of the 7 target shared antigens as measured by ELISA (n=15)
- IgG antibody levels increased with multiple doses.

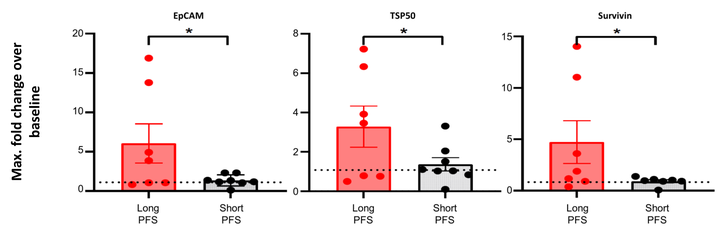




Patients with longer PFS (> 24 weeks) had:

- Increased number of CD8+ and CD4+ T cells
- Increased effector functionality (T cells secreted both IFN-γ and Granzyme B)
- Increased serum IgG antibody (for all 3 responsive antigens)
- Responded to higher number of vaccine antigens.

*p<0.05
**p<0.01
****p<0.0001



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