#147: Phase Ib open-label study to evaluate safety, tolerability, immunogenicity and efficacy of multiple subcutaneous injections of PolyPEPI1018 vaccine as an add-on immunotherapy to TAS-102 in participants with late-stage microsatellite-stable metastatic colorectal cancer (MSS mCRC) (OBERTO-201)

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Background / Rationale

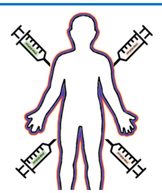
- Regorafenib and trifluridine/tipiracil (TAS-102) are treatment options for refractory mCRC as third-line therapy, with similar efficacy
- TAS-102 has statistically less toxicity of any grade compared with Regorafenib[1]
- MSS mCRC subjects do not benefit from checkpoint inhibitor immunotherapy; TAS-102 in combination with Nivolumab resulted in no improvement of PFS[2]
- 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[3]
- Here we report the initial results of the phase Ib study of PolyPEPI1018 vaccine plus TAS-102 in late-stage MSS mCRC patients.

Methods:

Patients with MSS mCRC who have progressed on ≤2 lines of prior chemotherapy regimen for mCRC received PolyPEPI1018 subcutaneously on days 1 and 15 and TAS-102 orally twice daily on days 1-5 and 8-15 of a 28-day cycle. Treatment continued for up to 7 cycles until disease progression or unacceptable toxicity. Blood and biopsies were collected for immunological assessments.

Study design

PolyPEPI1018 + Montanide™ S.C., Q2W + **TAS-102 35 mg/m² P.O Days 1-5 & 8-15**



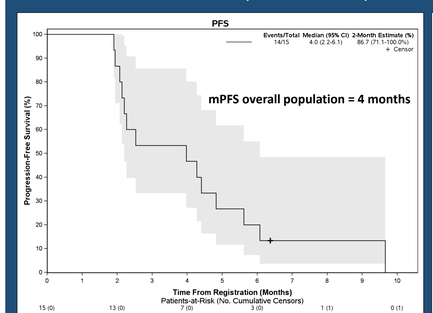
- Vaccination to 4 anatomical sites (each dose)
- Vaccination for 7 cycles or until PD
- OS follow-up for 1 year

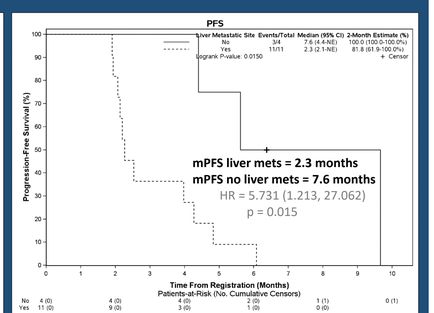
Key eligibility criteria:	Outcome measures:
• Metastatic CRC that is MSS (non-MSI-H) • Willing to undergo pre/post biopsies • 2 prior lines of therapy for advanced/mCRC • Measurable disease • ECOG PS 0-1 • No Active Brain Mets	**Primary endpoint:** • Safety **Secondary endpoints:** • PFS, ORR (per RECIST 1.1), OS • Immune-related markers • Change in TILs in pre/post biopsies • Clinical-marker correlations with HLA status

Patient 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 Met.**	
		N	4 (26.7%)
		Y	11 (73.3%)

Main conclusions

- PolyPEPI1018 in combination with TAS-102 is a novel regimen with clinical activity in non-liver MSS mCRC:
  - Robust immunological responses induced by multiple vaccine peptides for patients with longer PFS
  - Recruitment and infiltration of CD8+ T cells into the tumor
  - PolyPEPI1018 activity in combination with TAS-102 is consistent with previous clinical data obtained for combination with other chemotherapies[3]
  - mPFS = 7.6 months (95% CI 4.4 – NE)
  - OS = not fully mature (median follow up = 7.7 (95% CI 5.6 – NE) months)
  - DCR = 53% (patients with no-liver met controlled their tumor growth)
- Safety profile was similar to TAS-102 alone[4]
- Frequent dosing of PolyPEPI1018 to multiple injection sites was well-tolerated
- Limited to no clinical activity was noted in patients with liver metastatic disease





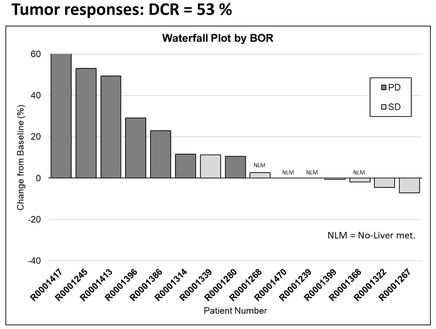
Results

No SAEs leading to treatment interruption were noted; Frequent dosing of PolyPEPI1018 did not significantly increase the frequency of local reactions

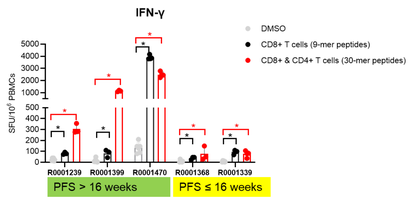
Treatment	Local reactions (max Grade)				
	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4
Cycle 1	7 (46.7%)	7 (46.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
All cycles	1 (6.7%)	9 (60.0%)	5 (33.3%)	0 (0.0%)	0 (0.0%)

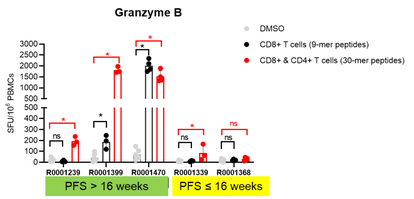
Adverse Events (at least possibly related to treatment)	Grade 2		Grade 3	
	N	%	N	%
Fatigue	5	33.3	3	20.0
Neutrophil count decreased	4	26.7	3	20.0
White blood cell decreased	5	33.3	1	6.7
Anemia	5	33.3		
Lymphocyte count decreased	1	6.7	3	20.0
Nausea	3	20.0	1	6.7
Diarrhea			2	13.3
Dysgeusia	2	13.3		
Anorexia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

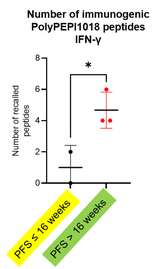
Tumor responses: DCR = 53 %

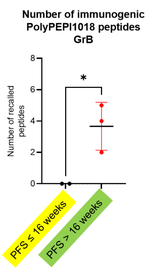


PolyPEPI1018 induced ex vivo detected effector T cell responses





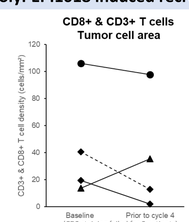


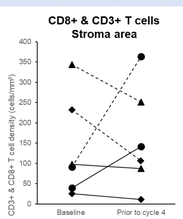


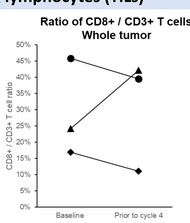
- PolyPEPI1018 vaccination induced both CD8+ and CD4+ T cells in each patient with available PBMC samples (n=5) as detected by ex vivo IFN-γ /GrB FluoroSpot
- Vaccine-specific CD8+ T cells have cytotoxic/effector functions
- **Patients with longer PFS (>16 weeks) had:**
  - Increased number of CD8 and CD4 T cells
  - Increased effector functionality (T cells secreted both IFN-γ and Granzyme B)
  - Responded to higher number of PolyPEPI1018 peptides (out of 6)

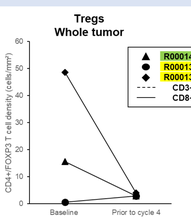
*p < 0.05

PolyPEPI1018 induced recruitment of tumor-infiltrating lymphocytes (TILs)









- Post-treatment recruitment of TILs into core tumor or stroma for 2/3 subjects as detected by Immunoscore CR TL®
- Increased density of CD8+ T cells post-treatment for patient with longer PFS
- No infiltration of Tregs after treatment

References

[1]Sonbol MB. Oncologist (2019) 24 (9)
[2]Patel MR. Cancer Med (2021) 10 (4)
[3]Hubbard JM. CCR (2022) 28 (13)
[4]Mayer RJ. NEJM (2015) 20 (372)

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