#TPS283: Trial in progress: 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)

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Abstract

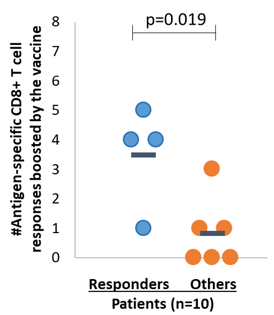
Background: Colorectal cancer (CRC) is among the top three most commonly occurring cancers globally. CRC is now routinely classified as MSI-high (MSI-H) or microsatellite-stable (MSS) based on the detection or absence of molecular markers of genetic instability, respectively. The efficacy of checkpoint inhibitor immunotherapy in MSI-H CRC has not been replicated in MSS CRC. 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 (CTAs) frequently expressed in patients with CRC. PolyPEPI1018 successfully restored and boosted pre-existing anticancer immunity of MSS mCRC subjects and triggered recruitment and infiltration of cytotoxic T cells into the tumor. In first line metastatic MSS CRC, PolyPEPI1018 in combination with fluoropyrimidine/bevacizumab vaccine was safe and demonstrated early evidence of clinical activity[1]. Therefore, we hypothesized that the combination of PolyPEPI1018 and atezolizumab will convert a "cold" MSS mCRC to a "hot" tumor and may increase the likelihood of inducing favorable antitumor immunity and subsequent clinical benefit.

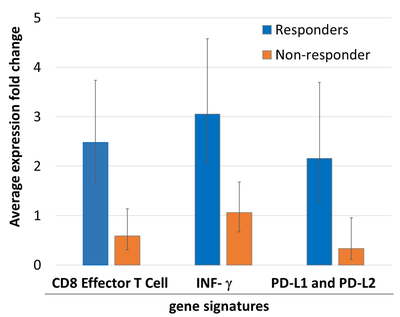
Methods: The study is a phase 2, multicenter, single-arm clinical trial of PolyPEPI1018 vaccine (1.2 mg, sc, every 3 weeks) and atezolizumab (1200 mg, iv, every 3 weeks) for patients with advanced or metastatic MSS CRC who have progressed on 2 or 3 lines of prior standard regimens. 28 patients will be enrolled at 3 US sites with a primary objective to assess the safety and tolerability of multiple doses of PolyPEPI1018 in combination with atezolizumab. Secondary endpoints include objective response rate (ORR) assessed by RECIST v1.1, vaccine induced immunological response rate (IRR), progression-free survival and overall survival. Correlative aims include assessing blood and tissue biomarkers (PD-L1, Immunoscore®IC, ctDNA, clinical tumor markers) for association with clinical benefit. An exploratory study is being conducted for co-development of a companion diagnostic based on HLA-genotype and computational personal epitope (PEPI) prediction test. A Simon 2-stage design will be used for the initial assessment of ORR. If pre-specified activity goal for the first stage of accrual (n=18) is met, additional 10 participants will be enrolled to the second stage. A formal review of safety will be performed after the initial 6 participants have received at least 2 cycles of study therapy. The study is open with 10 patients enrolled at time of submission.

Rationale

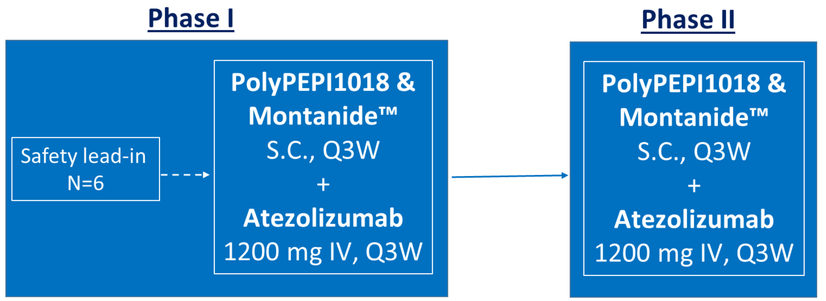
In a previous study conducted in MSS mCRC subjects on first-line maintenance treatment, PolyPEPI1018 vaccination[1]:

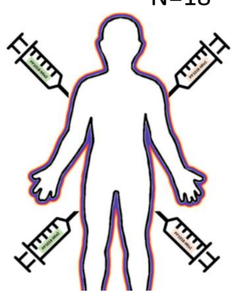
- restored and boosted spontaneous, HLA-dependent antitumor immunity driving clinical benefit,
- increased the frequency of cytotoxic tumor-infiltrating lymphocytes (TILs),
- upregulated PD-L1 expression (RNA) suggesting a potential synergy with atezolizumab as enhancer of antitumor immunity would result in subsequent clinical benefit.





Study design





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

Study cycle & week	SCR -3-0	C1 1	C2 4	C3 7	C4 10	C5 13	C6 16	C7…C34 19+	EoT	Safety FU EoT +90 days
Vaccine		✓	✓	✓	✓	✓	✓	✓		
Atezolizumab		Y	Y	Y	Y	Y	Y	Y		
Buccal swab (HLA)		⧖								
PBMC	♦	♦	♦	♦	♦	♦		♦	♦	
Plasma (ctDNA)	♠			♠	♠	♠			♠	
Biopsy	❁				❁					
CT	✇			✇		✇		✇	✇	

OS Follow up for up to 2 years

Enrollment criteria

Key inclusion criteria

- Measureable 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

Key exclusion criteria

- MSI high CRC
- Prior treatment with any Checkpoint inhibitor
- Prior anticancer therapy or live vaccine within 28 days
- History of autoimmune disease
- Known, active CNS metastases
- Significant liver cirrhosis
- Active HIV or HBV or HCV infection
- History of myocarditis or other cardiovascular disease, or chronic respiratory disease

Planned study duration

First subject was dosed in June 2022. Planned primary completion date is June 2024.

Objectives

Primary Objectives

- To evaluate the safety and tolerability of multiple doses of PolyPEPI1018 administered every-3-weeks in combination with atezolizumab in MSS CRC

Secondary Objectives

- To evaluate objective response rate (ORR) as assessed by the investigator using RECIST 1.1
- To evaluate the duration of response (DoR)
- To evaluate progression-free survival (PFS) as assessed by the investigator
- To evaluate overall survival (OS)
- To identify Personal EPItopes (PEPIs) based on HLA-genotype likely capable of inducing T cell responses
- To evaluate induction of immune responses against vaccine-specific tumor antigens

Exploratory Objectives

- To explore correlations between clinical activity (ORR, PFS, OS, DoR), immune response indicators, PDL1 status and other indicators of antitumor activity (e.g. clinical tumor markers or ctDNA)
- To explore PEPIs (HLA-genotype) as candidate CDx

References

[1]Hubbard JM. CCR (2022) 28 (13)

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