Evaluation of safety, immunogenicity and preliminary efficacy of PolyPEPI1018 vaccine in subjects with metastatic colorectal cancer (mCRC) with a predictive biomarker

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Abstract

Background: This study evaluated the safety, tolerability, immunogenicity and initial efficacy of PolyPEPI1018 as an addition to maintenance therapy in subjects with mCRC. PolyPEPI1018 peptide vaccine containing 12 unique epitopes derived from 7 cancer-specific antigens frequently expressed in mCRC. The predictive value of the novel Personal EpiTopes (PEPIs) test was also explored.

Methods:

- mCRC patients in first line setting received up to 3 doses of PolyPEPI1018 vaccine (0.2 mg/peptide) 12 weeks apart, just after transition to maintenance therapy with fluoropyrimidine and bevacizumab. Vaccine-specific T-cell responses were first predicted by PEPI test (using the patient's complete HLA genotypes) then measured by ELISPOT and intracellular Tumor Staining (ICT) after one cycle of vaccination. Tumor responses were evaluated by RECIST.

Results:

- Eleven patients were vaccinated with PolyPEPI1018. The vaccine was well-tolerated; common adverse events were transient skin reactions and flu-like syndrome. No serious adverse events related to the vaccine occurred. Initial analysis of 8 patients after a single dose demonstrated that 100% of patients had CD4+ T-cell response and 75% had CD8+ T-cell responses against at least 3 antigens. Both CD4+ and CD8+ T-cell responses were polyfunctional by the secretion of multiple cytokines determined by ex vivo ICST. PEPI test correctly predicted ELISPOT-measured CD8+ T-cell responses (PPV = 85%, p = 0.049). Of the 5 patients who received at least 2 doses of the vaccine, 3 experienced Stable Disease and 2 had unexpected tumor size reduction. Patients experiencing tumor shrinkage had higher number of predicted antigens than those without tumor response.

Conclusions:

- PolyPEPI1018 was safe, well-tolerated and induced unprecedented broad polyfunctional CRC-specific T-cell responses, similar to personalized neoantigen vaccines. The candidate biomarker demonstrated high accuracy for the prediction of subject's vaccine-specific CD8+ T-cell responses and further development of the PolyPEPI1018 vaccine with companion diagnostic is planned.

PolyPEPI1018 Vaccine

- Vaccine: 6 long peptides containing 12 immunogenic "hot-spots" (PEPIs) of 7 Tumor-specific Antigens selected based on the HLA-genotype of subjects from a clinical population.
- Adjunct: Mestinase (SA51VG)
- Administration: subcutaneous injection into 2 arms and 2 thighs
- Dose: 0.2 mg/peptide

OBERTO-101 Trial Design: maintenance therapy + PolyPEPI1018

- OBERTO-101 (NCT 03391222) No=11

Broad CRC-specific T cell responses were elicited after vaccination

- Patients with immunological responses:
  - CD8+ T-cell responses: 90% (9/10)
  - CD4+ T-cell responses against 23 antigens: 80% (8/10)
  - Both CD8+ and CD4+ T-cell responses: 90% (8/9)
- Ex vivo detected CD8+ T-cell responses: 85% (9/9)

Increased frequencies of circulating vaccine-specific T cells were detected in patients' blood, ex vivo

- Pre-existing immune responses were cross-reactive against the vaccine antigens confirming this peptide vaccine induced the targeted antigen on the tumor surface (supporting the vaccine design).

Durable treatment responses observed for MSS mCRC patients on PolyPEPI1018 vaccination

- 11 MSS mCRC patients were vaccinated with PolyPEPI1018 just after their transition to maintenance therapy with fluoropyrimidine and Bevacizumab.

- 3 out of 6 patients (Part B) control their disease for at least 10 months
- Of the 11 vaccinated patients on maintenance therapy, 4 had progressed disease (PD), 4 had stable disease (SD) and 3 experienced unexpected partial tumor remission (PR)
- PolyPEPI1018 vaccination restored (boosted) pre-existing immunity as well as induced novel antigen-specific T cell responses against multiple antigens.
- Polypeptide-specific immune responses were correctly predicted - confirming previous findings - that is able to predict subject's antigen-specific immune responses.

Continuous tumor responses observed upon vaccination

- Tumor volume reduction tended to correlate with both measured and predicted immunogenicity.

Multiimmunogenic immune responses (IR) indicate treatment benefit

- 100% of the Tumor antigens targeted by the vaccine were expressed in the patients' tumor
- PolyPEPI1018 vaccination restored (boosted) pre-existing immunity as well as induced novel antigen-specific T-cell responses.
- Multiimmunogenic immune responses exceed the ones observed with personalized neoantigen vaccines
- High frequencies of polyfunctional vaccine-specific T cells of both CD8+ and CD4+ type were detected.
- Patient-specific immune responses were correctly predicted - confirming previous findings - that is able to predict subject's antigen-specific immune responses.

Durable tumor responses indicate initial clinical efficacy in MSS mCRC patients

- The 30 vaccinated patients on maintenance therapy, had progressed disease at time of study entry, 4 had stable disease (SD) and 3 experienced unexpected partial tumor remission (PR) 3 of 30 patients (10%) control their disease for at least 10 months. 4 patients had second line treatment.

References:


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