Vaccination of MSI-H colorectal cancer patients with frameshift peptide antigens – a phase I/IIa clinical trial
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Background
Colorectal cancer is a heterogeneous tumor type. Whereas the majority of colorectal cancers show chromosomal instability, a subset of about 15% of colorectal cancers (CRC) have a deficient DNA mismatch repair (MMR) system and accumulate small mutations at repetitive DNA sequences, a phenotype termed high level microsatellite instability (MSI-H). MSI-H cancers are particularly characteristic for individuals with the inherited HNPCC (hereditary non-polyposis colorectal cancer) or Lynch syndrome, which is caused by germline mutations of the MMR genes. Mutation carriers have a high lifetime risk for the development of MSI-H cancers. Dense infiltration with lymphocytes is commonly observed in MSI-H CRC lesions. These pronounced immune responses may be explained by the generation of defined MMR deficiency-induced antigens (frameshift peptides, FSP).

Methods
We developed a vaccine (Micoryx, NCT01461148) that evaluates FSP vaccination in patients with MSI-H colorectal cancer.

The Vaccine
For the Micoryx FSP vaccine, three coding microsatellite instability-derived FSP antigens were selected (AIM2(-1), HT001(-1), TAF1B(-1)). These antigens are highly promising targets, because FSP antigens can be recognized by the immune system as foreign. MSI-H cancer cells produce FSP antigens as the result of insertion/deletion mutations at cMS sequences (arrows). Mutant genes, which are translated, can give rise to non-functional proteins. These proteins encompass an N-terminal wild type amino acid sequence (gray) and a C-terminal neopeptide or frameshift peptide sequence (red, blue). Through processing via the HLA class I and HLA class II antigen processing and presentation machinery, epitopes derived from FSP antigens can be presented on the surface of MSI-H cancer cells. Antigens presented by HLA class I antigens can be targets of CD8-positive T cell attack, whereas antigens presented by HLA class II antigens can be recognized by CD4-positive T cells.

Study Design
Phase I/IIa study of immunization with frameshift peptides administered with Montanide® ISA-51 VG in patients with advanced MSI-H colorectal cancer (MICORYX)

Results
FSP antigens can be recognized by the immune system as foreign. MSI-H cancer cells produce FSP antigens as the result of insertion/deletion mutations at cMS sequences (arrows). Mutant genes, which are translated, can give rise to non-functional proteins. These proteins encompass an N-terminal wild type amino acid sequence (gray) and a C-terminal neopeptide or frameshift peptide sequence (red, blue). Through processing via the HLA class I and HLA class II antigen processing and presentation machinery, epitopes derived from FSP antigens can be presented on the surface of MSI-H cancer cells. Antigens presented by HLA class I antigens can be targets of CD8-positive T cell attack, whereas antigens presented by HLA class II antigens can be recognized by CD4-positive T cells.

Conclusions
MSI-H CRC are highly immunogenic tumors that occur sporadically (15% of CRC) or in the context of Lynch syndrome.

References