PD – 008 Molecular characterization of immune microenvironment in colorectal cancers with microsatellite instability by digital RNA counting

M Giordano[1], R Moretto[2], R Giannini[3], G Zucchelli[2], F Pietrantonio[4], C Antoniotti[2], C Ugolini[5], F Morano[6], F Marmorino[2], E Sensi[1], A Belfiore[7], D Rossini[2], C Lupi[1], G Masi[2], B Borelli[2], E Ongaro[8], A Boccaccino[2], A Falcone[3], C Cremolini[2], G Fontanini[9]

[1]Divisione di Anatomia Patologica, Dipartimento di Chirurgia, Università di Pisa, Pisa, Italy, [2]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [3]University of Pisa, Pisa, Italy, [4]Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy, [5]Department of Laboratory Medicine, Section of Pathology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [6]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [7]Istituto Nazionale dei Tumori Foundation, Milan, Italy, [8]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [9]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

Introduction: Alterations in the mismatch repair (MMR) mechanism in colorectal cancers (CRCs) lead to high levels of microsatellite instability (MSI-h) causing considerable endogenous immune anti-tumor response, counterbalanced by immune inhibitory signals. We evaluated the mRNA immune-profile of a series of MSI-h CRCs to identify new potential targets for future CRC immunotherapy trials by combining an extensive gene expression analysis and the clinicopathological characteristics such as presence of metastases, staging, genotype and primary tumor sidedness.

Methods: Fifty primary MSI-h CRCs were analysed. Among these, 24 were non-metastatic, 13 had metachronous metastases and 13 had synchronous metastases. According to tumor staging 26 were stage I – II, 10 stage III and 14 stage IV at the time of diagnosis. Mutational status was as follows: 12 samples were RAS mutated, 22 BRAF mutated and 16 RAS and BRAF wild type. Finally, 36 tumors were right-sided and 14 left-sided. NanoString nCounter® PanCancer Immune Profiling Panel (Seattle, WA, USA), covering 730 immune-related genes, was employed to measure gene expression. A linear regression analysis was performed to investigate the differential gene expression related to above mentioned clinicopathological characteristics. The Benjamini-Yekutieli false discovery rate (FDR) was used for adjusting p-values. In this study we set a FDR$<$0.05 to select differentially expressed genes.

Results: Several immune-related genes resulted differentially expressed according to primary tumor sidedness. Most of the deregulated genes showed higher expression in right-sided compared to left-sided MSI-h CRCs and belong to the following "immune response categories": chemokines (STAT1, CXCL10, CXCL13), innate immune response (ATG5, MAP2K1), T-cell functions (IDO1, LAG3, PTPRC), antigen processing (HLA-DPA1, HLA-DPB1, PSMB7), cytotoxicity (GNLY, GZMA), adhesion (ITGAE), NK cell functions (KLRC2) and cell cycle check point (CASP3). No significant differences based on presence of metastases, tumor stage or mutational status were observed.

Conclusion: Immune-related genes investigated in this study are heterogeneously expressed in MSI-h CRCs. Interestingly, genes mainly implicated in the inhibition of the immune system are more expressed among right- than left-sided CRCs, thus suggesting a potential different responsiveness to checkpoint inhibitors. According to their putative role in the clinical practice, these preliminary results deserve further validation.