

36th World Cancer Conference & 3rd Edition of International Conference on **Colorectal Cancer**

October 11-13, 2018 Zurich, Switzerland

Gene panel mutation screening for a better molecular stratification of colorectal cancer patients

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Colorectal carcinoma (CRC) is one of the most commonly diagnosed cancers worldwide. The metastatic disease contributes to the high mortality rate reported for such tumors. Significant benefit on overall survival was brought about the introduction of monoclonal antibodies anti-EGFR and anti-VEGF used in combination with chemotherapy in metastatic CRC (mCRC). While anti-VEGF treatment does not require biomarker-based selection criteria, the potential efficacy of anti-EGFR antibodies is neglected to patients with activating mutations in *KRAS* and *NRAS* (RAS) genes, whose molecular analysis became a clinical routine. The advent of next generation sequencing (NGS) instruments, able to reach quick testing of multiple clinically-relevant hotspots, yet maintaining precision and low costs, allows the simultaneous determination of the mutation status of an expanding number of genes. Despite only few of these molecular biomarkers have gained clinical utility in the routine oncological practice, the acquisition of more complex cancer mutational patterns may provide more efficient tumor characterization for prognostic and predictive purposes and highlight actionable targets. We sequenced 639 mCRC samples by IT-PGM platform using a panel of hotspots and targeted regions of 22 genes (including RAS) commonly involved in CRCs. MSI analyses on 89 patients have been performed with a single fluorescent system comprising BAT25 and BAT26 mononucleotide repeats. We identified recurrent mutations ($\geq 1\%$) in 12/22 genes, being *KRAS*, *TP53* and *PIK3CA* the most frequently mutated ones. Statistical analysis indicated that the mutation associations follow a non-random distribution. Categorization of the cases on the base of *KRAS* and *p53* mutation status led us the definition of 8 mutation association patterns (MAPs) characterized by specific mutation associations. Analysis of the clinicopathological data available for 89 out of 639 cases indicates interesting trends for the associations of MAPs with specific parameters, some of which reached statistical significance. Application of NGS gene panel as a routine for the characterization of RAS/BRAF status required for predictive purposes in CRC patients may provide additional prognostic/predictive information, with no significant extra-costs.

Recent Publications

1. Van Cutsem E, et al. (2014) Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol. Suppl 3*:iii1-9.
2. Douillard J Y, et al. (2013) Panitumumab-folfox4 treatment and RAS mutations in colorectal cancer. *N Engl J Med.* 369(11):1023-34.
3. Belardinilli F, et al. (2015) Validation of the ion torrent PGM sequencing for the prospective routine molecular diagnostic of colorectal cancer. *Clin Biochem.* 48(13-14):908-10.
4. Malapelle U, et al. (2015) Less frequently mutated genes in colorectal cancer: evidences from next-generation sequencing of 653 routine cases. *J. Clin Pathol.* 69(9):767-771.

Biography

Francesca Belardinilli has completed her PhD in Biotechnology and since November 2012 she has joined the Laboratory of Molecular Oncology, Department of Molecular Medicine, Sapienza University of Rome, Italy. She has technical skills in molecular, cellular biology and statistics. Her most important expertise is in the molecular genetics of breast, colorectal and melanoma cancer. In particular, she is currently investigating the biological and clinical role of mutations observed in colorectal tumors, as well as their frequencies and associations. Recently, she has also focused her attention on evaluation of polygenic determinants of nonalcoholic fatty liver disease.

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