special symposium: advances in precision medicine of metastatic colorectal cancer

EMERGING DRUGGABLE TARGETS IN COLORECTAL CANCER

F. Di Nicolantonio
Department of Oncology, University of Torino, Candolo, ITALY

The analysis of the Tumor Cancer Genome Atlas (TCGA) network on colorectal cancer (CRC) samples has identified a plethora of genetic alterations that deregulate five main pathways: WNT, TGF-β, p53, PI3K and Receptor Tyrosine Kinase (RTK)-RAS signaling. Three or more pathways can be concomitantly disregulated in each tumor. How to exploit this knowledge? Among the low-hanging fruits, there are molecular alterations affecting several genes encoding for RTKs (including RET, ERBB3, FGFRs, TRKs, PDGFRA, ALK and KIT), which have been identified to occur at low prevalence (e.g. 0.5-2%) by the TCGA. Larger studies are needed to establish their prevalence in the general CRC population as well as in molecularly distinct subtypes. Additional druggable targets may be represented by genes disregulated in PI3K signaling, including IGF2, PIK3CA, PTEN or PIK3R1. However, caution should be taken to define therapeutic strategies based on the molecular status of a single gene. The complexity of the CRC molecular landscape strongly suggest a single genetic alteration may not per se represent a promising drug target, unless it is analyzed within the context of co-existing alterations leading to simultaneous activation of multiple oncogenic signaling pathways. Functional studies on the role of specific RTKs in CRC progression are largely missing and are needed to discriminate whether the above mentioned kinases could represent valuable targets in this disease. Nevertheless, it is likely that targeting one gene (one pathway) may not be sufficient to induce prolonged tumor remission, and that combined inhibition of two key signaling pathways in CRC could be more effective. Finally, recent transcriptomic analyses have highlighted the existence of 3-5 molecularly distinct CRC subtypes based on the expression of genes encoding for epithelial or mesenchymal (stem-like) phenotypes, or the presence of inflammatory or goblet-like signatures. These studies also suggest that the ensuing molecular subtypes may be differentially responsive to distinctive therapies. Therefore, it is possible that future drug targets will emerge from screening chemical or RNA interference libraries against preclinical CRC models recapitulating the molecular features of each subtype.

Disclosure: The author has declared no conflicts of interest.