Recent advances in molecular biology have fostered the development of innovative targeted therapies in CRC. Two fundamental achievements will impact in the way we develop new targeted therapies in CRC. First, the recently available large scale databases on the genomic landscape in patients with CRC, like the TCGA consortium, have provided paramount information on the genes that are frequently disregulated in CRC and has provided some fundamental data to differentiate, at least, two different patient populations with CRC: hypermutated and non-hypermutated tumours. The second approach has been built on the possibility of differentiating subtypes of CRC by gene profiling also in large datasets of patients with this disease. Both approaches are at the very beginning steps but have provided some seminal knowledge to establish different molecular subtypes in CRC. In this regard, we have clearly differentiated the BRAF V600E mutant CRC population that, although it accounts only for 5-8% of patients with CRC, has clear dependence/addiction on this mutated gene/protein. Preclinical studies have shown the dependence of these tumours on BRAF but also on some tyrosine kinase receptors that result activated as a compensatory mechanism of secondary resistance. At this time point several trials are evaluating the combination of BRAF or MEK inhibitors with EGFR inhibitors. Following the example of the BRAF mutated tumours, these diagnostic platforms will provide information on some other populations that may be more dependent on selected gene disregulations. Another important concept that has been established is the plasticity CRC has in terms of clonal selection and clonal evolution. It has been shown by different groups that patients with tumours that have wild-type RAS status, once they are treated with EGFR inhibitors – “treatment pressure” –, they start showing an increase in cells that bear RAS mutations. The clinical application of predictive biomarkers of response to molecular targeted agents has directed the definition of new paradigms in the development of new agents in oncology. The revolution in the knowledge of the biology and the characterization of different molecular subtypes of CRC as well as the availability of new targeted agents will translate in the next future in more therapeutic options in this disease.

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