GENETICS

In colorectal cancer, not all *KRAS* mutations are created equal

Recent work has challenged the accepted black and white dogma that colorectal cancer patients with wild-type *KRAS* benefit from cetuximab while those with mutant *KRAS* do not. The use of *KRAS* as an efficacy marker for treatment with anti-EGFR monoclonal antibodies is based on retrospective correlative analyses—the results led the FDA to modify the labels for cetuximab and panitumumab to restrict their use to patients with wild-type *KRAS*.

An international consortium of researchers, led by Sabine Tejpar and Alberto Bardelli, hypothesized that this binary separation may not be 100% accurate and, as Tejpar states, "there may be nuance where some patients with *KRAS* mutations derive benefit from anti-EGFR therapy and some patients with wild-type *KRAS* do not." To test their hypothesis they used a novel technology that exploited homologous recombination in human cells; "we introduced into wild-type *KRAS* cetuximab-sensitive cells the most common *KRAS* mutations... the derivative cells displayed dramatically different sensitivity to cetuximab, both *in vitro* and in animal models," Bardelli explains.

Based on these results, the researchers decided to group together as many series of clinical data regarding cetuximab efficacy in patients with established *KRAS*-mutation status as possible and to perform a pooled analysis. Tejpar described their approach as a "dirty method" but there was no large dataset available and as they used the raw data from each of the 579 patients from seven clinical trials this was "the best possible pooled analysis."

Tejpar explained that they had "a good notion of heterogeneity in *KRAS*" prior to study initiation and, in particular, anecdotal evidence and their preclinical experiments indicated that the Gly13Asp mutant behaved differently to other mutants.

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All the seven trials used in the pooled analysis had overall survival as the primary end point. Patients with Gly13Asp *KRAS* mutations who received cetuximab had significantly longer overall survival (7.6 months) than patients with other *KRAS* mutants (5.7 months). Interestingly, the overall survival after cetuximab treatment was not significantly different when comparing patients with wild-type tumors and Gly13Asp *KRAS* mutations.

The study also examined other *KRAS* mutations and the researchers were able to show that, in these patients, there was no significant difference in overall survival when comparing patients who received cetuximab with those who did not. This result indicates the Gly13Asp mutation might be a special case that should be treated differently to other *KRAS* mutants.

There are clearly some limitations to the work presented by Tejpar, Bardelli and colleagues. Tejpar pointed out that the patient cohort was heavily pretreated and had chemorefractory disease, and it is possible that patients with early-stage, chemotherapy-responsive disease may respond differently to cetuximab. In addition, it is obvious that a retrospective study of this nature is not conclusive. Indeed, Tejpar describes the results to be "hypothesis-generating work" and emphasized that it needs to be demonstrated in an independent data set before it can be described as practice changing. However, she also commented that with the publication of the work they wanted to "throw a stone in the pond" in terms of challenging the accepted dogma and current guidance. They also hoped to "move things forward in the molecular genetics of colorectal cancer."

Bardelli outlined the next stages for the research: "a prospective trial must be performed to confirm these results and the next step forward is to better understand the role of individual mutations on response and resistance to therapy." The development of a trial to examine the response of patients with Gly13Asp *KRAS* mutations to cetuximab is underway and the results will be awaited by all in the field with great interest.

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Original article De Roock, W. *et al*. Association of *KRAS* p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* **304**, 1812–1820 (2010)