Editorial Commentary

KRAS G12C inhibition with sotorasib in metastatic colorectal cancer

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Introduction

Colorectal cancer (CRC) is the third most prevalent cancer worldwide (1). Different initiatives and screening procedures try to improve early detection and therefore reduce mortality. But despite these initiatives and ongoing breakthroughs in the treatment of CRC, the 5-year survival rate is still only approximately 65% (1). Furthermore, the 5-year survival rate decreases substantially to approximately 14% when patients are diagnosed with advanced or metastatic colorectal cancer (mCRC).

Although treatment options have improved and expanded in mCRC, there is still an unmet need for more active targeted therapies. Possible chemotherapy regimens including oxaliplatin, irinotecan and fluoropyrimidines are used as first and second line strategies (2,3). The last decade targeted agents such as VEGF inhibitors and anti-epidermal growth factor receptor (EGFR) antibodies were approved in association with classic cytotoxic agents or in monotherapy (anti-EGFR) (4,5). In third and fourth line, tyrosine kinase inhibitors (TKI, e.g., regorafenib) and trifluridine-tipiracil were added after showing improved survival in pre-treated mCRC (6,7). These therapeutic options remain the backbone in the treatment of mCRC. Recently pembrolizumab was approved for microsatellite instability-high (MSI-H) and the combination of encorafenib and cetuximab for BRAF V600E mutant mCRC (8-10). Nevertheless, the median overall survival (OS) after first and second line treatment remains only 7–8 months (10). Therefore, developing novel therapeutic options is necessary.

The last 5 years have taught us that CRC is a very heterogeneous disease. In 2022, we characterize different subtypes to optimize patient- and tumor-driven personalized medicine. New insights into genetic and epigenetic changes involved in colorectal carcinogenesis have caused new ways of categorizing CRC and therefore new treatment strategies. For instance, we know that the Ras-Raf-mitogen-activated protein kinase (MAPK) signaling pathway is a crucial mediator in the development of CRC.

Mutations in Kirsten rat sarcoma viral (KRAS) oncogene homolog, which is part of the MAPK signaling pathway, are the most frequent alterations in all human cancers. KRAS/NRAS mutations are present in almost 50% of all mCRC (11), with KRAS G12C representing 3% of all mCRC (12,13). KRAS mutations promote uninhibited cell proliferation by activating BRAF and mitogen-activated protein kinase kinase (MEK) downstream in the MAPK pathway. KRAS is situated downstream from the EGFR (11). These KRAS mutations are often associated with resistance to specific targeted treatments, such as anti-EGFR antibodies. Seeing that KRAS mutant mCRC patients have worse outcomes than KRAS wild type mCRC, there is an unmet need for new and improved treatment options for these patient groups.

Since its discovery almost 40 years ago, RAS proteins have been regarded as undruggable until Ostrem *et al.* (14) found a different binding mechanism in KRAS G12C protein and therefore laying the foundation for the development of targeted KRAS G12C inhibitors. In 2020, Hong *et al.* (15) published the first phase 1 trial

(CodeBreaK100) with the KRAS G12C inhibitor sotorasib, showing clinical activity in monotherapy in solid organ tumors. New results of the following single-arm phase 2 trial with sotorasib have recently been published in *Lancet Oncology* (16).

Summary and discussion

CodeBreaK100 is an ongoing phase 1 and 2 basket trial evaluating the safety and efficacy of the selective KRAS G12C inhibitor sotorasib. Sotorasib is a covalent inhibitor that rapidly and irreversibly occupies KRAS G12C and diminishes its activity. In the phase 1 part (15) a total of 129 patients, mostly non-small cell lung cancer (NSCLC) and mCRC, were treated with monotherapy sotorasib in dose escalation and expansion cohorts. Primary endpoint was safety, whilst objective response rate was a secondary endpoint. The study included 42 patients with mCRC of whom all had received at least 2 prior lines of chemotherapy. Three patients (7.1%, 95% CI: 1.50–19.48) had a confirmed response and 31 patients (73.8%) had disease control. Sotorasib was well tolerated with grade 3 and 4 treatment related adverse effects occurring in 11.6% of all patients. A daily oral dose of 960 mg showed sufficient evidence to completely inhibit the KRAS G12C protein for more than 24 hours.

In the *Lancet Oncology*, Fakih *et al.* (16) present data on the subsequent phase 2 trial with sotorasib monotherapy in pretreated KRAS G12C mutant mCRC. This single-arm trial included 62 patients with KRAS G12C mutated mCRC who had progressed after receiving treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. All patients received the optimal dose of 960 mg daily until disease progression or development of unacceptable treatment-related adverse effects. The primary endpoint was objective response rate. Fakih *et al.* aimed for a response rate where the lower limit of the 95% CI was above 10%. However, only in 6 patients (9.7%, 95% CI: 3.6–19.9) objective response rates were observed. Therefore, the primary endpoint was not reached. Disease control was achieved in 51 patients (82.3%). At a median follow-up time of 11 months, the median progression free survival was approximately 4 months (95% CI: 2.8–4.2). This phase 2 trial confirmed a good tolerance with serious treatment-related adverse events observed in only 2 patients (3%), with no fatal events occurring. Grade 3 adverse events occurred in 6 patients (10%) with diarrhea being the most common.

When we look closer to the patient groups in the mCRC cohort, it is important to notice that these patients are heavily pretreated, with 42% having 4 or more previous lines of anti-cancer systemic therapy. Another important thing to notice, is that in the CodeBreaK100 basket trial the results in the NSCLC-group were far better, with response rates of 37.1% and a progression free survival of 6.8 months (95% CI: 5.1–8.2 months). These results caused approval of sotorasib by the US Food and Drug Administration in May 2021.

Significant limitations in this paper are that interpretation of data from subgroup analyses is limited due to small sample sizes. CodeBreaK100 trial didn't have a comparator arm and therefore making assumptions to its clinical importance is very difficult. What Fakih *et al.* did manage to show is that KRAS G21C inhibitors are safe and well tolerated in KRAS G12C mutated mCRC.

Remarks and future trials

In the CodeBreaK100 manuscript, we saw an important difference in response in NSCLC patients in comparison to CRC patients. These differences in response rates of targeted therapies across different tumor types of the same genetic alteration is regularly seen. The best example in CRC is seen in the BRAF V600E mutated cancers. Whereas treatment with a single agent BRAF inhibitor in metastatic melanoma produces response rates of up to 50–60%, these results could not be reproduced in mCRC. Indeed, several studies showed that inhibition with a BRAF inhibitor alone in BRAF V600E mutant did not lead a relevant activity, probably due to feedback activation of the MAPK pathway and also via cross talks. However, in the BEACON trial (9), it was shown that combining multiple inhibitors in the MAPK pathway improves the response rate of BRAF V600E inhibitors in mCRC. Therefore, the combination of a BRAF V600E inhibitor and an anti-EGFR antibody is now the standard of care as second line treatment in BRAF V600E mt mCRC.

Seeing that both KRAS and BRAF are part of the MAPK signaling pathway, similarities in resistance mechanisms can be hypothesized. Amodio *et al.* (17) showed that KRAS G12C CRC models have a higher basal receptor tyrosine kinase (RTK) activation, an important signaling rebound upon KRAS G12C inhibition and are responsive to growth factor stimulation. They identified EGFR signaling as the dominant mechanism of resistance to KRAS G12C blockade in mCRC. They showed that KRAS G12C mCRC retains their EGFR-MAPK dependency despite

KRAS G12C inhibition and therefore, just as in the BRAF V600E mt mCRC group, they can potentially benefit from the combination of an anti-EGFR antibody and a selective KRAS G12C inhibitor to partially overcome resistance mechanisms and improve resistance rates. This concept has recently been studied and endorsed in 2 small trials. Indeed, the combination of sotorasib and panitumumab in extension cohort of the CodeBreaK100 led to a higher response rate, compared to sotorasib alone (18). In the KRYSTAL-1 trial, adagrasib, another KRAS G12C tyrosine kinase inhibitor, led to a response rate of 22% in a small study, while the combination of adagrasib plus cetuximab led to a response rate of 43% in chemorefractory KRAS G12C mutant mCRC (19).

Although these data show first evidence that RAS can be successfully targeted, key questions for future trials remain open. To help make better patient selections, it is important to identify biomarkers that can predict response to KRAS G12C inhibition. Furthermore, we should improve our insights into the different resistance mechanisms to help advance future combination therapies. The multi-arm phase 1b CodeBreaK101 trial is underway to evaluate the safety and tolerability of a KRAS G12C inhibitor, sotorasib, in combination with other therapies, including an anti-EGFR antibody, in KRAS G12C mutated solid tumors (18,20). In the meantime, a randomized phase 3 study in second line treatment, randomizing patients to a standard chemotherapy (irinotecan-based) or to adagrasib plus cetuximab is ongoing to validate this concept (21). Also, other interesting KRAS G12C inhibitors in combination with TKI's targeting the MAPK pathway at different levels (e.g., ERK) and/or with checkpoint-inhibitors as well as inhibitors of the more frequently mutated KRAS G12D are under early development.

Conclusions

These first trials of treating patients with selective KRAS G12C inhibitors are an important step forward in acquiring new insights and concepts for the management of metastatic CRC. Although the primary endpoint in the CodeBreaK100 phase 2 trial was not reached, these results are encouraging and can be the basis for future trials. It is therefore clear as the authors stated, that a treatment with sotorasib or other selective KRAS G12C inhibitors is a promising new tool in the therapeutic landscape of mCRC. Future trials of KRAS G12C inhibitors in combination with other drugs, such as e.g., anti-EGFR antibodies, TKI's and/or checkpoint inhibitors, in order to block the pathway at different levels, will hopefully lead to higher activity and help broaden our therapeutic options for patients with this difficult to treat mutation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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