The impact of RAS mutation on the treatment strategy of colorectal cancer

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Abstract

Kirsten rat sarcoma (KRAS) is the most frequently mutated oncogene in colorectal cancer, being present in 30% of patients with localized disease and in almost half of the patients that develop metastatic disease. While the development of chemotherapy doublets and targeted therapy have improved survival in recent years, KRAS mutation still has a controversial role regarding its prognostic and predictive value both in the adjuvant and in the metastatic setting. The impact of KRAS mutation on treatment strategy remains to be better defined. The development of new KRAS inhibitors promising new treatment options is on the horizon.

Keywords: colorectal cancer, KRAS, adjuvant, metastatic

Introduction

According to the International Agency for Research on Cancer, the incidence of colorectal cancer is increasing worldwide, with 1,931,590 new cases diagnosed in 2020, ranking 3rd after breast and lung cancer [1]. Although developments in surgical, radiotherapy and chemotherapy treatments significantly improved survival in the last decades, with a five-year survival advantage of 7% for colon and 15% for rectal cancers between 1980' and 2000 (51% versus 58% for colon cancer and 44% versus 59% for rectal cancer) and with a 64% at 5 years relative survival rate for colorectal cancer (CRC), mortality remains high, with 935,173 new deaths reported in 2020 [2-4]. Data from the SEER 18 (2011-2017) (Surveillance, Epidemiology, and End Results Program) database reveal that 37% of cases are diagnosed in a localized stage, associating a 5-year relative survival of 90.6%, 36% are diagnosed with regional disease, which has already spread to the lymph nodes, survival decreasing to 72.2% at 5 years and 22% of patients are diagnosed with metastatic disease, with a 5-year relative survival of 14.7% [5]. The main cause of CRC mortality is represented by the development of metastases, the most common sites being the liver, the lungs, and the peritoneum, but bone and brain metastases have also been reported [6]. In the metastatic setting, the development of new cytotoxic agents and targeted therapies have improved overall survival (OS) for patients with stage IV CRC [7].

KRAS, the most frequent mutated oncogene in humans, is a member of a small GTPase protein family, which acts as a binary switch, influencing signal transduction of most growth factor receptors: EGFR, MET, and KIT [8]. More than 30% of CRC harbor activating mutations on the KRAS gene as one of the main carcinogenic mutations in the genome, occurring early in CRC carcinogenesis [9]. The mutation is more frequent in metastatic colorectal cancers involving around 45% of cases, compared with early-stage tumors, with a 15-37% frequency of mutations [10-12]. The KRAS gene is located on chromosome 12p12.1 and is encoded by 6 exons [13]. Most frequently, point mutations occur in codon 12 (82-87%) and 13 (13-18%) [14].

The G12C mutation in exon 2 is one of the most frequent mutations than involves 29.9% of colorectal cancer while the G12D mutation can be found in 2-4% of patients with colorectal cancer [15,16].

The development of drugs that impact survival in colorectal cancer is an ongoing battle that started more than 60 years ago, with every new anticancer agent setting a new milestone for median progression-free survival (PFS, Figure 1).
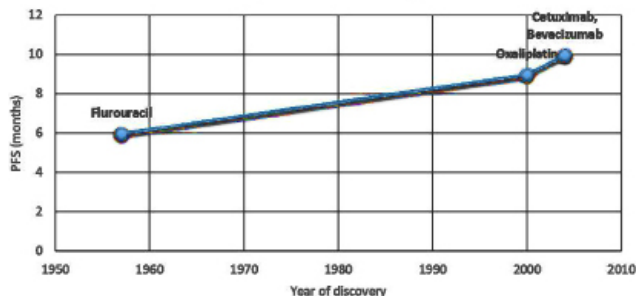

Figure 1. Improvement in progression-free survival due to new therapeutic developments.

Fluorouracil patented in 1956 and used in the clinic since 1962 is the backbone of colorectal treatment [17]. The best way of administration (bolus versus continuous intravenous) was studied for decades, with differences in efficacy and toxicities establishing the continuous intravenous fluorouracil as a standard of care [18]. The addition of oxaliplatin to fluorouracil and leucovorin, known worldwide as the De Gramont regimen, after its inventor, allowed for a median PFS of 9.0 months for the triple combination versus 6.2 months for the leucovorin-fluorouracil regimen and a statistically significant benefit in response rate (50.7% versus 22.3%, p=0.0001) in advanced disease [19]. Median OS was greatly improved by the introduction of monoclonal antibodies that target vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) [20]. Based on the fact that angiogenesis plays a key role in carcinogenesis, allowing tumors to grow, inhibition of VEGF, the main driver of sprouting angiogenesis by targeted therapies that suppress tumor growth by blocking the VEGF signaling pathway was studied for numerous solid cancers, including colorectal [21-23].

In 2004, Hurwitz conducted the first phase III trial that demonstrated the efficacy of the anti-angiogenic agent bevacizumab, a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A, in combination with standard chemotherapy, with superior OS (23 vs. 15.3 months) and PFS (10.6 vs. 6.2 months) compared to the chemotherapy only arm [24].

Cetuximab, the first monoclonal antibody that targeted EGFR was able to induce EGFR internalization with degradation after it was bound to the external domain of the EGFR, inhibiting cellular growth, differentiation, and stimulating apoptosis [25].

The presence of KRAS mutation has a prognostic role in CCR independently of stage and a particular important predictive role in stage IV disease, being a marker for resistance to EGFR targeted antibodies [26-29]. The impact of RAS mutation on the treatment strategy in colorectal cancer is a topic that is still a subject of controversy, but emerging evidence will hopefully help clinicians better understand its importance.

Methods

The present paper summarizes the evidence regarding the impact of KRAS mutation on the treatment strategy in colorectal cancer, in the adjuvant and the metastatic setting. A systematic search of PubMed / Medline, and Web of Science databases was performed until 29 September 2021, using the search terms: "colorectal cancer", "treatment", "adjuvant", "metastatic", and "KRAS". From the 375 records initially identified, after recursive searches and cross-references were carried out, 187 full-text articles were assessed for eligibility; 56 articles that published results from clinical trials and reviews were finally included in the qualitative analysis of this review to provide data regarding the impact of KRAS mutation on treatment strategy. Case-report articles were excluded. Figure 2 presents the algorithm used to identify the eligible studies. Additional searches of the same databases were performed to identify suitable background information. The present study was performed following the standard guidelines for systematic reviews [30].

Impact of KRAS mutation on adjuvant treatment

In the adjuvant setting, the impact of KRAS mutation on the adjuvant treatment is not yet very well defined, but there is emerging evidence that KRAS mutant cancers stage II and III that harbor a mutation are associated with a worse prognosis than wild type tumors [31].

The first study that investigated the role of KRAS status in the adjuvant setting was based on the data collected on CKVO 90-11 trial, which included patients with stage III colon cancer, treated with fluorouracil/levamisole versus fluorouracil/levamisole/leucovorin. 205 patients had samples that were available for KRAS exon 1 and 2 testing. No association was found between KRAS mutations and DFS [32].

In 2010, Ogino et al. conducted a study that selected 508 patients from the randomized adjuvant chemotherapy CALGB 89803 trial, that compared FOLFIRI versus FUFOL regimens as adjuvant therapy for patients with stage III resected colon cancer. 35% of patients had KRAS mutations, detected by pyrosequencing. According to their report, 5-year DFS, RFS (relapse-free survival) and OS in

the *KRAS*-mutated vs. *KRAS*-wild-type subgroups were very similar: 62% vs. 63% (log-rank p=0.89); 64% vs. 66% (p=0.84); and 75% vs. 73% (p=0.56), respectively [33]. A limitation of this study is related to the selection of chemotherapy regimens used, the addition of irinotecan was never demonstrated to add a benefit in the adjuvant setting and it was soon abandoned in favor of oxaliplatin, which was able to show a beneficial effect for stage II high risk and stage III colorectal cancer [34,35].

Translational analysis of the results from the PETACC-3 phase 3 randomized study, including specimens from 1,404 patients with stage II and III colon cancer receiving adjuvant treatment with fluorouracil/leucovorin with or without irinotecan, failed to demonstrate the prognostic value of KRAS mutation for either OS or RFS [36].

Since the MOSAIC study, oxaliplatin-based adjuvant chemotherapy has been the standard treatment for stage III colon cancer, reducing the risk of recurrence and improving OS in this group of patients [37].

Lee et al. published in 2014 the results of a study that analyzed KRAS and BRAF mutational data from 437 patients who received adjuvant chemotherapy with the FOLFOX regimen after curative surgery for stage III or stage II high-risk colon cancer. The 26.5% of patients that had a KRAS mutation in codons 12 and 13 had a significantly worse 3-year disease free survival (DFS) of 79% compared with 92% in the wild type population (p=0.006) [38].

It appears that in the group of patients, candidates for adjuvant treatment, the subtype of KRAS mutation matters, with G13D (3-year DFS 76%, *p*=0.008) being significantly associated with poor DFS. In the same study, the G12D mutation was not associated with prognosis (3-year DFS 86%, *p*=0.61) [38].

According to PETACC-8, a phase 3 randomized study that enrolled patients with stage III colon cancer with R0 resection to receive 12 cycles of FOLFOX4 biweekly +/-cetuximab (only for KRAS wild-type patients), the trial was not able to demonstrate a benefit of adding cetuximab in the adjuvant setting, not validating KRAS status as a predictive factor for treatment response [39,40]. Post hoc analysis of data collected prospectively from PETACC-8 demonstrated the detrimental role KRAS mutation has on colon cancer outcome, being associated with a statistically significant increased risk of relapse and shorter DFS for codon 12 mutations and a borderline significance for codon 13 mutations [40,41]. An interesting observation is the fact that in patients with MSI (Microsatellite unstable) tumors, KRAS status was not prognostic [41].

The NCCTG N0147 phase 3 trial, testing the efficacy of FOLFOX6 biweekly +/-cetuximab also failed to demonstrate a benefit of adding cetuximab to standard FOLFOX chemotherapy for stage III colon cancer but was able to notice a difference in DFS for the wild type and mutant subgroups with 74.6% for the former and 67.1% for the latter [42].
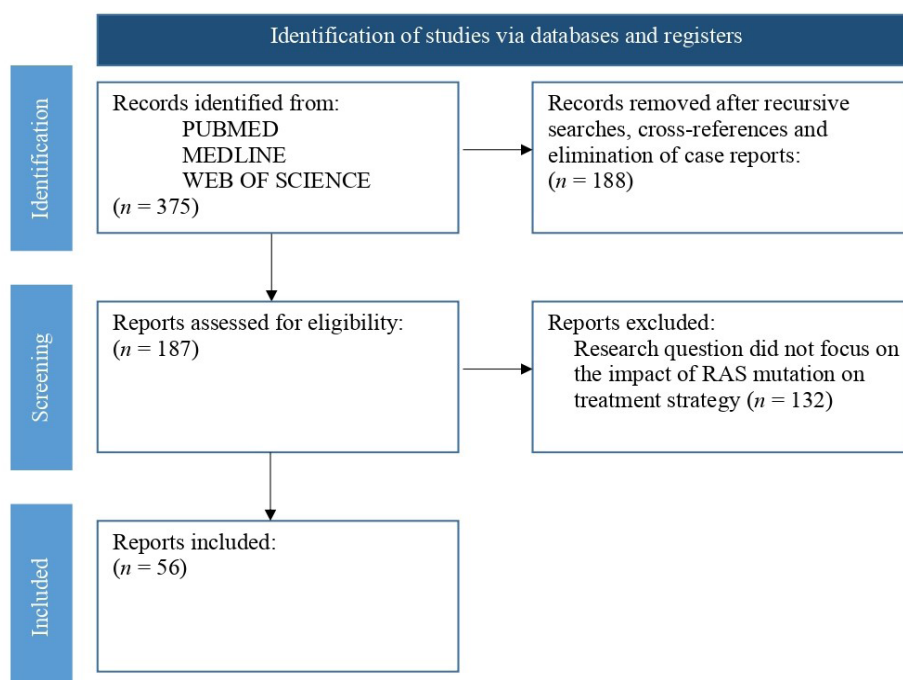

Figure 2. Flow chart showing the strategy to identify eligible studies.

The discrepancies between all these trials in the adjuvant setting require further investigation in a study that will stratify patients on both KRAS mutational status and MMR (defective DNA dispatch repair) status.

The main characteristics of the studies included for review are summarized in table I below.

Impact of KRAS mutation on the treatment in the metastatic setting locoregional treatment. resectable liver metastases

With a median survival of 8 months for patients with untreated colorectal liver metastases, complete resection of liver lesions is a strategy that was included in the treatment armamentarium, in order to improve survival [43].

Following curative resection of liver metastases, KRAS mutant patients have a decreased OS and a higher risk of recurrence compared with their KRAS wild type counterparts, probably due to a more aggressive intrahepatic growth pattern [44,45]. According to a study conducted by Brudvik, which included 633 patients, 36.2% being RAS mutant, the positive margin after hepatic resection was significantly higher in the KRAS mutant population, with a rate of 11.4% versus 5.4% for wild-type KRAS (p=0.007). RAS mutation (HR 1.629; p=0.044) and a positive margin (HR 3.360, p<0.001) were independently associated with worse overall survival [46]. To improve survival in this group of patients, Margonis is proposing more extensive anatomical hepatectomies [47]. This strategy must be validated in larger clinical trials before being adopted in clinical practice. A topic of intense debate is the discordance of KRAS mutation status between primary tumors and their metastases. Studies reported discordances ranging from 4 to 32% to 100% concordance [48-55]. An Italian team managed by Ardito analyzed KRAS status for both the primary tumor and completely resected liver metastases in 107 patients and found a discordance incidence of 15.9% [56]. The main characteristics of these studies are presented in table II below.

Table I. Research on the impact of KRAS mutation on adjuvant treatment.

Study	Subjects	Stage	Regimen	% KRAS mutant	DFS	OS	Key points and pitfalls
CKVO 90-11 [32]	205	III	Fluorouracil/levamisole vs. Fluorouracil/levamisole +leucovorin	28%	No statistical difference	No statistical difference	• Fluorouracil /levamisole is now a substandard treatment option • Only exon 1 and 2 were analysed
CALGB 89803 [34]	508	III	FOLFIRI vs. FUFOL	35%	No statistical difference	No statistical difference	• 5 year DFS 62% vs. 63% for mutated vs wild type KRAS groups • 5 year OS 75% vs. 73% for mutated vs wild type KRAS groups • Irinotecan adds no benefit in the adjuvant setting
PETACC-3 [36]	1404	II and III	FOLFIRI vs. FUFOL	37% 36% stage II 37.5% stage III	No statistical difference	No statistical difference	• 5 year DFS of 70% in both groups • 5 year OS of 76% vs. 77% in mutant vs wild type KRAS groups • Irinotecan adds no benefit in the adjuvant setting
Lee et al. [38]	388	II+III	FOLFOX4	26.5%	Statistical significant difference at 3 years	Not reported	• 3 year DFS 72% vs. 92% for KRAS mutant vs wild type groups • FOLFOX was validated as the standard adjuvant treatment • Low proportion of KRAS mutation
PETACC-8 [39-41]	2559	III	FOLFOX4 vs. FOLFOX4+Cetuximab (KRAS wild type)	38%	Statistical significant difference at 3 years	Statistical significant difference at 3 years	• 3 year DFS of 69,.4% vs. 77.1% for KRAS mutant versus KRAS wild type group • Low number of subjects with codon 13 mutation • Codon 12 mutation is associated with an increased risk of relapse • No benefit of adding cetuximab
NCCTG N0147 [42]	2686	III	FOLFOX6 vs. FOLFOX6+Cetuximab (KRAS wild type)	34%	Statistical significant difference at 3 years	No statistical significant difference at 3 years	• 3 year DFS of 67.1% vs. 74.6% in KRAS mutant versus wild type group • 3 year OS of 87.9% vs. 87.5% in mutant vs wild type KRAS groups • No benefit of adding cetuximab

DFS-disease free survival; OS-overall survival.

Table II. Research on the impact of KRAS mutation on the treatment in the metastatic setting-resectable disease.

Study	Subjects	% KRAS mutant	Key points and pitfalls

Kemeny et al. [44]	169	26%	• DFS at 3 years:
			   - 46% for KRAS wild type
			   - 30% for KRAS mutant
			• OS at 3 years:
			   - 95% for wild type
			   - 81% for KRAS mutant
			• KRAS mutant patients have a decrease OS and a higher risk of recurrence compared with their KRAS wild type counterparts
			• More aggressive intrahepatic growth pattern
			• Intensive treatment regimen-resection, intraarterial chemotherapy, intravenous chemotherapy

Brudvik et al. [46]	633	36.2%	• R1 resection and RAS mutation associated with worse OS • RAS mutant and CEA>4.5 ng/mL associated with increased rate of positive margins • R1-11.4% in the KRAS mutant population • R1-5.4% in the KRAS willd type population

Margonis et al. [47]	389	36%	• DFS at 5 years:
			   14.4% in the nonanatomical resected group
			   46.4% in the anatomically resected group
			• More extensive anatomical hepatectomies for KRAS mutant patients

DFS-Disease free survival; OS-Overall survival; RFS-Relapse free survival; R1 resection-Positive resection margin

Unresectable disease. Systemic treatment
KRAS mutation as a predictive biomarker of response to anti-EGFR therapy

Targeting the EGFR gene is a therapeutic strategy tested for metastatic colorectal cancer for the first time with cetuximab, a chimeric IgG1 monoclonal antibody, which received FDA approval in 2004 after evaluation of results from three studies. The largest data came from the study conducted by Cunningham et al. on 329 randomized patients whose disease had progressed during or within three months after treatment with an irinotecan-based regimen to receive either cetuximab and irinotecan or cetuximab monotherapy. With a response rate in the combination-therapy group was significantly higher than that in the monotherapy group (22.9 percent [95 percent confidence interval, 17.5 to 29.1 percent] vs. 10.8 percent [95 percent confidence interval, 5.7 to 18.1 percent], p=0.007) and a median time to progression significantly greater in the combination-therapy group (4.1 vs. 1.5 months, p<0.001 by the log-rank test), cetuximab demonstrated clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer [57].

In 2007 the results of a phase III clinical trial including 463 patients evaluated the efficacy of panitumumab, a fully human monoclonal antibody directed against the epidermal growth factor receptor, administered to patients with 1% or more EGFR tumor cell membrane staining that had progressive metastatic CCR during or within 6 months of the most recent chemotherapy regimen. The control group received the best supportive care. The results were encouraging, with panitumumab significantly prolonging PFS (hazard ratio [HR], 0.54; 95% CI, 0.44 to 0.66, [p<0.0001]). Objective response rates also favored panitumumab over BSC; after a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC (p<0.0001) [58].

With only 10% of patients responding to anti-EGFR antibodies, the molecular mechanisms underlying clinical response or resistance to these agents required further studies [59]. Lievre et al. analyzed 30 patients receiving treatment with cetuximab plus irinotecan and found that 13 from the 19 non-responders group had a KRAS mutation (68.4%; 95% CI, 43.5-87.5%), while 11 patients with a clinical response to cetuximab were KRAS wild type [0%; 95% confidence interval (95% CI), 0-28.5%], (p=0.0003) [60]. Therefore, the presence of *KRAS* mutation was significantly associated with the absence of response to cetuximab. This observation was validated in a later trial where samples from 394 patients randomly assigned to receive cetuximab plus best supportive care or best supportive care alone were analyzed for activating mutations in exon 2 of the KRAS gene. Among the group with KRAS mutated tumors, there was no significant difference between those who were treated with cetuximab and those who received supportive care alone with respect to overall survival (hazard ratio, 0.98; p=0.89) or progression-free survival (hazard ratio, 0.99; p=0.96) [61].

For panitumumab, KRAS status was ascertained in 427 patients and response rates to panitumumab were 17% and 0%, for the wild type and mutant groups, respectively, efficacy being confined to patients with wild type tumors [62].

The European Society of Medical Oncology and the National Comprehensive Cancer Network guidelines for colorectal cancer recommend the use of anti-EGFR agents panitumumab and cetuximab with a chemotherapy backbone or in monotherapy in first and further treatment lines only in the KRAS wild type tumors [63,64].

Not all KRAS mutations are equivalent in the effect on drug resistance, but more detailed subgroup analyzes are required before using anti-EGFR antibodies for KRAS mutant tumors. A retrospective analysis of 579 mCRC patients with chemorefractory disease included 32 patients with p.G13D mutation, with significantly longer OS and PFS compared with other KRAS mutations (median OS 7.6-mo vs. 5.7-mo, p=0.005; median PFS 4-mo vs. 1.9-mo, p=0.004) [65]. Evaluation of cetuximab and panitumumab therapy in these tumors in prospective randomized trials may be warranted. The main characteristics of these studies are summarized in table III.

Strategies to overcome acquired resistance mechanisms in clinical practice

The emergence of *RAS* mutations in tumors that were initially *RAS* wild-type is a mechanism of acquired resistance to anti-EGFR monoclonal antibodies [66]. One of the hypotheses of the mechanism involved is that during the anti-EGFR therapy, initially undetected mutated clones are able to proliferate and become predominant in the tumor. During the subsequent treatment, not anti-EGFR-based, EGFR sensitive clones would proliferate. This is the proof of concept for anti-EGFR rechallenge [67].

In order to test the efficacy of anti-EGFR rechallenge, Santini et al enrolled 39 irinotecan-refractory patients who had a clinical benefit after a line of cetuximab- plus irinotecan-based therapy and then a progression of the disease for which underwent new line chemotherapy and finally, after a clear new progression of the disease, were retreated with the same cetuximab-plus irinotecan-based therapy. With an overall response rate of 53.8% and a median progression-free survival of 6.6 months, cetuximab-based therapy rechallenge may achieve an important clinical benefit [68].

Table III. Research on the impact of KRAS mutation on the treatment in the metastatic setting-unresectable disease-systemic treatment.

Study	Subjects	% KRAS mutant	Key points and pitfalls
Lievre et al. [60]	30	43%	• mOS 16.3 months for wild type population 6.9 months for KRAS mutant population • increased EGFR copy number was found in 10% of patients and was associated with an objective response rate to cetuximab • KRAS mutation-associated with resistance to cetuximab and worse prognosis
Karapetis et al. [61]	394	43.4%	• mOS 9.5 vs. 4.8 months in favor of wild type group receiving cetuximab comparative with BSC 4.5 vs. 4.6 months for cetuximab versus BSC in the KRAS mutant group • mPFS 3.7 vs. 1.9 months in favor of wild type group receiving cetuximab comparative with best supportive care 1.8 months for both cetuximab and BSC in the KRAS mutant group • KRAS status-valid biomarker that predicts response to cetuximab, even in heavily pretreated patients • Only exon 2 mutations were tested
Amado et al. [62]	427	43%	• mPFS 12.3 weeks vs. 7.3 weeks for panitumumab vs. BSC in KRAS wild type group • ORR- 17% for panitumumab in the KRAS wild type group vs. 0% in the KRAS mutant group • Baseline patients characteristics were balanced between wild type and KRAS mutant groups for both panitumumab and BSC to avoid bias • KRAS mutation predict for lack of clinical benefit to panitumumab therapy
De Roock et al. [65]	579 32 pG13D mutant	40% 14.5% pG13D mutation	• mOS 7.6 months for pG13D vs. 4 months for other KRAS mutations • mPFS 5.7 months for pG13D vs. 1.9 months for other KRAS mutations • ORR-not significantly different between patients with pG13D mutated and other KRAS mutated tumors • KRAS wild type tumors have higher ORR-26.4% vs. 6.3% • Small number of patients

mOS-median overall survival; ORR-overall response rate; mPFS-median progression free survival.

Tumor DNA's genetic alterations can be non-invasively analyzed on plasma circulating tumor DNA (ctDNA), allowing for evaluation of tumor heterogeneity repetitively, providing a molecular profile of tumor evolution under treatment [69,70].

The CRICKET trial prospectively evaluated the rechallenge strategy with irinotecan and cetuximab as a third-line treatment for patients with initial response and then progression with a first-line irinotecan- and cetuximab-containing therapy, and receiving second-line chemotherapy plus bevacizumab. RAS mutations were found in circulating tumor DNA collected at rechallenge baseline in 12 of 25 evaluable patients (48%). Patients who obtained response had no mutations detected, liquid biopsy being a good method to select the best candidates for rechallenge [71].

Hope for future developments. KRAS targeting

For the last thirty years, many efforts have been made in order to target the most frequently mutated oncogene, but with no clinically significant success [72,73]. Direct RAS inhibition by molecules that bind the RAS-GTP pocket proved unsuccessful, probably due to the high affinity between GTP and RAS [74]. Strategies for indirectly targeting KRAS were explored, like HRAS targeting [75], the use of antisense oligonucleotides performed by Ross et al. [76] or the inhibition of post-translational modification [77], but with an unsatisfactory clinical activity until recently.

The investigation of the crystal structure of the mutant protein revealed a pocket beneath the effector binding switch II region, conducted by Ostrem and colleagues [78], allowing the development of multiple drugs that are trying to target KRAS.

Sotorasib, a covalent KRAS G12C oral inhibitor that irreversibly binds to the switch II pocket, locking the mutant KRAS in the inactive GDP-bound state was evaluated in phase I/II study that included 42 patients with colorectal cancer, 7.1% having a confirmed response and 73.8% having disease control, with a median progression-free survival of 4 months [79].

The results were significantly lower regarding overall response and median progression-free survival in the colorectal subgroup compared with the subgroup of the patient with non-small cell lung cancer, suggesting either that *KRAS* p.G12C is not the dominant oncogenic driver for colorectal cancer or that other pathways, such as EGFR or Wnt mediate oncogenic signaling beyond *KRAS* [80,81].

Combining sotorasib with agents that block these pathways are options that will be explored and results are encouraging, as shown by similar proof of concept studies in BRAF V600E-mutant colorectal cancer [82], with sotorasib and panitumumab combination being already under investigation in the CodeBreak 101 trial.

Adagrasib, another covalent KRAS G12C inhibitor, investigated within the phase I/II KRYSTAL-1 trial, showed an overall response rate of 17% in the 18 participants with CRC [83]. Combination strategies associating adagrasib with other agents remain to be explored [84].

Onvansertib, a first-in-class highly-selective adenosine triphosphate competitive inhibitor of the serine/threonine polo-like-kinase 1 enzyme, is being developed by Cardiff Oncology in combination with standard-of-care FOLFIRI and bevacizumab for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer. Preliminary results show radiographic responses across multiple *KRAS* mutation variants, which speaks to a key advantage of onvansertib over competing agents targeting individual mutations [85].

An interesting observation of a retrospective study performed in China is that the median survival time for *KRAS*-mutation mCRC patients with diabetes on metformin is 37.8 months longer than those treated with other hypoglycemic drugs in combination with standard systemic therapy, raising the question if metformin could be used associated to standard chemotherapy regimens [86].

Conclusions

KRAS mutant colorectal cancer occurs in more than one third of patients and is associated with a worse prognosis both in the adjuvant and in the metastatic setting. More data need to be collected and analyzed in order to better understand the role of each particular mutation on prognosis, both in the adjuvant and in the metastatic setting and their predictive value for different locoregional or systemic treatment approaches. In order to obtain them, more patients need to have access to clinical trials worldwide, as genetic heterogeneity is to be expected.

Although progress has been made with the development of sotorasib, adagrasib, and onvansertib, these are not yet available in clinical practice and many questions remain to be answered regarding their use in order to better select patients and adopt combination strategies that will provide better patient outcomes.

In summary, after 4 decades of research on targeting undruggable targets, the scientific endeavors now can translate into clinical practice, but a sustained effort is still required to best adapt treatments to patients' needs.

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