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KRAS p.G12C mutated-targeted treatments in metastatic colorectal cancer: a systematic review and meta-analysis

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Abstract

Background Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide. The presence of the *KRAS* G12C mutation in patients with CRC is associated with poor responses to standard therapies and worse outcomes. This study systematically reviewed and analyzed the existing evidence on the efficacy of *KRAS* G12C inhibitors.

Methods PubMed, Scopus, and ISI Web of Knowledge were searched, along with conference proceedings, posters, and major oncology journals. Eligibility criteria included clinical trials involving adult patients with *KRAS* G12C-mutant CRC. Data on treatment outcomes, study design, and patient demographics were extracted and analyzed using a random-effects model, with heterogeneity assessed via I^2 statistics.

Results Seventeen trials, comprising 663 patients with *KRAS* G12C-mutant metastatic CRC, were included. Monotherapy with *KRAS* G12C inhibitors demonstrated an objective response rate of 23%, while combination therapies with agents such as cetuximab and panitumumab showed a higher response rate of 43%. Stable disease rates were also higher in monotherapy (62%) compared to combination therapy (44%). The highest disease control rates were observed with combination therapies (96%). The overall progressive disease rate was lower with combination therapies (1%) than with monotherapies (10%).

Conclusions The results indicate that *KRAS* G12C inhibitors, particularly in combination with other agents, show promising efficacy in treating metastatic CRC. High heterogeneity across studies suggests variability due to small sample sizes and early-phase trial designs. While preliminary data are promising, further large-scale phase III trials are essential to establish these inhibitors as a standard treatment for *KRAS* G12C-mutant CRC.

Keywords Colorectal cancer, *KRAS* G12C mutation, targeted therapy, *KRAS* G12C inhibitors, meta-analysis

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Introduction

Colorectal cancer ranks as the third most prevalent cancer and the second leading cause of cancer-related mortality in the United States and worldwide [1,2]. Despite progress in surgical and systemic treatments, patients with advanced colorectal cancer (CRC) still face a challenging prognosis, with a 5-year survival rate of approximately 14% in unselected stage IV disease. Importantly, selected patients may achieve substantially better long-term survival through aggressive local approaches, including hepatic metastasectomy, radiofrequency ablation, or even liver transplantation [3-6].

A major effort has been directed toward understanding the oncogenetic background and the pathogenetic mechanisms of cancer cell proliferation, tumor development, and metastasis. CRC oncogenesis involves a broad spectrum of mutations, leading to substantial intratumoral heterogeneity, which reflects clonal diversity within individual tumors rather than merely the prevalence of mutations across cohorts [7]. Approximately 75-80% of cases are related to the accumulation of multiple mutations, most commonly in TP53, APC, BRAF, PTEN, and PI3K, while RAS family mutations (*KRAS*, *NRAS*, *HRAS*) occur in more than 40% of cases. KRAS proteins belong to the guanosine triphosphatase (GTPase) family and transmit signals from activated cell-surface receptors—such as epidermal growth factor receptor (EGFR)—to the nucleus, via the MAPK and PI3K pathways. Guanine nucleotide exchange factors (GEFs), such as SOS and GTPase-activating proteins (GAPs), regulate the cycling of *KRAS* between active GTP-bound and inactive GDP-bound states. Both the *KRAS* gene and its encoded proteins have been extensively studied for their oncogenic role in malignancies [8-10].

Among the RAS mutations, *KRAS* alterations predominate, with codon 12 substitutions being the most frequent. The principal variants include G12D (glycine to aspartic acid), G12V (glycine to valine), G12C (glycine to cysteine), G12A (glycine to alanine), and G12S (glycine to serine) [11-13]. These nucleotide substitutions lead to constitutive activation of MAPK and PI3K signaling, thereby promoting uncontrolled proliferation [10]. Although persistent pathway activation contributes significantly to tumorigenesis, cancer development is multifactorial and cannot be attributed solely to KRAS protein accumulation.

The presence of the *KRAS* G12C mutation in CRC is associated with poorer responses to standard therapies and an unfavorable prognosis [13,14]. Targeted *KRAS* G12C inhibitors, such as sotorasib, adagrasib, and divarasib, have demonstrated clinically meaningful improvements in objective response rate (ORR) and progression-free survival (PFS) in non-small-cell lung cancer (NSCLC) [15]. However, randomized trials have not yet demonstrated a significant benefit in terms of overall survival (OS). In the CodeBreaK 200 trial, sotorasib improved PFS compared with docetaxel (5.6 vs. 4.5 months; hazard ratio [HR] 0.66 [95% CI: 0.51, 0.86]; P=0.002) and showed a higher ORR (28% vs. 13%; P<0.001), but no OS advantage (10.6 vs. 11.3 months; HR 1.01 [95% CI: 0.77, 1.33]; P=0.53) [16]. Similarly, in the KRYSTAL-1 trial, adagrasib achieved an ORR of 43% with median OS ~14 months in a single-arm setting, while the phase III KRYSTAL-12 study showed a PFS benefit vs. docetaxel (5.5 vs. 3.8 months; HR 0.58 [95% CI: 0.45–0.76], *P*<0.0001), with OS data still immature [17,18].

The present systematic review and meta-analysis aim to summarize the available evidence regarding *KRAS* G12C-directed therapies in metastatic CRC (mCRC) and to evaluate their efficacy in terms of ORR and PFS, considering both monotherapy and combination strategies.

Materials and methods

Aim of the study

The objective of this study was to identify and examine the current evidence on pharmacological agents that specifically target the *KRAS* G12C mutation in CRC, and to evaluate their efficacy in both monotherapy and combination therapy contexts.

Identification of studies

We searched PubMed, Scopus, and ISI Web of Knowledge Central Register of Trials, with filter "human" and "adults". We used "G12C" and ("colon" or "rectal" or "colorectal") and "treatment" as a searching algorithm. The search covered the period January 2020 to September 2025, and was last updated in September 2025. For each included trial, the date of inclusion corresponds to the first public report (often as a conference poster or abstract). Whenever subsequent peer-reviewed publications or updated datasets became available in clinical trial registries or journals, these were also incorporated to provide the most complete dataset for each study. Based on the title and abstract, we downloaded or requested full articles. Duplicates across databases were identified and removed using EndNote software, followed by manual verification. Reference lists in these trials were checked to identify any other published or unpublished data. In order to minimize the loss of relevant data not found by library searches, we hand-searched the references of review articles and evaluated symposia proceedings, poster presentations, and the last 5 years' major oncology conferences of the American Society of Clinical Oncology, European Society for Medical Oncology, American Society of Clinical Oncology GI, and European Society for Medical Oncology GI. We also searched the last 5 years of 6 major oncology journals (JCO, Lancet Oncology, Lancet, Annals of Oncology, New England, JAMA Oncology). Two researchers performed parallel independent assessments of the manuscripts. Discrepancies between the reviewers' findings were discussed and resolved with the involvement of a third researcher.

Study eligibility

Patients included in the trial had to have a histologically confirmed diagnosis of an unresectable or mCRC harboring

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a *KRAS* G12C mutation in the tumor tissue or circulating tumor DNA on the basis of polymerase chain reaction or next-generation sequencing. We included only patients with CRC. Studies referring to solid tumors were excluded unless they specifically identified patients with CRC. Additionally, all patients included in the studies had to be adults. The study only included clinical trials of G12C drugs, regardless of whether they were randomized or not. Case reports were excluded. Both completed and ongoing studies with published results (including interim analyses and poster presentations) were eligible. Only studies published in English were included.

Data extraction

From each eligible study we recorded the study's name and ID; the study design; the number of patients initially scrutinized and the number of patients eligible and analyzed; the patients' performance status; all the previous treatments and the current treatment (*KRAS* G12C inhibitor monotherapy or in combination with other treatments); the molecular profile; and the numbers of patients who had a complete response, partial response, stable disease or progressive disease, as well as the PFS, with their 95% confidence intervals (CI).

Risk of bias evaluation

Due to the nature of the available evidence—most data originating from early-phase trials, abstracts, or conference posters—the risk of bias assessment was particularly challenging. The ROBINS-I tool, although designed for non-randomized studies, proved inadequate in this context, and uniformly rated most abstracts as having "serious risk of bias," largely reflecting incomplete reporting rather than true methodological flaws. In addition, because fewer than 10 studies reported each outcome, formal statistical tests for publication bias (funnel plot inspection, Egger's test) were not feasible, as their application under such conditions would produce unreliable and potentially misleading results. These limitations are acknowledged in the interpretation of our findings.

Statistical analysis

We performed a meta-analysis of proportions and present overall pooled estimates with inverse-variance weights obtained from a random-effects model, as well as their respective 95%CI [19]. We were able to calculate the pooled rates of objective response, stable disease, and progressive disease when the number of cases for the corresponding outcomes was provided in the studies. ORR referred to the patients with either a partial or a complete response. Results were shown overall, as well as by subgroups based on monotherapy or combined therapy. Statistical heterogeneity was assessed using the I^2 statistic. Values of 25, 50, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively [20]. All statistical analyses were performed using Stata version 14 (Stata Corp, College Station, TX, USA).

Protocol and reporting

This review was conducted in accordance with the PRISMA 2020 guidelines, the completed PRISMA checklist is provided in Supplementary Table 1. No protocol was registered in PROSPERO; however, all methods were pre-specified prior to data extraction to ensure transparency.

Results

Search and selection processes results

The electronic searches were applied in October 2024 and returned 408 studies: 167 in PubMed, 119 in Scopus, and 122 in ISI Web of Knowledge. Of these, 355 were excluded by abstract or title, or as duplicates, and 44 by full-text article analyses. As a result, only 7 eligible trials were identified from database searches, and in most of them, the available data were only presented at conferences. Screening for abstracts of major oncology conferences until October 2024 led to the identification of 10 further eligible studies. However, relevant data from these studies were available in their poster presentations (Fig. 1).

Characteristics of the included studies

Overall, we analyzed data from 17 clinical trials involving 663 patients with *KRAS* G12C-mutated mCRC. Three studies were phase 1, 1 study was a pooled analysis of 2 phase 1 trials, 5 studies were phase 1-1B, 5 studies were phase 1-2, 1 study was phase 2, and 1 was a randomized phase 3 trial with 3 arms. Detailed information on previous lines of therapy was provided in 7 studies, while the trial by Siena *et al*, investigating sotorasib plus panitumumab and FOLFIRI, required no prior line of systematic treatment for metastatic disease [21].

All patients had been pretreated with chemotherapy, and some had additionally received an EGFR inhibitor (cetuximab or panitumumab), anti-vascular endothelial growth factor therapy, or immunotherapy. In 2 studies by Hong and Desai in 2023 [22,23] it was mentioned that patients had previously received a *KRAS* G12C inhibitor. The age range was from 29-87 years (Table 1).

Monotherapy

Sacher's study on divarasib as monotherapy included 55 patients, with a total PFS of 5.6 months (95%CI 4.1-8.2). Twenty patients had an objective response, 27 had stable disease, and 6 had progressive disease [24].

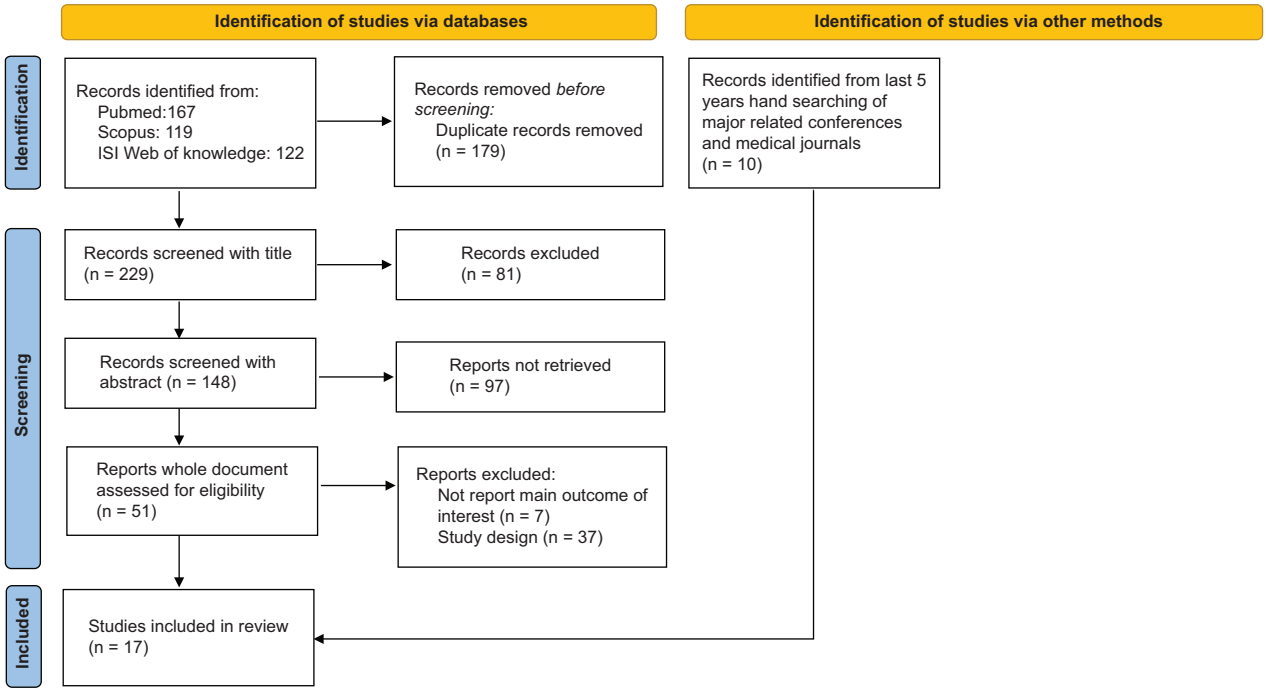

Figure 1 Flow chart

In Sai-Hong Ou's study on adagrasib as monotherapy in patients with advanced solid tumors, the overall PFS for CRC was not reported. Four patients with CRC received adagrasib as monotherapy, with 1 having an objective response and 3 having stable disease [25].

Two studies by Fakih and Hong focused on sotorasib as monotherapy [14,26]. In Fakih's study, 62 patients participated, with 6 having an objective response, 45 having stable disease, and 11 having progressive disease, with a total PFS of 4 months (95%CI 2.8-4.2). In Hong's study, 42 patients participated, with 3 having an objective response, 28 having stable disease, and 10 having progressive disease, with a total PFS of 4 months.

Two studies focused on olomorasib (LY3537982). Murciano-Goroff *et al* evaluated 56 patients with *KRAS* G12C-mutant advanced solid tumors, including 17 patients with CRC [27]. The median number of prior systemic therapies was 2 (range 0-8), and the patients received LY3537982 monotherapy in doses ranging from 50-200 mg b.i.d. One patient had an objective response, 13 had stable disease, and only 1 had progressive disease. A study by Heist *et al* enrolled 157 patients with advanced *KRAS* G12C-mutant solid tumors, including 32 CRC [28]. The median age was 65 years (range 36-85), and the median number of prior systemic therapies was 3 (range 0-11), with 29 of the 157 patients having received prior *KRAS* G12C inhibitor treatment. Of 32 patients with CRC, 9% had an objective response, 75% stable disease, and 3 patients had progressive disease.

Garralda's study on divarasib included 153 patients with advanced *KRAS* G12C-positive solid tumors, 61 with CRC, and 33.3% of them had an objective response. The median number of prior systemic therapies was 2, with a range of 0-8, and none of the patients had received prior *KRAS* G12C inhibitor treatment [29].

Yuan's study on IBI351 (GFH925) enrolled 56 mCRC patients with *KRAS* G12C mutations; their median age was 58 years, and 60.7% of the patients were male. Additionally, 60.7% of the patients had liver metastasis, 73.2% had an ECOG performance status of 1, and 60.7% had received at least 2 prior lines of treatment. A total of 48 patients were studied at the 600 mg b.i.d. dose, of whom 45.8% showed an objective response and 43.8% stable disease. In the other 7 patients, only treatment-related adverse events were studied [30,31].

Chul Cho's study on D3S-001 included 42 patients with advanced/metastatic solid tumors harboring *KRAS* G12C mutations, comprising 13 with CRC, of whom 9 had never been treated with a *KRAS* G12C inhibitor (G12Ci) before; 77.8% of them had an objective response, and 11.1% had stable disease. The median follow-up period was 6.8 months, and 50% of the patients were still receiving treatment at the time of the analysis [32,33].

Ruan's study on D-1553 enrolled 24 patients with locally advanced or mCRC harboring *KRAS* G12C mutations, with a median age of 61.5 years (range 44-74); 54.2% of the patients were male. The majority of patients (66.7%) had received 2 or more prior lines of therapy, and 95.8% had stage IV disease. The confirmed partial response rate was 20.8% (5 out of 24 patients), and the disease control rate was 95.8% [34].

Combination therapy

Desai's study focused on divarasib plus cetuximab [23], with 24 patients participating. Sixteen had an objective response, and 8 had stable disease, with no progressive disease. The PFS was 8.1 months (95%CI 5.5-12.3).

Table 1 Basic study characteristics

Study/treatment [ref.]	Study type	Median age (years)	Previous treatment	Patients
Fakih, 2023 (sotorasib + panitumumab [34]	Phase 3 randomized	59	FOLFOXIRI, FOLFOX, FOLFIRI, trifluridine/ tipiracil, regorafenib	53
Desai, 2023 (divarasib + cetuximab) [23]	Phase 1b	60	FOLFOXIRI, FOLFOX, FOLFIRI, bevacizumab, prior *KRAS* G12C inhibitor	24
Yaeger, 2023 (adagrasib ± cetuximab) [38]	Phase 1–2	54	FOLFOXIRI, FOLFOX, FOLFIRI anti-VEGF, anti-EGFR, regorafenib/trifluridine, anti-PD-1/ PD-L1	71
Kuboki, 2024 (sotorasib + panitumumab) [35]	Phase 1b	55	FOLFOXIRI, FOLFOX, FOLFIRI, anti-VEGF, trifluridine, regorafenib	40
Hong, 2023 (sotorasib + panitumumab + FOLFIRI) [22]	Phase 1b	53	FOLFIRI, sotorasib	31
Siena, 2024 (sotorasib + panitumumab + FOLFIRI) [21]	Phase 1b	60	No prior systemic therapy for metastatic disease	40
Song, 2024 (ifebemtinib + D-1553) [37]	Phase 1b/2	Not reported	At least 1 prior line of systemic therapy	15
Sacher, 2023 (divarasib)* [24]	Phase 1	58	FOLFOX, FOLFIRI, FOLFOXIRI, bevacizumab	55
Sai-Hong Ou, 2022 (adagrasib)* [25]	Phase 1/1b	58	Not reported	4
DS Hong, 2021 (sotorasib) [26]	Phase 1	58	At least 2 prior lines of systemic therapy	42
Fakih, 2022 (sotorasib) [14]	Phase 2	55	FOLFOXIRI, bevacizumab, trifluridine/tipiracil, regorafenib, anti-PD-1/PD-L1	62
Murciano-Goroff, 2024 (LY3537982)* [27]	Phase 1–2	Not reported	Median 2 prior lines (range 0-8)	56
Garralda, 2024 (divarasib) [29]	Phase 1	Not reported	Median 2 prior lines (range 0-8)	153
Heist, 2024 (LY3537982)* [28]	Phase 1–2	61	Median 3 prior lines (range 0-11), *KRAS* G12C inhibitor	32
Yuan, 2023 (IBI351) [30,31]	Pooled analysis of 2 phase 1 studies	58	At least 2 prior lines of systemic therapy	56
Chul Cho, 2024 (D3s-001) [32,33]	Phase 1–2	Not reported	Median 2 prior lines (range 0-6)	42
Ruan, 2024 (D-1553) [34]	Phase 1–2	59	Median 2 prior lines (range 1-6)	24

*Demographics refer to all patients with KRAS-G12C solid tumors included in these trials

FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1

One study focused on sotorasib plus panitumumab with 40 patients [35]. Twelve had an objective response, 25 had stable disease, and 3 had progressive disease, with a PFS of 5.7 months (95%CI 4.2-7.7).

Another study with 31 patients also focused on sotorasib plus panitumumab and FOLFIRI [22]. It was reported that 58.1% had a response and 93.5% had stable disease. This study was available only as a poster, so further data could not be collected.

Fakih *et al* investigated sotorasib in combination with panitumumab [36] in a randomized phase 3 clinical trial. Patients were divided into 3 arms: 53 patients received sotorasib plus panitumumab at a dose of 240 mg; 53 patients received sotorasib plus panitumumab at a dose of 960 mg; and 54 patients received standard care. For our analysis, we were interested in the first 2 arms. Among the 53 patients who received the 240 mg dose, 3 had an objective response, 33 had stable disease, and 13 had progressive disease, with a PFS of 3.9 months (95%CI 3.7-5.8). Among the 53 patients who received the 960 mg dose, 14 had an objective response, 24 had stable disease, and 12 had progressive disease, with a PFS of 5.6 months (95%CI 4.2-6.3).

Siena's study on sotorasib plus panitumumab enrolled 40 treatment-naïve patients with *KRAS* G12C-mutated mCRC: 30 of them had an objective response, 7 had stable disease, and only 1 had progressive disease [21].

Song's study, focused on D-1553 with ifebemtinib (IN10018), enrolled 15 patients with *KRAS* G12C-mutant mCRC, all of whom had received at least 1 prior line of therapy: 50% had an objective response and 35.7% had stable disease [37].

Another study compared adagrasib monotherapy to the combination therapy of adagrasib and cetuximab [38]. In the monotherapy arm, 43 patients participated, with 8 having an objective response, 29 having stable disease, and 6 having progressive disease, with a total PFS of 5.6 months (95%CI 4.1-8.3). In the combination therapy arm, 28 patients participated,

with 13 having an objective response, 15 having stable disease, and none having progressive disease, with a PFS of 6.9 months (95%CI 5.4-8.1) (Table 2).

Meta-analysis outcomes

Objective response rate

Fig. 2 presents data from CRC patients who received a *KRAS* G12C inhibitor, either as monotherapy or in combination with other drugs, and presented an objective response, partial or complete. Divarasib, adagrasib, sotorasib, and D-1553 were studied as monotherapies and in combination with cetuximab or panitumumab. As monotherapies, the ORRs ranged from 7-36%. When combined with cetuximab or panitumumab or panitumumab and FOLFIRI or ifebemtinib, the rates ranged between 6% and 75%. There were also 3 drugs, all non-FDA approved, which were studied as monotherapies only. Overall, the combination therapies showed a higher total ORR of 43% compared to 23% for the monotherapies. Combination therapies seem to be more effective in achieving a positive response in the treatment of CRC with *KRAS* G12C inhibitors, apart from treatment with D3S-001.

The highest ORR observed was for monotherapy with D3S-001, which had an ORR of 78% [31]. The lowest was for the combination therapy of sotorasib 240 mg plus panitumumab, with an ORR of 6% [34]. Overall, the combined ORR for all therapies mentioned in the document was 32%.

For monotherapy, the heterogeneity value was 84.79%, while for combination therapy, the heterogeneity value was 94.96%, both suggesting a high degree of heterogeneity among the studies in this group.

Stable disease rate

Fig. 3 shows data from patients who received different *KRAS* G12C inhibitors, either as monotherapy or in combination with other drugs, and presented stable disease. For monotherapy, the stable disease rate ranged from 11-87%, with an overall rate of 62%. For combination therapy, the rate varied from 17-63%, with an overall rate of 44%. The overall stable disease rate across all studies was 55%.

The highest stable disease rate reported was among the monotherapy studies: 87% for patients treated with LY3437982 [27]. The lowest was also among the monotherapy

Table 2 Outcomes of studies on monotherapy or combination therapy

Study/treatment [ref.]	Patients	Objective response	Stable disease	Progressive disease
Combination therapy				
Fakih, 2023 (sotorasib + panitumumab 960 mg) [36]	53	14 (26.4%)	24 (45.3%)	12 (22.6%)
Fakih, 2023 (sotorasib + panitumumab 240 mg) [36]	53	3 (5.7%)	33 (62.3%)	13 (24.5%)
Desai, 2023 (divarasib + cetuximab) [23]	24	16 (66.7%)	8 (33.3%)	0
Yaeger, 2023 (adagrasib + cetuximab) [38]	28	13 (46.4%)	15 (53.6%)	0
Kuboki, 2024 (sotorasib + panitumumab) [35]	40	12 (30.0%)	25 (62.5%)	3 (7.5%)
Hong, 2023 (sotorasib + panitumumab + FOLFIRI) [22]	31	18 (58.1%)	29 (93.5%)	0
Siena, 2024 (sotorasib + panitumumab + FOLFIRI) [21]	40	30 (75.0%)	7 (17.5%)	1 (2.5%)
Song, 2024 (ifebemtinib + D-1553) [37]	15	7 (46.7%)	5 (33.3%)	Not Reported
Monotherapy				
Sacher, 2023 (divarasib) [24]	55	20 (36.4%)	27 (49.1%)	6 (10.9%)
Ou, 2022 (adagrasib) [25]	4	1 (25.0%)	3 (75.0%)	0
Hong, 2021 (sotorasib) [26]	42	3 (7.1%)	28 (66.7%)	10 (23.8%)
Fakih, 2022 (sotorasib) [14]	62	8 (12.9%)	45 (72.6%)	11 (17.7%)
Yaeger, 2023 (adagrasib) [38]	43	8 (18.6%)	29 (67.4%)	6 (14.0%)
Murciano-Goroff, 2024 (LY3537982) [27]	15	1 (6.7%)	13 (86.7%)	1 (6.7%)
Garralda, 2024 (divarasib) [29]	45	15 (33.3%)	Not Reported	Not Reported
Heist, 2024 (LY3537982) [28]	32	3 (9.4%)	24 (75.0%)	3 (9.4%)
Yuan, 2023 (IBI351) [30,31]	48	22 (45.8%)	21 (43.8%)	Not Reported
Chul Cho, 2024 (D3S-001) [32,33]	9	7 (77.8%)	1 (11.1%)	Not Reported
Ruan, 2024 (D-1553) [34]	24	5 (20.8%)	18 (75.0%)	1 (4.2%)

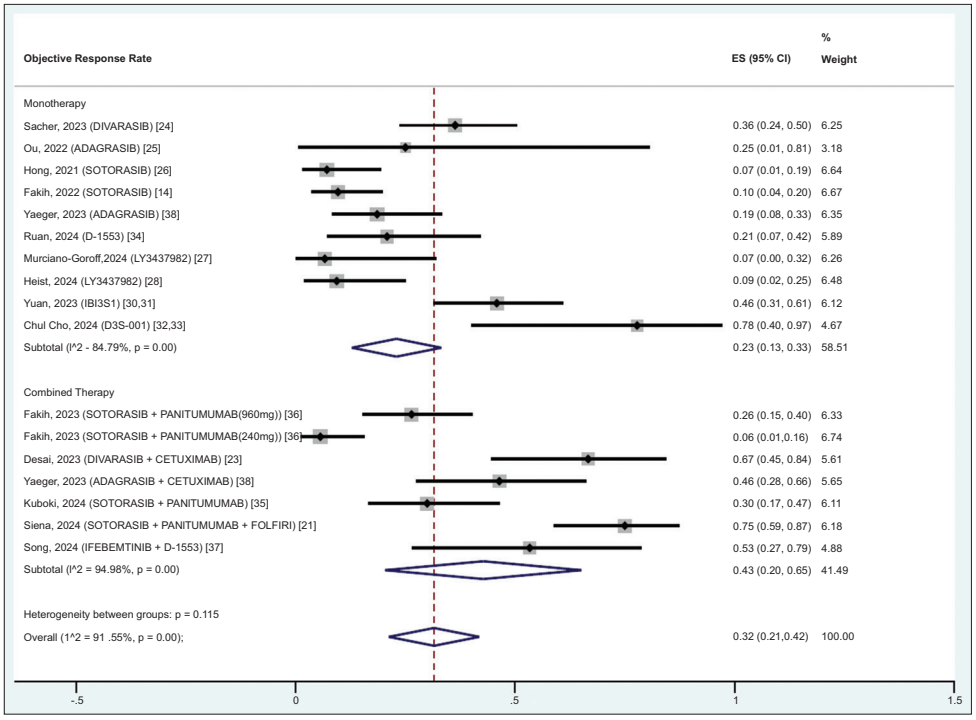

Figure 2 Dendrogram presenting analysis of objective response rate
CI, confidence interval

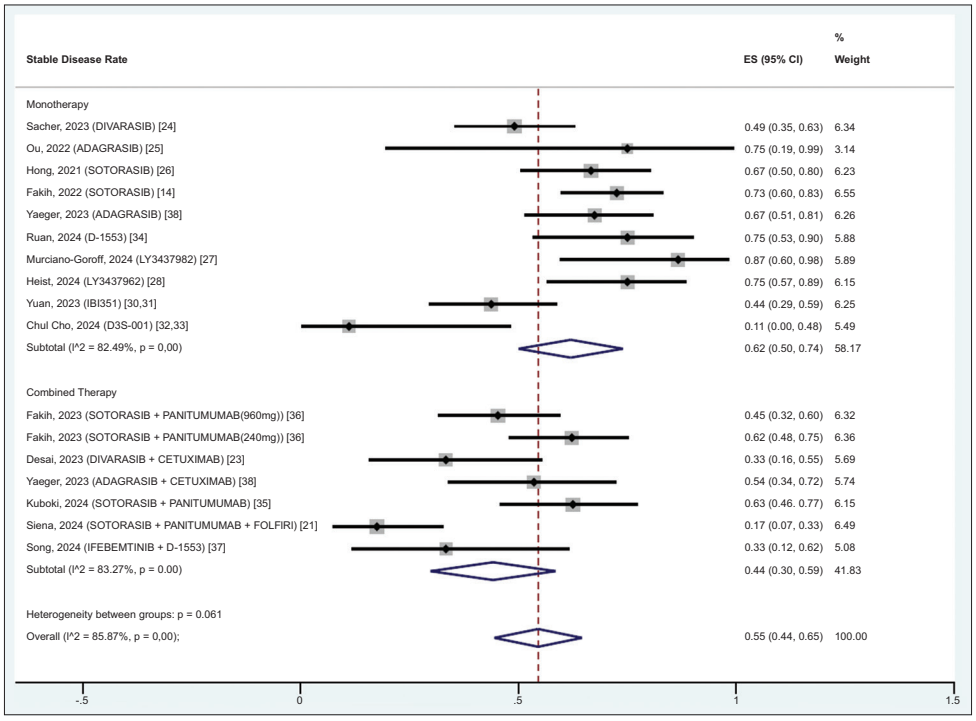

Figure 3 Dendrogram presenting analysis of stable disease rate
CI, confidence interval

studies: 11%, as reported by the study of Chul Cho *et al* for D3S-001 [32,33].

There was high heterogeneity in the monotherapy and combination therapy groups, with the I^2 values being 82.49%

and 83.27%, respectively. These values indicate the degree of heterogeneity among the studies in each group. For the overall stable disease rate across all studies, the I^2 value was 85.87%, suggesting a high level of heterogeneity across all the included studies.

Disease control rate

Fig. 4 presents data from patients who received a *KRAS* G12C inhibitor and presented with disease control. In treatment with monotherapies, the ORRs ranged from 1-96%. When combined with cetuximab or panitumumab or panitumumab and FOLFIRI or ifebemtinib, the rates also ranged between 1% and 93%. Overall, the combination therapies showed a higher total disease control rate of 96%, compared to 89% for the monotherapies.

The highest disease control rate observed was for monotherapy with D-1553 [34,39]. Overall, the combined ORR for all therapies mentioned in the document is 32%.

For monotherapy, the heterogeneity value was 84.79%, while for combination therapy it was 94.96%, both suggesting a high degree of heterogeneity among the studies in this group.

Progressive disease rate

Fig. 5 displays data from patients who received a *KRAS* G12C inhibitor, either as monotherapy or in combination with other drugs, and presented progressive disease. Divarasib, adagrasib, sotorasib and D-1553 were studied as monotherapies, and in combination with cetuximab or panitumumab or panitumumab and FOLFIRI or ifebemtinib. As monotherapies, the progressive disease rates ranged from 0-24%. When combined with cetuximab or panitumumab or panitumumab, the rates were between 0% and 25%. Overall, the combination therapies showed a lower total progressive disease rate of 0% (95%CI 0.00-0.01) compared to 10% (95%CI 0.04-0.16) for the monotherapies. Combination therapies seem to be more effective in achieving the lowest possible progressive disease rate.

The highest progressive disease response rate was observed for the combination therapy of sotorasib plus panitumumab at 240 mg, at 25% [36], while the lowest was 0% for monotherapy with adagrasib [25] and the combination therapies with divarasib plus cetuximab [23], adagrasib plus cetuximab [38], and sotorasib plus panitumumab plus FOLFIRI [22]. Overall, the combined progressive disease rate for all therapies mentioned in the document was 1% (95%CI 0.00-0.02).

For monotherapy, the heterogeneity value was 79.84%, indicating high heterogeneity among the studies. Similarly, for combination therapy, the heterogeneity value was 81.60%, suggesting a high degree of heterogeneity among the studies in this group.

Discussion

In the present review, we estimated the efficacy of *KRAS*-G12C inhibitors in mCRC. *KRAS*-G12C inhibitors

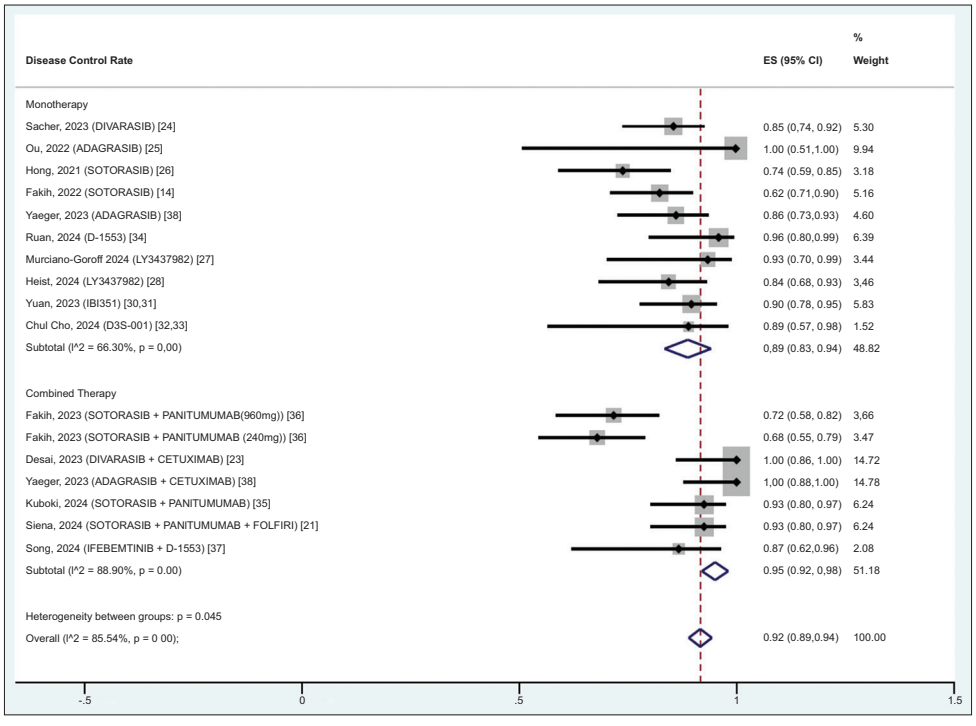

Figure 4 Dendrogram presenting analysis of disease control rate
CI, confidence interval

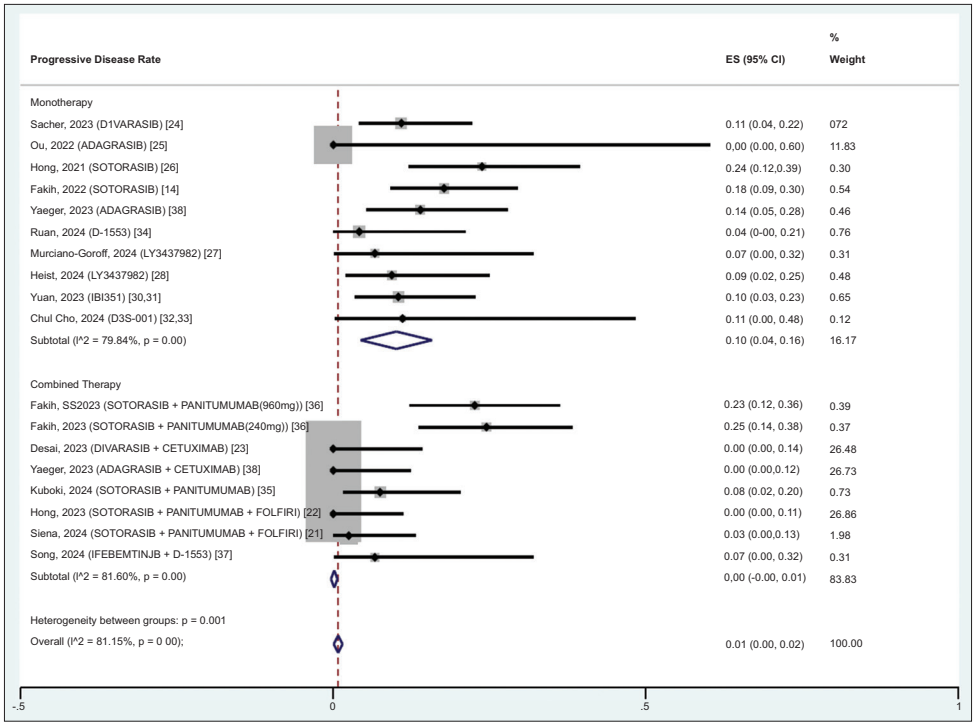

Figure 5 Dendrogram presenting analysis of progressive disease
CI, confidence interval

as monotherapy and as combination treatment appear to improve patients' clinical outcomes. The majority of patients had stable disease or an objective response. Patients treated with D3S-001 monotherapy, or a combination therapy of sotorasib with panitumumab and FOLFIRI, had the highest ORR, 78% (95%CI 0.40-0.97) and 75% (95%CI 0.59-0.87), respectively [21,32]. On the other hand, patients who received sotorasib and panitumumab at 240 mg presented with the biggest progressive disease rate at 25% (95%CI 0.14-0.38) [34].

All our meta-analyses demonstrated substantial heterogeneity. We attribute this primarily to the limited number of studies, the small patient populations, the early-phase design of most trials, and the diversity of agents investigated. Moreover, some included studies enrolled patients previously treated with *KRAS* G12C inhibitors, which may have influenced subsequent responses and further contributed to variability. Importantly, this degree of heterogeneity indicates that pooled estimates should be interpreted with caution, as differences in trial design, patient selection, and prior therapeutic exposures may significantly impact reported outcomes. From a clinical perspective, such variability underscores that treatment efficacy cannot be assumed to be uniform across all settings, highlighting the need for adequately powered, randomized phase III trials to establish the true benefit of *KRAS* G12C inhibitors in mCRC.

Just a single systematic literature review on the efficacy of *KRAS*G12C inhibitors in the treatment of CRC had been published up to May 2024; moreover, this review was only a narrative one. The findings indicate that *KRAS*G12C mutations are linked to a lesser response to conventional therapies and shorter RFS in patients with CRC. The introduction of targeted agents has the potential to reverse these unfavorable outcomes. Agreeing with our results, this systematic literature review refers to the positive results of the CodeBreak 300 trial, where sotorasib and panitumumab were used. Other *KRAS*G12C inhibitors are presented, such as divarasib and adagrasib as monotherapy, and the authors of the review expected that the combination of these agents with anti-EGFR therapies could improve even more patients' clinical outcomes, an expectation that is confirmed by the numbers of our meta-analysis [40].

This meta-analysis was conducted to investigate the efficacy and toxicity of *KRAS*G12C inhibitors, but it included studies of all types of solid tumors. Out of 10 studies analyzed, only 5 of them reported results from CRC patients, and all these were included in our meta-analysis. According to Dang *et al*, the PFS rate of patients with CRC and *KRAS*G12C mutation who underwent therapy with *KRAS*G12C inhibitors was 0.357 (95%CI 0.234-0.490) at 6 months and 0.137 (95%CI 0.086-0.196) at 12 months, while OS was 0.881 (95%CI 0.811-0.938) at 6 months and 0.530 (95%CI 0.433-0.625) at 12 months. All these sub-analyses were performed on a percentage of the studies, given the lack of data. For this reason, we chose not to present these sub-analyses in our review, but we consider it worthwhile to mention these results [41].

To the best of our knowledge, this is the first meta-analysis of clinical studies on *KRAS*-G12C inhibitors for CRC. This is the only study that has focused exclusively on CRC, rather than on solid tumors in general, given that data on NSCLC are of superior quality and more abundant. Only FDA-approved drugs, which are hence available to clinical practitioners, are

included. We present the available results of all therapies, monotherapy or combined, separately and overall. As far as limitations are concerned, *KRAS*-G12C inhibitors were developed in the last 4 years and as a result, all studies included are recently published, with a small number of participants and in their early stages. At least 15 more agents are in the pipeline and have shown promising data, but so far, there has been no approval or published results. Data on OS were available in only 2 of 17 studies, and so were not included. Two studies among those included are ongoing and have not published all of their data, while 9 were only published as e-posters at conferences.

Overall, the first data from the use of *KRAS*G12C inhibitors in mCRC are very promising. Data from randomized phase III trials in the mCRC setting are therefore of extreme importance to promote the use of these agents in standard clinical care.

Summary Box

What is already known:

- *KRAS* G12C mutations occur in approximately 3-4% of colorectal cancers (CRCs), and are associated with resistance to standard chemotherapy and anti-epidermal growth factor receptor (EGFR) therapy
- The development of covalent *KRAS* G12C inhibitors (such as sotorasib and adagrasib) has changed the therapeutic landscape in non-small-cell lung cancer, but evidence in CRC remains limited
- Most available data for *KRAS* G12C-mutant CRC originate from early-phase, small, non-randomized clinical trials
- The efficacy of combination strategies with anti-EGFR antibodies is under clinical investigation

What the new findings are:

- This is the first meta-analysis exclusively focusing on *KRAS* G12C-mutant metastatic CRC (mCRC)
- Combination regimens of *KRAS* G12C inhibitors with EGFR blockade show a markedly higher overall response rate (43%) compared with monotherapy (23%)
- Combination therapy achieves a lower progressive disease rate (1%) and the highest disease control rate (96%)
- These results highlight the potential of *KRAS* G12C inhibitors as a promising targeted strategy in mCRC and underscore the need for large, randomized phase III trials

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Supplementary material

Supplementary Table 1 PRISMA 2020 Checklist (Completed)

Section/Topic	Item #	Checklist Item	Reported in Manuscript
TITLE	1	Identify the report as a systematic review.	Title identifies as systematic review and meta-analysis
ABSTRACT	2	Provide a structured abstract.	Structured abstract provided
INTRODUCTION	3	Describe rationale.	Rationale clearly stated
INTRODUCTION	4	Describe objectives.	Objectives stated under "Aim of the study"
METHODS – Eligibility	5	Specify inclusion/exclusion criteria.	Inclusion/exclusion criteria explicitly described
METHODS – Information Sources	6	Specify all sources.	PubMed, Scopus, ISI Web, conferences, journals
METHODS – Search Strategy	7	Present full search strategy.	Search terms and timeframe described
METHODS – Selection Process	8	Describe study selection.	Two independent reviewers + third reviewer resolution
METHODS – Data Collection	9	Describe data collection process.	Data extraction items predefined
METHODS – Data Items	10	List all outcomes and variables.	ORR, SD, PD, PFS, demographics, study design
METHODS – Risk of Bias Assessment	11	Describe RoB assessment.	Narrative assessment due to limited reporting
METHODS – Effect Measures	12	Specify effect measures.	Proportions (ORR, SD, PD), PFS with 95%CI
METHODS – Synthesis Methods	13	Describe synthesis.	Random-effects meta-analysis using metaprop
METHODS – Reporting Bias Assessment	14	Describe reporting bias assessment.	Not feasible due to<10 studies per outcome
METHODS – Certainty Assessment	15	Certainty of evidence.	Not applicable (early-phase heterogeneous data)
RESULTS – Study Selection	16	Report numbers screened/included.	Provided and shown in PRISMA flowchart
RESULTS – Study Characteristics	17	Describe included studies.	Table 1 and detailed narrative
RESULTS – Risk of Bias	18	Present RoB assessment.	Narrative risk-of-bias discussion included
RESULTS – Individual Study Results	19	Present individual study results.	Table 2 + study-level outcomes in text
RESULTS – Synthesis Results	20	Present results of syntheses.	Figures 2–5 + pooled estimates
RESULTS – Reporting Biases	21	Report on reporting bias.	Not assessed formally; justified
RESULTS – Certainty of Evidence	22	Certainty of evidence.	Not applicable due to study designs
DISCUSSION – Summary of Evidence	23	Summarize evidence.	Main findings summarized
DISCUSSION – Limitations	24	Discuss limitations.	Extensive limitations described
DISCUSSION – Conclusions	25	Provide interpretation.	Clear conclusions provided
OTHER – Registration	26	Provide registration info.	No PROSPERO registration (reported)
OTHER – Support	27	Describe support/funding.	Conflict of interest reported; no funding declared