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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Drugs of choice in patients with G12C mutation in colorectal cancer: a systematic review and meta-analysis

Θεραπευτικές επιλογές για ασθενείς με μετάλλαξη G12C στον καρκίνο του παχέος εντέρου: συστηματική ανασκόπηση και μετα-ανάλυση

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths globally. The KRASG12C mutation, linked to poor responses to standard therapies, affects a subset of CRC patients. KRASG12C inhibitors, effective in non-small cell lung cancer, are now under investigation for CRC treatment.

Objectives: The primary aim of this study is to evaluate the clinical efficacy of KRASG12C inhibitors in patients with metastatic CRC. Additionally, the study aims to assess the potential of combination therapies compared to monotherapy regimens.

Methods: A literature search was conducted in PubMed, Scopus, and ISI Web of Knowledge, alongside oncology conference proceedings. Clinical trials involving KRASG12C-mutated CRC patients were included.

Results: Seventeen trials involving 663 patients were reviewed. Monotherapy with KRASG12C inhibitors showed a 23% objective response rate, while combination therapies achieved 43%. Disease control rates were higher with combination therapies (96%) than monotherapies. Progressive disease was lower with combination therapies (1%) compared to monotherapy (10%).

Conclusions: KRASG12C inhibitors, especially in combination regimens, demonstrate promise for metastatic CRC. High heterogeneity among studies highlights the need for larger phase III trials to validate these findings.

Keywords: Colorectal cancer, Targeted therapy, KRASG12C inhibitors, Meta-analysis

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Ο καρκίνος του παχέος εντέρου είναι ο τρίτος συχνότερος και δεύτερη αιτία θανάτου από καρκίνο παγκοσμίως. Η μετάλλαξη KRASG12C συνδέεται με περιορισμένη ανταπόκριση στη θεραπεία. Οι αναστολείς KRASG12C, που φάνηκαν αποτελεσματικοί στον μη μικροκυτταρικό καρκίνο πνεύμονα, διερευνώνται τώρα στον καρκίνο του παχέος εντέρου.

Στόχοι: Ο κύριος στόχος της μελέτης είναι η αξιολόγηση της αποτελεσματικότητας των αναστολέων KRASG12C σε ασθενείς με μεταστατικό καρκίνο παχέος εντέρου. Επιπλέον, η μελέτη αξιολογεί την υπεροχή της συνδυασμένης θεραπείας σε σύγκριση με τη μονοθεραπεία.

Μέθοδοι: Πραγματοποιήθηκε βιβλιογραφική ανασκόπηση στις βάσεις δεδομένων PubMed, Scopus και ISI Web of Knowledge, καθώς και στα μεγαλύτερα ογκολογικά συνέδρια. Περιλήφθηκαν κλινικές δοκιμές με ασθενείς με μεταστατικό καρκίνο παχέος εντέρου που φέρουν τη μετάλλαξη KRASG12C .

Αποτελέσματα: Εξετάστηκαν 17 μελέτες με 663 ασθενείς. Η μονοθεραπεία με αναστολείς KRASG12C παρουσίασε αντικειμενικής απόκρισης 23%, ενώ οι συνδυασμένη θεραπεία 43%. Τα

ποσοστά ελέγχου της νόσου ήταν υψηλότερα στη συνδυασμένη θεραπεία (96%) συγκριτικά με τη μονοθεραπεία. Το ποσοστό εξέλιξης της νόσου ήταν χαμηλότερο στη συνδυασμένη θεραπεία (1%) από ό,τι στη μονοθεραπεία (10%).

Συμπέρασμα: Οι αναστολείς KRASG12C, δείχνουν πολλά υποσχόμενοι στη θεραπεία του μεταστατικού καρκίνου παχέος εντέρου. Η υψηλή ετερογένεια μεταξύ των μελετών υπογραμμίζει την ανάγκη για δοκιμές φάσης ΙΙΙ προς επιβεβαίωση των ευρημάτων.

Λέξεις-κλειδιά: Καρκίνος παχέος εντέρου, Στοχευμένη θεραπεία, Αναστολείς KRASG12C, Μετα-ανάλυση

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 made in surgical and drug interventions, patients with advanced colorectal cancer still face grim prognosis, with a 5-year survival rate of approximately 14%.[3,4,5,6]

A great effort has been made to understand and target the oncogenetic background and the pathogenetic mechanisms of cancer cell proliferation and tumor development and metastasis. A broad spectrum of different mutations is related to Colorectal Cancer (CRC) oncogenesis which as a result presents high heterogeneity,[7] with the 75-80% of cases accounted for accumulation of mutations. Usually, these mutations are presented on TP53, APC, BRAF, PTEN and PI3K, while these related to the RAS family (KRAS, NRAS, HRAS) occur in more than 40% of cases. The KRAS proteins belong in the guanosine triphosphatases family (GTPase) and are involved in transducing the signal from activated receptors of the cell membrane like the epidermal growth factor receptor (EGFR), to the nucleus through the membrane-associated kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways.[8,9,10] Guanine nucleotide exchange factors (GEFs) such as the son of sevenless (SOS) and GTPase-activating proteins (GAPs) regulate the activity and affinity of KRAS protein with GTP [15,16]. Both the gene and the proteins have been thoroughly studied for their oncogenetic role in malignancies. KRAS mutations are the predominant type among the RAS family, with KRASG12 mutations being the most common among them.[11,12,13] G12D (Glycine to Aspartic acid), G12V (Glycine to Valine), G12C (Glycine to Cysteine), G12A (Glycine to Alanine) and G12S (Glycine to Serine) account for the investigated codon 12 mutations. These nucleotide exchanges lead to the continuous activation of the proliferation-associated MAPK & PI3K pathways which results in the accumulation of active proteins and thus tumor development.[14]

The presence of the KRASG12C mutation in CRC is associated with a less favorable response to treatment and a poor prognosis.[15] Nonetheless, KRASG12C targeted drugs, like Sotorasib, Adagrasib, and Garsorasib, have been developed and their application in non-small cell lung cancer

has shown positive results in prolonging patients' survival, [16] while their preliminary application in metastatic colorectal cancer is investigated in ongoing randomized clinical trials.[17,18]
The present systematic review of the literature and meta-analysis, aims to sum the comprehensive, available evidence for the use of KRASG12C directed drugs in colorectal cancer and assess the Progression Free Survival (PFS) of patients receiving this intervention.

MATERIALS AND METHODS

Aim of the Study

The objective of this study is to identify and examine the current evidence on pharmacological agents that specifically target the KRASG12C mutation in colorectal cancer (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 last search was updated in September 2024 including the latest publications from ESMO Congress (September 13-17). Based on the title and abstract, we downloaded or requested full articles. Reference lists in these trials were checked to identify any other published or unpublished data. In order to minimize the possibility to lose relevant data that couldn't be unearthed by library searches, we hand-searched the references of review articles and evaluated symposia proceedings, poster presentations, and last five years major oncology conferences American Society of Clinical Oncology, European Society for Medical Oncology, American Society of Clinical Oncology GI, European Society for Medical Oncology GI. We also searched the last five years of six 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 should have had a histologically confirmed diagnosis of an unresectable or metastatic colorectal cancer harboring a KRASG12C mutation in the tumor tissue or circulating tumor DNA on the basis of polymerase chain reaction or next-generation sequencing. We included exclusively patients with colorectal cancer. Studies referring to solid tumors were

excluded unless they specifically identified patients with colorectal cancer. Additionally, all patients included in the studies should have been adults. The study only included clinical trials of G12C drugs, regardless of whether they were randomized or not. Case reports were excludedWe included both completed and ongoing studies with published results.

Data extraction

From each eligible study we recorded study's name and the ID, study's 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 (KRASG12C inhibitor monotherapy or in combination with other treatments), the molecular profile, the number of patients that had complete response, partial response, stable disease or progressive disease and progression free survival with their 95% CI.

Risk of Bias Evaluation

In this systematic review, the risk of bias evaluation faced challenges, as a significant portion of the data is derived from conference posters rather than full scientific publications. The use of the ROBINS-I tool, which is designed for more structured, comprehensive studies, proved inadequate for this type of data. When applied, most posters were categorized as serious risk of bias, a classification that does not necessarily reflect the actual quality or reliability of their findings.

Statistical Analysis

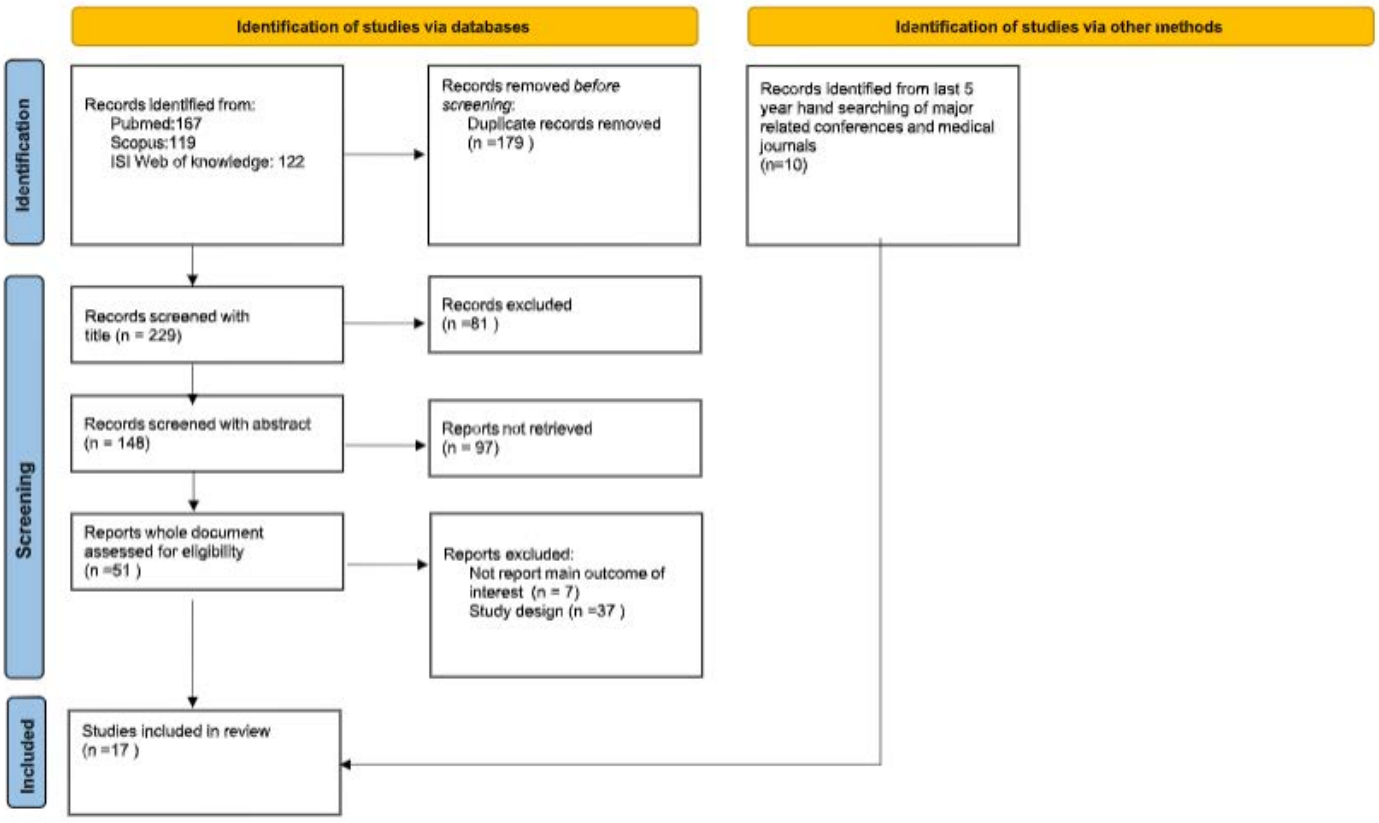
We performed a meta-analysis of proportions and present overall pooled estimates with inverse-variance weights obtained from a random-effects model, as well as their respective 95% confidence intervals.[19] We were able to calculate the pooled rates of objective response, stable disease and progressive disease, when the number of cases for the corresponding outcomes were provided in the studies. Objective response rate referred to the patients with either partial or complete response. Results were shown overall, as well as by subgroups of monotherapy and combined therapy. Statistical heterogeneity was assessed using the I2 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).

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 articles analyses. As a result, only 7 eligible trials were identified from database searches. Nonetheless, data from most of the trials available was only presented in conference. Screening for abstracts of major oncology conferences, which took place until October 2024, led to the identification of 10 further eligible studies. However, relevant data from these studies were available in their poster presentations. (Figure 1)

Figure 1: Flow chart



Characteristics of the included

Overall data from 17 clinical trials involved 663 patients with KRASG12C mutated metastatic colorectal cancer. Three studies were phase 1, one study was a pooled analysis of two phase 1 trials, five studies were phase 1-1B, five studies were phase 1-2, one study was phase 2 and one was a randomized phase 3 trial with 3 arms. Detailed information on previous lines of therapy was provided in 7 studies, while the trial for Sotorasib plus Panitumumab plus Folfiri by Siena et al. required no prior line of systematic treatment for metastatic disease.[21]

All patients had been pretreated with chemotherapy, and some had additionally received an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab), anti-VEGF therapy, or immunotherapy. In two studies, by David S. Hong and Desai (2023), [22,23] it was mentioned that patients had previously received a KRASG12C inhibitor. The age range was from 29 to 87 years. (Table 1)

Table 1: Basic study characteristics

NAME/TREATMENT	STUDY TYPE	AGE	PREVIOUS TREATMENT
Fakih,2023 (SOTORASIB + PANITUMUMAB)	PHASE 3 RANDOMIZED	35-82	oxaliplatin, irinotecan, and fluoropyrimidine (93.4%), trifluridine and tipiracil (13.2%), regorafenib (4.7%)
Desai,2023 (DIVAGRASIB + CETUXIMAB)	PHASE 1B	33-87	5-FU/capecitabine (100%), oxaliplatin (93,1%), irinotecan, (82,8%)bevacizumab (82,8%), KRAS G12C inhibitor (17,2%)
Yaeger,2023 (ADAGRASIB + CETUXIMAB/ADAGRASIB)	PHASE 1-2	29-79	Fluoropyrimidine, oxaliplatin , irinotecan, anti-VEGF ,anti-EGFR , regorafenib-trifluridine or both and PD-1 or PD-L1
Kuboki,2024 (SOTORASIB + PANITUMUMAB)	PHASE 1B	31-79	Oxaliplatin, irinotecan, fluopyrimidine and anti-angiogenic(100%), regorafenib and trifluride (18%), regorafenib and/or trifluridine (33%)
Hong, 2023 (SOTORASIB + PANITUMUMAB + FOLFIRI)	PHASE 1B	53(median)	Median prior lines of systemic therapy was 2 (range: 1-6), with 33% and 67% of pts receiving 1 or ≥ 2 prior lines, respectively; 97% had prior fluoropyrimidine and 73% had prior irinotecan. Two pts in dose exploration received prior Soto.
Siena, 2024 (SOTORASIB + PANITUMUMAB + FOLFIRI)	PHASE 1B	60(median)	No prior systematic therapy for metastatic disease
Song, 2024 (IFEBEMTINIB + D-1553)	PHASE 1B/2		At least 1 previous line of systemic therapy
Sacher,2023 (DIVAGRASIB)*	PHASE 1	34-81	fluoroyracil or capecitabine (100%), oxaliplatin (98%), irinotecan (84%), bevacizumab (62%)
Sai-Hong Ou, 2022 (ADAGRASIB)*	PHASE 1/1B	40-76	NA (prior systemic therapy)
D.S Hong, 2021 (SOTORASIB)*	PHASE 1	33-83	At least 2 previous lines of systemic therapy
Fakih, 2022 (SOTORASIB)	PHASE 2	49-61	Oxaliplatin (100%), Irinotecan (100%), Fluoropyrimidine (100%), Bevacizumab (90%), Trifluridine–tipiracil (TAS-102) (31%), Regorafenib (31%), Anti-PD1 or anti-PDL1 2 (3%)
Murciano-Goroff,2024* (LY3437982)	PHASE 1-2	NA	Lines of therapy: median 2, range 0-8
Garralda,2024* (DIVAGRASIB)	PHASE 1	NA	Lines of therapy: median 2, range 0-8
Heist,2024 (LY3437982)*	PHASE 1-2	36-85	Lines of therapy: median 3, range 0-11
Yuan,2023 (IBI351)	POOLED ANALYSIS OF TWO PHASE 1 STUDIES	58(median)	At least 2 previous lines of systemic therapy
Chul Cho, 2024 (D3S-001)*	PHASE 1-2	NA	NA
Ruan, 2024 (D-1553)	PHASE 1-2	44-74	Lines of therapy: median 2, range 1-6

Note: NA = Not Answered.

*Demographics refer to all patients with KRASG12C solid tumors included in these trials.

Monotherapy

In Sacher's study on divagrasib as monotherapy, 55 patients participated 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]

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

Two studies focused on sotorasib as monotherapy by D.S. Hong and Fakih.[26,27] In D.S. 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. 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).

Two studies focused on olomorasib (LY3537982) by Murciano-Goroff and Heist.[28,29] In Murciano-Goroff's study involved 56 patients with KRASG12C-mutant advanced solid tumors, including 17 patients with CRC. 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 BID. One patient has objective respone, 13 having stable disease and only 1 progressive disease. In Heist' study enrolled 157 patients with advanced KRASG12C-mutant solid tumors, including 32 CRC. The median age was 65 years (range 36-85), and the median number of prior systemic therapies was 3 (range 0-11), with 29 patients of the 157 having received prior KRASG12C inhibitor treatment. From 32 patients with CRC 9% had objective response, 75% stable disease and 3 patients had progressive disease.

In Gerralda's study on divagrasib included 153 patients with advanced KRASG12C-positive solid tumors, 61 with colorectal cancer (CRC) and the 33.3% of them had an objentive respone. The median number of prior systemic therapies was 2, with a range of 0-8, and none of the patients had received prior KRASG12C inhibitor treatment.[30]

In Yuan's study on IBI351 (GFH925) enrolled 56 metastatic colorectal cancer patients with KRASG12C mutations, with a median age of 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 two prior lines of treatment. A total of 48 patients were studied at the 600 mg BID dose having 45,8% objective response and 43.8% stable disease. For the other 7 patients were studied only Treatment-Related Adverse Events. [31]

In Chul Cho's study on D3S-001 included 42 patients with advanced/metastatic solid tumors harboring KRASG12C mutations, comprising 13 with CRC from whom 9 have never been treated with a KRASG12C inhibitor (G12Ci) before and 77.8% of them had 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]

In Ruan's study on D-1553 enrolled 24 patients with locally advanced or metastatic colorectal cancer harboring KRASG12C mutations, with a median age of 61.5 years (range 44-74), and 54.2% of the patients were male. The majority of patients (66.7%) had received two or more prior lines of therapy, and 95.8% had stage IV disease. The confirmed partial response (PR) rate was 20.8% (5 out of 24 patients) and the disease control rate (DCR) was 95.8%. [33]

Combination Therapy

Desai's study focused on divagrasib 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).

One study focused on sotorasib plus panitumumab with 40 patients.[34] 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 also focused on sotorasib plus panitumumab with 31 patients.[35] 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.

In Fakih's study on 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 are interested in the first two 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).

In Siena's study on sotorasib plus panitumumab enrolled 40 treatment-naïve patients with KRASG12C-mutated metastatic colorectal cancer (mCRC), 30 of them had objective response, 7 had stable disease and only one had progressive disease. [21]

In Song's study focused on D-1553 with ifebemtinib (IN10018) enrolled 15 patients with KRASG12C-mutant metastatic colorectal cancer (CRC), all of whom had received at least one prior line of therapy, 50% had objective response and 35,7% had stable disease. [37]

Furthermore, a comparative evaluation of adagrasib monotherapy was conducted in comparison 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)

Table 2: Outcomes of studies on monotherapy or combination therapy.

CURRENT TREATMENT	CASE SAMPLE	OBJECTIVE RESPONSE RATE	STABLE DISEASE	PROGRESSIVE DISEASE
COMBINATION THERAPY				
Fakih,2023 (SOTORASIB + PANITUMUMAB(960mg))	53	14	24	12
Fakih,2023 (SOTORASIB + PANITUMUMAB(240mg))	53	3	33	13
Desai,2023 (DIVAGRASIB + CETUXIMAB)	24	16	8	0
Yaeger,2023 (ADAGRASIB + CETUXIMAB)	28	13	15	0
Kuboki,2024 (SOTORASIB + PANITUMUMAB)	40	12	25	3
Hong, 2023 (SOTORASIB + PANITUMUMAB + FOLFIRI)	31	58.1% (1 pt prior Soto)	93.5% (1 pt prio Soto)	0
Siena, 2024 (SOTORASIB + PANITUMUMAB + FOLFIRI)	40	30	7	1
Song, 2024 (IFEBEMTINIB + D-1553)	15	50%	35,70%	NA
MONOTHERAPY				
Sacher, 2023 (DIVAGRASIB)	55	20	27	6
Sai-Hong Ou, 2022 (ADAGRASIB)	4	1	3	0
D.S Hong, 2021 (SOTORASIB)	42	3	28	10
Fakih, 2022 (SOTORASIB)	62	6	45	11
Yaeger, 2023 (ADAGRASIB)	43	8	29	6
Murciano-Goroff,2024 (LY3437982)	15	1	13	1
Garralda,2024 (DIVAGRASIB)	45	33,3%	NA	NA
Heist,2024 (LY3437982)	32	9%	75%	3(pt, not %)
Yuan,2023 (IBI351)	48	45,8%	43,8%	NA
Chul Cho, 2024 (D3S-001)	9	77,8%	11,1%	NA
Ruan, 2024 (D-1553)	24	5	18	1

Note: NA = Not Answered, pt = patients, Soto = Sotorasib

Meta-analysis outcomes

Objective response rate

Figure 2. Dendrogram presenting analysis on objective response rate

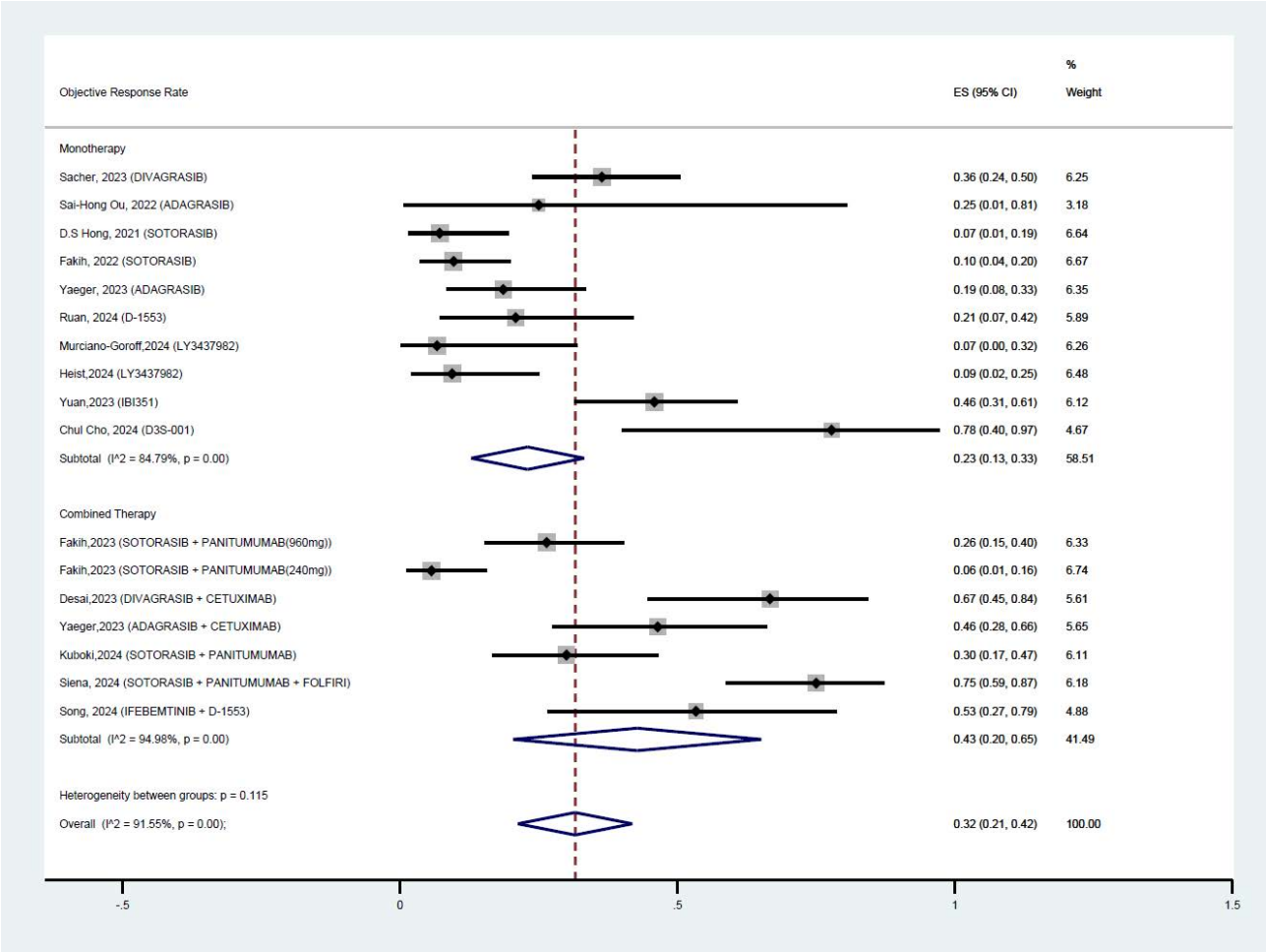


Figure 2. presents the data on patients who received a KRASG12C inhibitor, either as monotherapy or in combination with other drugs, and presented an objective response, partial and complete, of colorectal cancer. Divagrasib, adagrasib, sotorasib and D-1553 were studied as monotherapies and in combination with cetuximab or panitumumab. As monotherapies, the objective response rates ranged from 7% to 36%. When combined with cetuximab or panitumumab or panitumumab and folfiri or ifebemtinib, the rates ranged between 6% and 75%. There were also three drugs, all non-FDA approved which were studied as monotherapies only. Overall, the combination therapies showed a higher total objective response rate of 43% compared to 23% for the monotherapies. Combination therapies seem to be more effective in achieving a positive response in the treatment of colorectal cancer with KRASG12C inhibitors apart from treatment with D3S-001.
The highest objective response rate observed was for the monotherapy with D3S-001 which had an objective response rate of 78%.

The lowest objective response rate observed was for the combination therapy of Sotorasib 240mg plus panitumumab, with an objective response rate of 6%.
Overall, the combined objective response rate for all therapies mentioned in the document is 32%. For monotherapy, the heterogeneity value is 84.79% while for combination therapy, the heterogeneity value is 94.96%, both suggesting a higher degree of heterogeneity among the studies in this group.

Stable disease rate

Figure 3. Dendrogram presenting analysis on stable disease rate

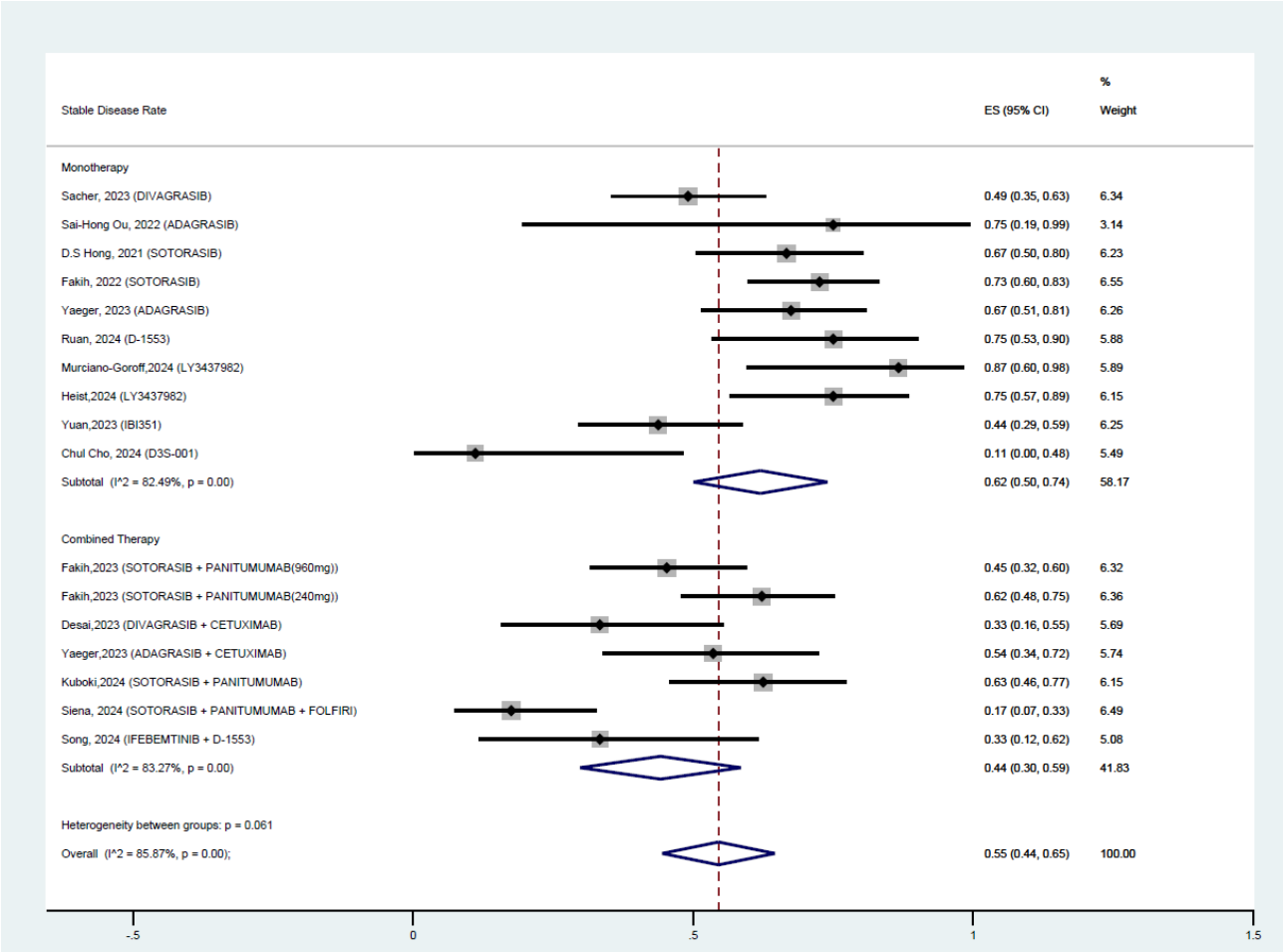


Figure 3. shows the data on patients who received different KRASG12C inhibitors, either as monotherapy or in combination with other drugs, and presented stable disease. For monotherapy, the stable disease rate ranged from 11% to 87%, with an overall rate of 62%. For combination therapy, the rate varied from 17% to 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. The lowest stable disease rate reported was also among the monotherapy studies, 11%, as reported by the study of Chul Cho et al. in 2024 on D3S-001.

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 higher level of heterogeneity across all the included studies.

Disease control rate

Figure 4. Dendrogram presenting analysis on disease control rate

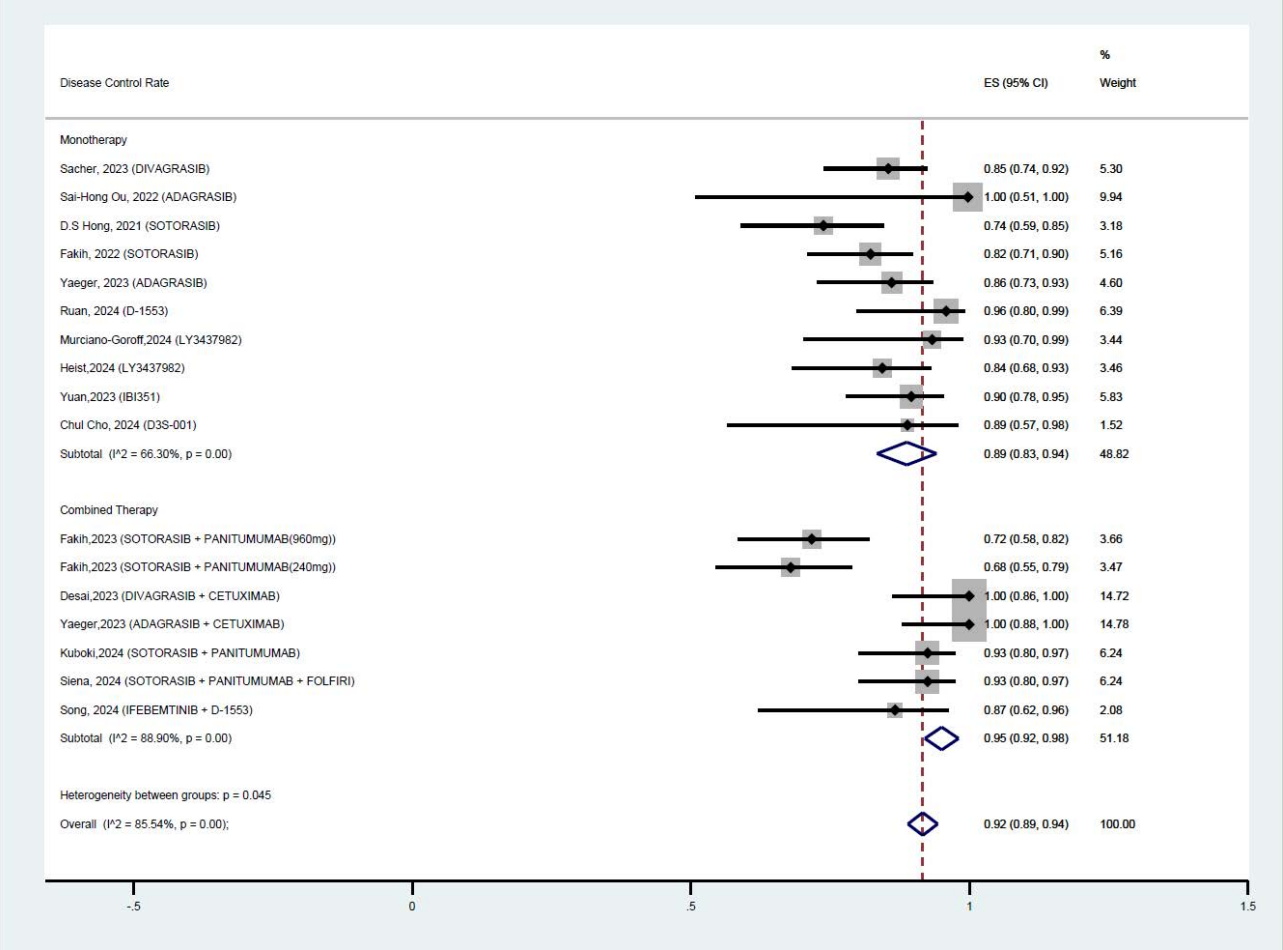


Figure 4. presents the data on patients who received a KRASG12C inhibitor and presented with disease control. In treatment with monotherapies, the objective response rates ranged from 1% to 96%. When combined with cetuximab or panitumumab or panitumumab and folfiri or ifebemtinib, the rates ranged also 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 the monotherapy with D-1553.

Overall, the combined objective response rate for all therapies mentioned in the document is 32%. For monotherapy, the heterogeneity value is 84.79% while for combination therapy, the heterogeneity value is 94.96%, both suggesting a higher degree of heterogeneity among the studies in this group.

Progressive disease rate

Figure 5. Dendrogram presenting analysis on progressive disease

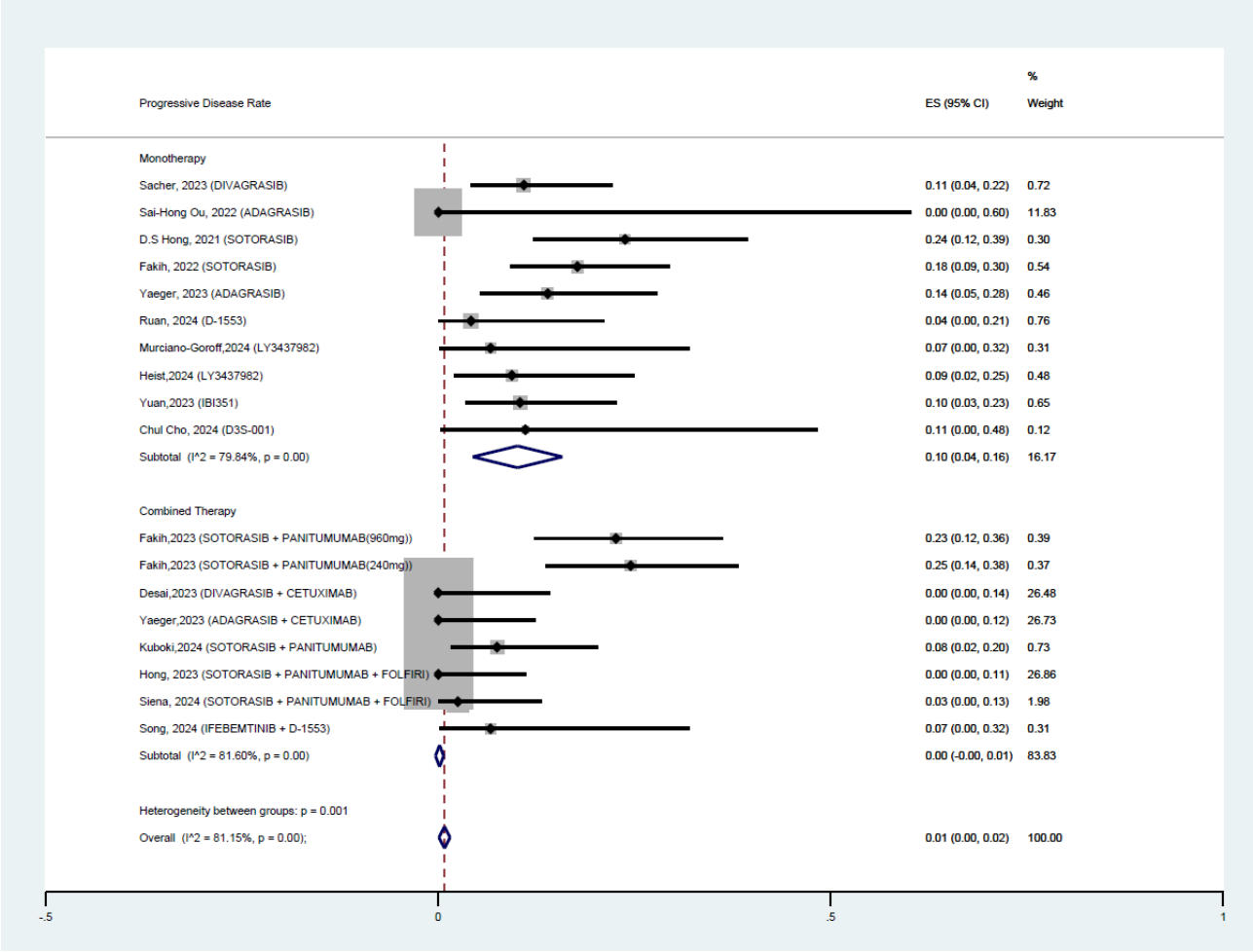


Figure 5. displays the data on patients who received a KRASG12C inhibitor, either as monotherapy or in combination with other drugs, and presented progressive disease. Divagrasib, adagrasib, sotorasib and D-1553 were studied as monotherapies and in combination with cetuximab or panitumumab or panitumumab and folfiri or ifebemtinib. As monotherapies, the progressive disease rates ranged from 0% to 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 in the combination therapy of Sotorasib with Panitumumab at 25% while the lowest one was 0% for the monotherapy with Adagrasib and the combination therapies with Divagrasib plus Cetuximab, Adagrasib plus Cetuximab and Sotorasib plus Panitumumab plus Folfiri.

Overall, the combined progressive disease rate for all therapies mentioned in the document is 1% (95% CI 0.00, 0.02).

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

DISCUSSION

In the present review, we estimate the efficiency of KRASG12C inhibitors in metastatic colorectal cancer. KRASG12C inhibitors 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 in combination therapy of sotorasib with panitumumab and folfiri had the highest objective response rate of 78% (95% CI 0.40-0.97) and 75% (95% CI 0.59-0.87), respectively. On the other hand, patients who received sotorasib and panitumumab at 240 mg presented with the biggest progressive disease rate, 25% (95% CI 0.14-0.38).

All our meta-analyses presented a large heterogeneity. We consider the small number of studies, the small sample in each study, their early stages, all the studies presented are phase 1 or 2 clinical trials and only one of them is a phase 3 randomized clinical trial, and the different agents studied as the main reasons behind this result. Even when the studies with high risk of bias or outlier results were excluded an important degree of heterogeneity was still present which enhances our point of view.

A single systematic literature review on the efficacy of KRASG12C inhibitors in the treatment of colorectal cancer (CRC) has been published up to May 2024. However, this review was only a narrative one. The findings indicate that KRASG12C mutations are linked to reduced response to conventional therapies and reduced 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 CodeBreak 300 trial, where sotorasib and panitumumab were used. Other KRASG12C inhibitors such as divarasib and adagrasib as monotherapy are presented and the authors of the review expected that the combination of these agents with anti-EGFR therapies may improve even more patients' clinical outcomes, an expectation that is confirmed by the numbers of our meta-analysis. [39]

A meta-analysis was conducted on the efficacy and toxicity of KRASG12C inhibitors, but it included studies of all types of solid tumors. Out of ten studies analyzed, only five of them reported CRC patients' results and all these are included in our meta-analysis. According to Dang et al. PFS of patients with CRC and KRASG12C mutation who underwent therapy with KRASG12C 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 and overall survival (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 due to lack of data. For this reason, we chose not to present these sub-analyses in our review, but we consider these results important to refer to. [40]

To the best of our knowledge this is the first meta-analysis of clinical studies on KRASG12C 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, and as a result available for clinical practitioners, are included. We present the available results of all therapies, monotherapy or combined, separately and overall. As far as limitations are concerned, KRASG12C inhibitors were developed in the last four years and as a result all studies included are recently published, with a small number of participants and in early stages. At least fifteen more agents are in progress and have shown promising data but lack of approval and published results. Data on OS were available only in 2 out of 17 studies and it is not included. Two studies of those included are ongoing and have not published all of their data while nine were only published as e-posters at conferences.

Overall, the first data for the use of KRASG12C inhibitors in metastatic colorectal cancer are very promising. Data from randomized phase III trials in metastatic colorectal cancer setting are therefore of extreme importance to promote the use of these agents in standard clinical care.

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