Editorial

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Adagrasib plus cetuximab – a novel therapy in the KRAS G12C mutated colorectal cancer treatment

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Colorectal cancer (CRC) is the third most common type of cancer globally, with over 1.9 million cases diagnosed in 2022. According to GLOBOCAN, it is also the second most common cause of cancer-related mortality, leading to more than 900 000 deaths annually[1].

In about 40% of CRC patients, the disease is associated with missense mutations in the Kirsten rat sarcoma (KRAS) oncogene with most mutations occurring at codons 12, 13, and 61[2]. One such mutation, KRAS glycine-to-cysteine mutation at codon 12 (KRAS G12C), is found in almost 3% of CRC patients[3]. Patients with the KRAS G12C mutation generally have poorer life expectancy, progression-free survival, and disease-free survival compared to those with wild-type KRAS or other non-G12C mutations[3].

Treating KRAS G12C mutated CRC has long been a challenge. Anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab and panitumumab are ineffective in treating metastatic CRC in patients with KRAS G12C mutations. This ineffectiveness stems from the downstream activation of the MAPK pathway which occurs independently of EGFR inhibition[4].

Similarly, KRAS G12C inhibitors such as sotorasib and adagrasib which bind covalently to the inactive GDP-bound state of KRAS have shown limited results due to high basal receptor tyrosine kinase (RTK) activation[5]. Moreover, feedback activation of the EGFR pathway in CRC was observed to be another significant challenge[5].

Despite the high prevalence and poor overall survival rate associated with KRAS G12C mutated CRC, there were previously no pharmacological options specifically targeting this mutation. 10 However, on 21 June 2024, the Food and Drug Administration Authority (FDA) approved adagrasib in combination with cetuximab for this aggressive disease after promising results were noticed in the trials[6].

Cetuximab, a monoclonal antibody that inhibits EGFR signaling was combined with adagrasib, a KRASG12C inhibitor to enhance the inhibition of KRAS-dependent signaling and overcome adaptive feedback. This combination delays resistance and improves outcomes (Table 1)[7]. The combination therapy demonstrated an impressive response rate of 46% with a median response duration of 7.6 months and a median progression-free survival of 6,9 months[7].

This novel therapy represents a significant milestone in CRC treatment, as the response rate for adagrasib monotherapy was only 19% with a median response duration of 4.3 months and a median progression-free survival of 5.6 months[7].

Although this therapy marks a significant advancement, some side effects were observed in at least 20% of the patients. The most common adverse effects were nausea (62%), diarrhea (56%), and vomiting (53%). Other notable side effects included dermatitis (47%), fatigue (47%), dry skin (41%), headaches (31%), dizziness (25%), maculopapular rash (25%), and stomatitis (22%)[7].

Given the high prevalence of CRC, projections suggest that the number of new cases could rise to 2.5 million by 2035[10], and there is an immediate need to explore additional treatment options. However, the recent approval of the adagrasib-cetuximab combination has demonstrated remarkable outcomes, improving progression-free survival and response rates and proving to be a critical therapeutic advance for KRAS G12C- mutated CRC by targeting both the KRAS and EGFR pathways.

While this therapy has many benefits, future research is required to address a number of important gaps. First, since resistance to this combination therapy develops over time, it is essential to understand the molecular mechanism of resistance. It is important to explore possible pathways that could potentially bypass KRAS G12C mutations, and strategies to overcome or delay resistance should be a top priority. Additionally, there is an urgent need for clinical trials that involve a broader patient population, especially pediatric and pregnant patients, for whom the safety and efficacy of the therapy remain unexplored. Another crucial avenue of study is the development of combination therapies with other KRAS or RTK inhibitors to enhance overall survival outcomes and even prolong disease-free lifespans.

Since KRAS G12C-mutated CRC is an aggressive form of disease long-term studies should also focus on assessing potential side effects from continuous therapy usage for long time. To ensure that the therapy provides long-term benefits without unanticipated complications, a more thorough examination of the response's durability over an extended period of time is necessary (future options).

Ethical approval

None.

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Table 1

Features of ADAGRASIB and CETUXIMAB

Features	ADAGRASIB (MRTX849)	CETUXIMAB
Type	Small-molecule inhibitor[8]	Monoclonal antibody[9]
Target	KRAS G12C mutant protein[8]	EGFR[9] (reference correction)
Mechanism of action	Inhibits KRAS-dependent signaling[8]	Inhibits EGFR signaling[9]
Pharmacokinetics	Approximately 23–24 hours[8]	Approximately 112 hours[9]
Administration	Orally[8]	Intravenous[9]
Dosage	600 mg orally twice daily[7]	Initial loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly or 500 mg/m^2 biweekly[9]

Consent

None.

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Author contribution

AK: Conceptualization, drafting the manuscript, final approval, and agreement to be accountable for all aspects of the work. SC, TH, MAH: Drafting the manuscript, final approval, and agreement to be accountable for all aspects of the work.

Conflicts of interest disclosure

The authors declare no conflict of interest in preparing this article.

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It will be available upon reasonable request.

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