Real-World Survival Outcomes in KRAS(G12C) Metastatic Colorectal Cancer in the United States and Canada: A Systematic Literature Review

RWD159

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INTRODUCTION

- Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and a leading cause of cancer death in the US, with approximately 149,500 new cases and 52,980 deaths in 2021. Approximately 22% of new cases are metastatic, with a 5-year survival rate of 14.7%[1]
- Mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) occur in approximately 40% of CRC cases, with KRAS-G12C comprising a distinct subset that accounts for nearly 3% of metastatic CRC (mCRC) globally[2]
- KRAS-G12C mutation is associated with poorer prognosis in terms of progression-free survival and overall survival compared to other KRAS mutations as well as KRAS wild type tumors
- As KRAS-G12C mutant mCRC emerges as a potentially targetable subset emphasizes the need for systematic evaluation of treatment pattern and survival outcomes in real word scenario

OBJECTIVE

- This systematic literature review evaluated real-world survival outcomes associated with systemic therapies in adults with KRAS-G12C mutant mCRC

METHODS

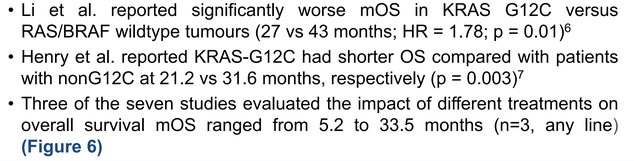
- Embase® and Medline® were searched using a combination of relevant keywords related to KRAS-G12C Mutation and CRC
- A standard two-review and quality control process, aligned with Cochrane and Health Technology Assessment guidelines, was employed to ensure robust evidence generation.
- The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor[3]
- Data were collected using the inclusion/exclusion criteria guided by the PICOS approach **(Figure 1)**

Figure 1: Pre-defined PICOS eligibility criteria

RESULTS

- Among the 297 screened publications, seven studies fulfilled the predefined eligibility criteria and were included in the review **(Figure 2 and 3)**
- All were retrospective cohort studies, with six studies conducted in the US and one in Canada

Figure 2: Study Characteristics



- Among 20,161 mCRC patients, 4.9% presented with KRAS-G12C mutation

Treatment Patterns:

- Overall, five studies assessed the effect of treatment on survival rates, while two described the proportion of patients receiving therapies across different lines of treatment **(Figure 4)**
- Oxaliplatin-based chemotherapy was the most commonly utilized first-line therapy (60.3% and 85.7%, n=2), while irinotecan-based regimens were primarily used in the second-line setting (56.5% and 85.1%, n=2).
- Third-line treatments included FOLFOXIRI (Folinic Acid + Fluorouracil + Oxaliplatin + Irinotecan), regorafenib, TAS-102 (trifluridine and tipiracil) and clinical trial (therapy unspecified)

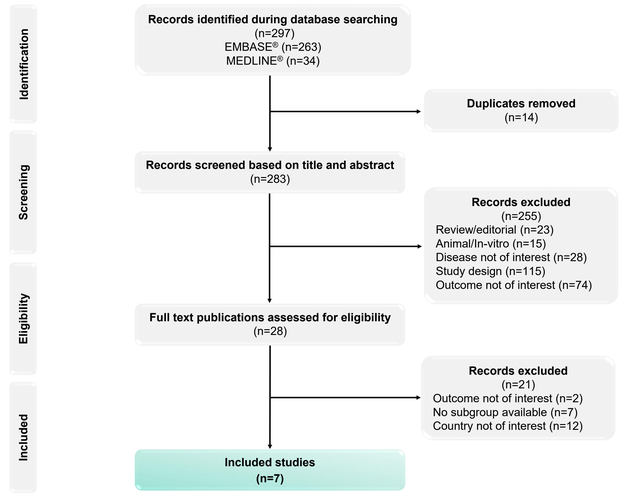
Progression Free Survival (PFS):

- Overall, five studies reported median PFS (mPFS) across the chemotherapy-treated KRAS- G12C mutant patients **(Figure 5)**
- mPFS ranged from 1.3 to 20.9 months (n=5, any line) In the first-line setting, mPFS ranged from 4.8 to 20.9 months (n=5), while in the second-line and third-line settings, mPFS ranged from 1.8 to 6.8 months (n=3), and 1.3 to 6.3 months (n=3), respectively
- Only single study reported, the mPFS along the fourth line of therapy with 3.0 months[1]

Overall Survival (OS):

- All seven studies reported OS among patients with KRAS-G12C mutations, of which four studies assessed the associated clinical burden
- George et al. reported significantly lower median OS (mOS) in KRAS-G12C mutations versus other KRAS mutations (23.0 vs 27.1 months; p<0.001)[4], while Abid et al. reported an mOS of 5.2 years among KRAS G12C-mutant patients[5]
- Li et al. reported significantly worse mOS in KRAS G12C versus RAS/BRAF wildtype tumours (27 vs 43 months; HR = 1.78; p = 0.01)[6]
- Henry et al. reported KRAS-G12C had shorter OS compared with patients with nonG12C at 21.2 vs 31.6 months, respectively (p = 0.003)[7]
- Three of the seven studies evaluated the impact of different treatments on overall survival mOS ranged from 5.2 to 33.5 months (n=3, any line) **(Figure 6)**

Figure 3: PRISMA diagram for the screening process

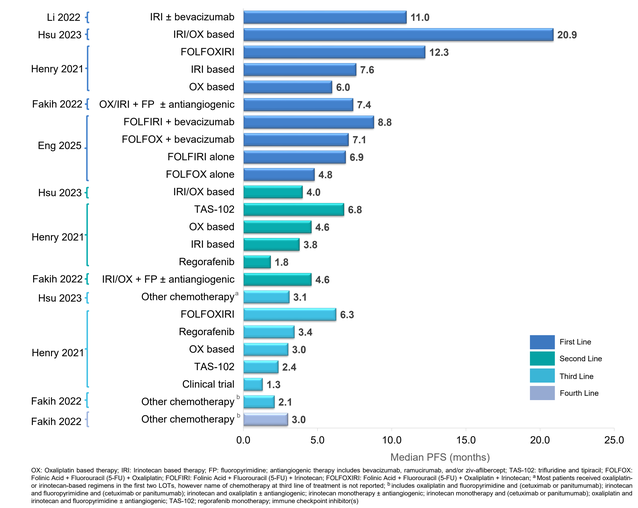


EMBASE: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure 4: Proportion of patients receiving different lines of therapy

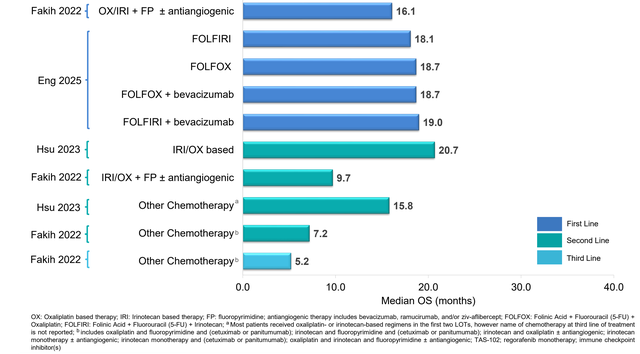
Oxaliplatin based therapy includes oxaliplatin and fluoropyrimidine/capecitabine ± antiangiogenic (bevacizumab, ramucirumab, and/or ziv-aflibercept); Irinotecan based therapy: Irinotecan and fluoropyrimidine/capecitabine ± antiangiogenic; FOLFOXIRI: Folinic Acid + Fluorouracil (5-FU) + Oxaliplatin + Irinotecan; TAS-102: trifluridine and tipiracil; 5-FU: 5-Fluorouracil; "Other" includes oxaliplatin and fluoropyrimidine and (cetuximab or panitumumab); irinotecan and fluoropyrimidine and (cetuximab or panitumumab); irinotecan and oxaliplatin ± antiangiogenic; irinotecan monotherapy ± antiangiogenic; irinotecan monotherapy and (cetuximab or panitumumab); oxaliplatin and irinotecan and fluoropyrimidine ± antiangiogenic; TAS-102; regorafenib monotherapy; immune checkpoint inhibitor(s)

Figure 5: Progression free survival across the included studies



OX: Oxaliplatin based therapy; IRI: Irinotecan based therapy; FP: fluoropyrimidine; antiangiogenic therapy includes bevacizumab, ramucirumab, and/or ziv-aflibercept; TAS-102: trifluridine and tipiracil; FOLFOX: Folinic Acid + Fluorouracil (5-FU) + Oxaliplatin; FOLFIRI: Folinic Acid + Fluorouracil (5-FU) + Irinotecan; FOLFOXIRI: Folinic Acid + Fluorouracil (5-FU) + Oxaliplatin + Irinotecan; [a] Most patients received oxaliplatin- or irinotecan-based regimens in the first two LOTs, however name of chemotherapy at third line of treatment is not reported; [b] includes oxaliplatin and fluoropyrimidine and (cetuximab or panitumumab); irinotecan and fluoropyrimidine and (cetuximab or panitumumab); irinotecan and oxaliplatin ± antiangiogenic; irinotecan monotherapy ± antiangiogenic; irinotecan monotherapy and (cetuximab or panitumumab); oxaliplatin and irinotecan and fluoropyrimidine ± antiangiogenic; TAS-102; regorafenib monotherapy; immune checkpoint inhibitor(s)

Figure 6: Overall survival across the included studies



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LIMITATIONS

- The observational nature of the included evidence carries an inherent possibility of selection bias
- Given the variability in treatment regimens and lines of therapy, direct cross-study comparisons were methodologically limited, reflecting the heterogeneous nature of real-world clinical practice

Conclusion:

- Real-world survival outcomes remain poor for chemotherapy-treated KRAS-G12C mutant mCRC compared with RAS/BRAF wild-type or other KRAS mutations, highlighting a significant unmet need
- While the FDA has approved adagrasib plus cetuximab and sotorasib plus panitumumab for previously treated KRAS G12C-mutated mCRC, real-world evidence supporting their clinical effectiveness remains limited

References: 1. Fakih et al. *The Oncologist*. 2022 Apr 26; 27(8):663-674; **2.** Eng et al. *Annals of Oncology*. 2025 36(1); **3.** Moher D et al., PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015; 4(1):1; **4.** George et al., *J Clin Oncol*. (2020) 38:15; **5.** Abid, et al., *J Clin Oncol.* (2022): 191-191; **6.** Li et al., *Ther Adv Med Oncol*. 2022; **7.** Henry et al. *JCO Precis Oncol*, 5 (2021): 613-621

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