Burden of Illness of Adult Patients with Metastatic Colorectal Cancer Bearing the KRAS p.G12C Mutation — A Systematic Literature Review

EE155

Ziyan Chen[1], Marko Rehn[2], Christian Eichinger[3], Istvan Majer[4]

[1]Amgen Inc., Tampa, FL, USA; [2]Amgen Inc., Thousand Oaks, CA, USA; [3]Oxford PharmaGenesis, Oxford, UK; [4]Amgen (Europe) GmbH, Rotkreuz, Switzerland

BACKGROUND

- Worldwide, colorectal cancer (CRC) is the third most common type of cancer and a leading cause of cancer-related death[1]
- Kirsten rat sarcoma viral oncogene homolog (KRAS) glycine 12 to cysteine (p.G12C) mutation has been identified as a putative oncogenic driver in several types of solid tumor. The KRAS p.G12C mutation is estimated to occur in approximately 3% of patients with CRC[2,3]
- There are several KRAS p.G12C-targeting therapies that are currently in development for the treatment of patients with mCRC. For example, the recent phase 2 CodeBreaK 100 study of sotorasib monotherapy reported an overall response rate of 9.7% in heavily pretreated chemo-refractory patients,[4] and the phase 3, randomized controlled CodeBreaK 300 study evaluating the efficacy and safety of sotorasib and panitumumab versus investigator's choice (trifluridine and tipiracil, or regorafenib) in a similar patient population is ongoing
- Considering the expected increase in targeted therapies and knowledge base regarding clinical outcomes with KRAS G12C-mutated mCRC, there is a need to consolidate the existing evidence on real-world clinical, economic, and humanistic outcomes of patients with KRAS p.G12C-mutated mCRC

OBJECTIVE

- This systematic literature review (SLR) aimed to identify and summarize available evidence on the disease burden and unmet need in chemorefractory patients with mCRC who have either (1) progressed/experienced disease recurrence on or after ≥2 prior lines of therapy (LoT), or (2) progressed/experienced disease recurrence on or after therapy with a triplet drug combination consisting of fluoropyrimidine, irinotecan, and oxaliplatin given for mCRC. Patients with KRAS mutation (KRASm) and KRAS p.G12C were of special interest.

METHODS

- This SLR was conducted in line with the published Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 checklist.[5] Search strategies and eligibility criteria were developed in alignment with population, intervention, comparator(s), outcome(s), and study design(s) (PICOS) elements (see Table 1)
- Data sources and search strategy: Electronic searches were performed on the Ovid® platform in 3 databases (Embase, MEDLINE, and the Cochrane Library) covering full publications published since 2012 and conference abstracts since 2018. In addition, hand searches were performed to identify evidence from relevant databases of health technology assessment (HTA) agencies, regulatory bodies, and clinical guidelines. The searches were performed on 25 May 2022
- Citation Screening and Full Text Review: Title and abstract screening and full-text review were performed against the predefined eligibility criteria by two reviewers independently. Any discrepancies in screening decisions were resolved by a third reviewer
- Data Extraction and quality assessment: One person extracted data from included articles and a second person checked each data point for accuracy. A risk of bias assessment for included full-text publications was performed for all clinical effectiveness evidence using the Newcastle-Ottawa Scale.[6] Quality of the included studies was assessed by a single reviewer

Table 1. Study Eligibility Criteria

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with KRAS-mutated mCRC who have progressed or experienced disease recurrence on or after ≥2 prior lines of therapy, or fluoropyrimidine, irinotecan, and oxaliplatin given for metastatic disease (chemo-refractory patients)	Known KRASm-negative status for full study population
Interventions/comparators	Any	N/A
Outcomes	Clinical and epidemiology outcomes, treatment patterns, humanistic, economic burden	Economic evidence from clinical trials
Study types	Observational/RWE studies Any types of economic studies	Preclinical studies, editorials, letters
Time horizon	Published since 2012 for database searches, since 2018 for conference abstracts	N/A

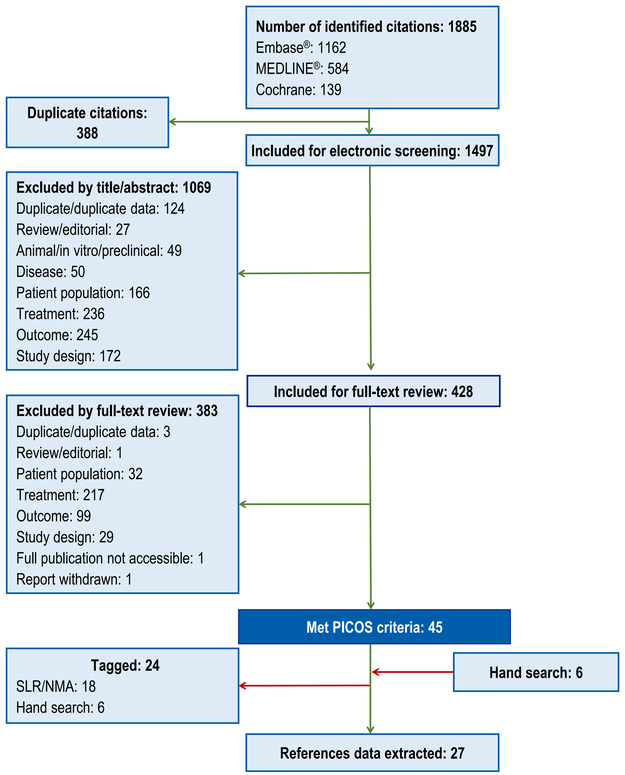
mCRC: metastatic colorectal cancer; KRAS: Kirsten rat sarcoma viral oncogene homolog; KRASm: KRAS mutation; N/A: not applicable; PICOS: patient, intervention, comparator(s), outcome(s), and study design(s); RWE: real-world evidence

RESULTS

Study selection

- Out of the 1,885 screened citations, 45 studies were identified as relevant. Of these, 27 were primary publications from which data were extracted. The remaining 18 publications were SLRs and/or network meta-analyses, which were included without data extraction (see Figure 1)
- Relevant outcomes were reported for the different disease burden endpoints as follows:
  - 7 publications reported data on the prevalence of the KRAS p.G12C mutation and 4 publications reported treatment patterns according to KRAS genotype
  - 17 publication reported real-world clinical outcomes for patients with KRASm. Median overall survival (OS) and/or progression-free survival (PFS) were reported in 11 publications. 7 publications reported on prognostic factors
  - 9 publications presented results of economic burden, and 2 publications described economic evaluations
  - No evidence was found for humanistic burden

Figure 1. PRISMA Flow Diagram



NMA: network meta-analysis; PICOS: patient, intervention, comparator(s), outcome(s), and study design(s); PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; SLR: systematic literature review

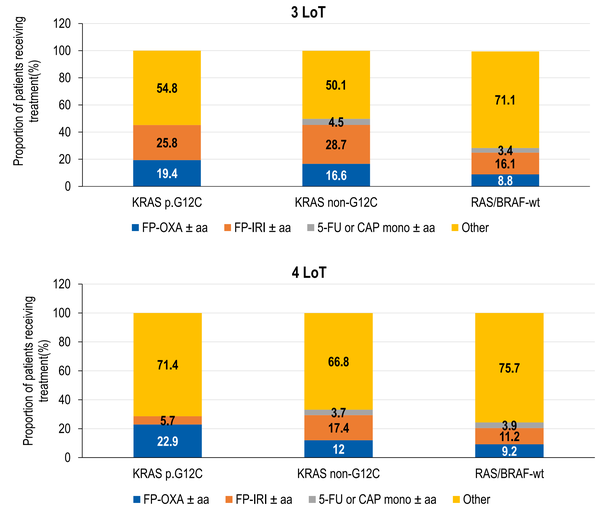
Epidemiology Burden

- The prevalence of KRAS p.G12C ranged from 1.8% to 6% in chemo-refractory patients with mCRC
- The prevalence of KRAS p.G12C ranged from 5% to 21.2% within patients with KRASm mCRC
- Based on a US clinical genomic database, the prevalence of KRAS p.G12C was similarly distributed across LoT: 3.7% in the third LoT and 3.9% in the fourth LoT[7]

Treatment Patterns

- Chemo-refractory patients with KRASm received fluoropyrimidine-based chemotherapy with or without oxaloplatin, irinotecan and antiangiogenic agents, or trifluridine/tipiracil and regorafenib monotherapy. Patients with KRAS wild-type (KRASwt) mCRC commonly received anti-epidermal growth factor receptor (anti-EGFR) therapy in addition to chemotherapy (see Figure 2)[7-9]
- Treatment patterns for patients with KRAS p.G12C mutation did not differ significantly from those in patients with other KRASm[7]

Figure 2. Treatment received by mCRC patients in the 3rd line of therapy and 4th line of therapy



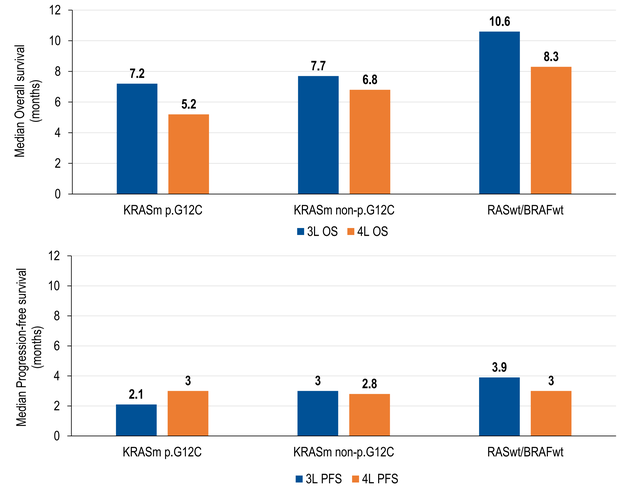
Other: regimens that included a combination of oxaliplatin or irinotecan and fluoropyrimidine, irinotecan and oxaliplatin, and irinotecan monotherapy in combination with cetuximab or panitumumab; oxaliplatin, irinotecan and fluoropyrimidine, irinotecan and oxaliplatin, and irinotecan monotherapy with or without antiangiogenic agents; trifluridine and tipiracil; regorafenib monotherapy; immune checkpoint inhibitors

5-FU: 5-fluorouracil; aa, antiangiogenic agents; BRAF: B-raf proto-oncogene serine/threonine kinase; CAP: capecitabine; FP: fluoropyrimidine; IRI: irinotecan, KRAS: Kirsten rat sarcoma viral oncogene homolog; mono: monotherapy; LoT: line of therapy; OXA: oxaliplatin; p.G12C: glycine 12 to cysteine mutation; RAS: rat sarcoma viral oncogene homolog; wt: wild-type

Overall Survival and Progression-Free Survival

- Figure 3 shows the median OS and PFS estimates for patients with mCRC by KRAS mutation status and LoT as published by Fakih et al. using a US clinical genomic database.[7] The median OS was numerically lower in patients with KRAS p.G12C-mutated mCRC than in patients with other mCRC genotypes across all LoT. The estimated median real-world PFS (rwPFS) in the third LoT was shorter in patients with KRASm p.G12C than in other genotype groups whereas rwPFS was similar in the fourth LoT across group
- Mutations in the KRAS gene were reported as being associated with significantly shorter OS in 2 publications comparing outcomes in patients with KRASm and KRASwt mCRC (HR ranged 1.25–2.5).[10,11] Two studies reported that OS was numerically shorter in patients with KRAS p.G12C than in patients with other KRASm mCRC7.[12,13] One publication reported no differences between patients with KRAS p.G12C-mutated mCRC and those with other KRASm (hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.74–1.42).[14] In another publication, comparing outcomes in patients with KRAS codon 13-mutated mCRC and KRAS codon 12-mutated mCRC, no significant differences in OS (HR 0.84, 95% CI 0.41–1.72) and PFS (HR 0.91, 95% CI 0.45–1.79) was reported[13]

Figure 3. PFS and OS outcomes for mCRC patients by KRAS status and line of therapy



BRAF: B-raf proto-oncogene serine/threonine kinase; KRAS: Kirsten rat sarcoma viral oncogene homolog; OS: overall survival; PFS: progression-free survival; p.G12C: glycine 12 to cysteine mutation; RAS: rat sarcoma viral oncogene homolog; wt: wild-type

Economic burden and economic evaluations

- All identified publications reported outcomes related to the economic burden of testing for KRASm; none of the studies reported healthcare resource utilization and costs in chemo-refractory patients with KRASm
- Among the included studies, 3 concluded that testing for KRAS/RAS mutations before an anti-EGFR therapy is initiated was more cost-effective than administering the therapy without testing

KEY FINDINGS

- In total, 45 studies were identified. Of these, 27 were primary publications and 18 were SLRs and/or NMAs.
- Overall, there is little evidence reported in the literature on the disease burden of heavily pretreated chemotherapy-refractory mCRC patients harboring KRASm
- Data on real-world clinical outcomes for patients with KRAS p.G12C-mutated mCRC are scarce. OS was reported to be shorter in patients with KRAS p.G12C-mutated mCRC than in patients with other KRASm and KRASwt patients, although this finding was not consistent across all identified studies. Patient populations and treatments received in the included studies were heterogenous therefore generalizability of the findings is limited
- Evidence for economic burden was identified only regarding testing for KRAS/RAS mutations. None of the publications reported costs or cost-effectiveness analyses for patients with KRASm including KRAS p.G12C. Overall, there is a substantial lack of economic and humanistic evidence in this population

Disclosures:

ZC, MR, and IM are employees of Amgen and hold Amgen stocks. CE was paid consultant to conduct the SLR. JT has provided consultancy for Amgen.

This study was supported by Amgen Inc. Medical writing and editorial support was provided by Tim Harrison.

Contact Information: Ziyan Chen zchen03@amgen.com

References:

1. WHO. 2020 statistics. https://www.who.int/en/news-room/fact-sheets/detail/cancer (accessed May 26, 2021)
2. Fakih M, Tu H, Hsu H, et al. *Cancer. Oncologist.* 2022 Aug 5;27(8):663-674.
3. Hil H, Shivani A, Archana B, et al. *Journal of Clinical Oncology.* 2023 41:4_suppl, 41-41.
4. Fakih MG, Kopetz S, Kuboki Y, et al. *Lancet Oncol.* 2022;23:115-24.
5. Page MJ, McKenzie JE, Bossuyt PM, et al. *BMJ.* 2021;372: n71.
6. DP, Ricard I, Heinemann V, et al. *Ann Oncol.* 2016;27:1746-1753.
7. Fakih M, Tu H, Hsu H, et al. *Oncologist.* 2022a;26:26.
8. Landsman-Blumberg PB, Carter GC, Johnson BH, et al. *Clinical Colorectal Cancer.* 2014;13(3):178-184.
9. Min ST, Roohullah A, Tognela A, et al. *Asia-Pacific Journal of Clinical Oncology.* 2022;18(2):e56-e63.
10. Adenis A, de la Fouchardiere C, Paule B, et al. *BMC Cancer.* 2016;16(1) (no pagination).
11. Ma CJ, Huang CW, Chang TK, et al. *Translational Oncology.* 2019;12(3):502-512.
12. Bazarbashi S, Hakoun AM, Gad AM, et al. *Current Oncology.* 2019;26(1):e24-e29.
13. Osterlund E, Ristimaki A, Kytola S, et al. *Frontiers in Oncology.* 2022;12 (no pagination).
14. Daddizio V, Basso M, Rossi S, et al. *Molecular Diagnosis and Therapy.* 2016;20(1):65-74.