Abstract 4169
Poster SA79

Targeted Review and Gap Assessment for Refractory Metastatic Colorectal Cancer Without Liver Metastases

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OBJECTIVE

Emerging evidence suggests that patients with metastatic colorectal cancer refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (refractory mCRC) and without liver metastases represent a potentially distinct subpopulation for treatment

A targeted literature review and evidence gap assessment was conducted to understand the availability of epidemiological, clinical, comparative effectiveness, and economic data for this patient population

CONCLUSIONS

- **This targeted literature review and evidence gap assessment identified a lack of epidemiological, comparative effectiveness, and economic data for patients with refractory mCRC without liver metastases**
- **Addressing these evidence gaps is necessary to inform research, identify unmet needs, and assess the value of currently available and investigational treatments for this patient population**

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ACKNOWLEDGMENTS

Editorial support was provided by Twist Medical and funded by Exelixis, Inc.
The study is sponsored by Exelixis, Inc., Alameda, CA, USA.

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Presented at ISPOR 2025, Montreal, QC, Canada, May 13–16, 2025

BACKGROUND

- Globally in 2022, colorectal cancer (CRC) was the third most diagnosed cancer (~1.9 million new cases; 9.6% of all cancers) and the second most common cause of cancer deaths (~900,000 deaths; 9.3% of all cancers)[1]
- Advanced or metastatic CRC (mCRC) has a poor prognosis, with 5-year overall survival of ~15%[2]
- Fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy regimens are standard-of-care therapies for mCRC, with several other therapies used in a later-line setting
- Although liver metastases are present in most patients with refractory mCRC, those without liver metastases may derive the greatest benefit from treatment with a tyrosine kinase inhibitor (TKI) in combination with an immune checkpoint inhibitor (ICI)
  - Results from a global phase 3 trial of a TKI and ICI combination in previously treated mCRC suggested that the subgroup of patients without liver metastases experienced a relative benefit in terms of survival and response versus those with liver metastases[3]
  - The microenvironment of liver tumors is immunosuppressive and can confer resistance to immunotherapy,[4–7] indicating that patients with refractory mCRC without liver metastases represent a potentially distinct subpopulation for treatment
- Reviewing the available epidemiological, clinical, comparative effectiveness, and economic data for patients with refractory mCRC without liver metastases will help to identify any evidence gaps specific to this population

METHODS

- Searches were conducted on MEDLINE (PubMed; individual searches for epidemiological, clinical, comparative effectiveness, and economic evidence), ClinicalTrials.gov, and websites of relevant international scientific societies (for treatment guidelines) and health technology assessment (HTA) bodies (for submitted economic analyses) (**Figure 1**)
- Eligibility criteria were defined ahead of searches and used to select relevant records from the search results (**Table 1**)
- Relevant records were identified by a single researcher, who first screened titles (and abstracts, where available, for PubMed searches) to select potentially relevant records and then screened the full text of these records to confirm they aligned with the prespecified eligibility criteria
- A structured gap assessment that considers the domains of unmet need/epidemiology, clinical efficacy/safety, comparative effectiveness, and value for money (economic evidence) was then conducted to identify areas with limited data on refractory mCRC without liver metastases

Figure 1. Data Sources and Search Strategy for Targeted Literature Review

Unmet Need/Epidemiology
- PubMed
- Treatment guidelines

Clinical Efficacy/Safety and Comparative Effectiveness
- PubMed
- ClinicalTrials.gov
- Hand searches of reference lists from SLRs

Economic
- PubMed
- HTA body websites

Search Strategy

All searches were carried out in June 2024:
- Four PubMed searches (epidemiology, clinical, comparative effectiveness, and economic)
- To identify treatment guidelines, a targeted search of the websites of clinical organizations:
  - NCCN, ESMO, ASCO, JSCCR, and SEOM
- To identify relevant submissions to HTA bodies, a targeted search of HTA body websites:
  - CDA, HAS, ICER, IQWiG, NICE, and PBAC
- To identify additional RCTs, a targeted search of ClinicalTrials.gov

ASCO, American Society of Clinical Oncology; CDA, Canada's Drug Agency; ESMO, European Society for Medical Oncology; HAS, Haute Autorité de Santé; HTA, health technology assessment; ICER, Institute for Clinical and Economic Review; IQWiG, Institute for Quality and Efficiency in Health Care; JSCCR, Japanese Society for Cancer of the Colon and Rectum; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomized controlled trial; SEOM, Spanish Society of Medical Oncology; SLR, systematic literature review.

Table 1. Eligibility Criteria for Targeted Literature Review

	Inclusion Criteria	Exclusion Criteria
Population	• Adults with chemotherapy-refractory mCRC[a]	• People without a diagnosis of mCRC • Animals; in vitro studies • Other disease areas; healthy volunteers
Intervention	• Treatments for chemotherapy-refractory mCRC approved in the United States and/or Europe	• Other interventions
Comparator	• Any systemic treatment or placebo	• Other comparators
Outcome	• Epidemiology: Incidence, prevalence, and mortality/survival • Clinical efficacy/safety and comparative effectiveness: Any clinical efficacy or safety outcomes (e.g., overall survival, adverse events) • Economic: Any economic or utility outcomes (e.g., incremental cost-effectiveness ratio, healthcare resource utilization, costs, health-state utility values)	• Outcomes not related to mCRC
Study Design	• Epidemiology: Any (focus on real-world data) • Clinical efficacy/safety and comparative effectiveness: RCTs with published evidence and indirect treatment comparisons • Economic: Economic evaluations, economic burden studies, healthcare resource utilization studies, studies reporting utility values, and HTA body submission reports • Guidelines: Treatment guidelines from oncology organizations	• Study protocols • Case reports • Reviews[b]
Language	• English	• Non-English
Date	• Epidemiology: Last 10 years • Clinical: No date restriction • Economic: Last 10 years (no date restriction for utilities) • Guidelines: Last 5 years	• See inclusion criteria
Country	• United States, Canada, Germany, Spain, France, Italy, United Kingdom, Australia, and Japan	• Other countries

[a]Records for refractory mCRC specifically without liver metastases were noted during the screening process. [b]Relevant publications were used for hand searches of reference lists from SLRs.

HTA, health technology assessment; mCRC, metastatic colorectal cancer; RCT, randomized controlled trial; SLR, systematic literature review.

RESULTS

- This targeted literature review identified several evidence gaps:
  - Epidemiological Evidence
    - No epidemiology studies reporting incidence rates for refractory mCRC without liver metastases were identified, and only one study was found that reported survival outcomes for this population
      - An analysis of Surveillance, Epidemiology, and End Results population-based data for the United States found 1-year cause-specific survival among patients with bone or brain metastasis was not significantly different between those with and those without liver metastases[8]
    - No observational studies reporting epidemiological or survival data for patients with refractory mCRC (with or without liver metastases) were identified
  - Treatment Guidelines
    - No treatment recommendations were provided specifically for mCRC without liver metastases in the treatment guidelines from the United States, Europe, and Japan[9–11]
  - Clinical Evidence
    - Of the 14 identified clinical trials in refractory mCRC for approved therapies in the United States and Europe, only six reported outcome data for patients without liver metastases (**Table 2**)
  - Comparative Effectiveness Evidence
    - No comparative effectiveness studies reporting indirect treatment comparisons in refractory mCRC included an analysis for patients without liver metastases
  - Economic Evidence
    - No economic study or HTA body submission report on refractory mCRC included cost of illness, cost-effectiveness, budget impact, or utilities in refractory mCRC without liver metastases

Table 2. Clinical Trials for Approved Therapies in Refractory mCRC Reporting Outcomes for Patients Without Liver Metastases

Trial Name	ClinicalTrials.gov Identifier	Phase	Intervention	Comparator	Primary Endpoint
FRESCO[12]	NCT02314819	3	Fruquintinib	Placebo	OS
FRESCO-2[13]	NCT04322539	3	Fruquintinib	Placebo	OS
RECOURSE[14]	NCT01607957	3	Trifluridine/ tipiracil	Placebo	OS
SUNLIGHT[15]	NCT04737187	3	Trifluridine/ tipiracil with bevacizumab	Trifluridine/ tipiracil	OS
Xu et al., 2017[16]	NCT02196688	2	Fruquintinib	Placebo	PFS
Yoshino et al., 2012[17]	N/A	2	Trifluridine/ tipiracil	Placebo	OS

mCRC, metastatic colorectal cancer; N/A, not applicable; OS, overall survival; PFS, progression-free survival.