Epidemiology, Prognosis, and Health-Related Quality of Life in HER2-Positive, RAS Wild-Type, Metastatic Colorectal Cancer: A Literature Review and Qualitative Synthesis

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INTRODUCTION

- CRC is the third most diagnosed cancer and second leading cause of cancer-related mortality globally;[1,2] approximately 25% of patients develop metastatic CRC.[3]
- HER2-positive, RAS WT mCRC is a small but clinically meaningful subgroup, occurring in approximately 2–6% of metastatic cases,[4, 5] within an evolving biomarker-testing and targeted-treatment landscape.
- Epidemiological outcomes and the impact of treatment health-related quality of life (HRQoL) remain poorly characterized in this population.

OBJECTIVES

1. To conduct a targeted literature review (TLR) and synthesize evidence on the proportion of HER2 and RAS genotypes, biomarker testing practices, biomarker-specific prognostic implications, treatment patterns and patient preferences in patients with HER2+, RAS WT mCRC.
2. To systematically identify (systematic literature review [SLR]) and qualitatively describe the impact of treatment on HRQoL in patients with HER2+, RAS WT, mCRC.

METHODS

- A TLR and SLR were conducted: Searches for the TLR were conducted in MEDLINE and searches for the SLR were conducted across multiple databases (i.e., Embase, MEDLINE, Cochrane Database of Systematic Reviews), all via the Ovid® platform from inception to October 2025.
- Both TLR and SLR database searches were supplemented by grey literature (ClinicalTrials.gov, bibliographies) and major oncology conferences (January 2023 to October 2025).
- Eligible studies were randomized and non-randomized trials, single-arm and observational/real-world studies in adults (≥ 18 years) with HER2+, RAS WT locally advanced, unresectable mCRC who received systemic therapy and reported efficacy, effectiveness or safety outcomes.
- Evidence identified was critically reviewed and synthesized qualitatively.

RESULTS

Epidemiology TLR

Evidence Base and Study Characteristics

- From 226 electronic database records and 756 grey-literature records, 87 unique studies comprising 43,783 patients with mCRC were identified; the most common reason for exclusion was no HER2+ patients (n = 45 studies.)
- Most studies were published between 2021 and 2025 and were predominantly retrospective real-world analyses (n = 46 studies)
- Evidence was geographically diverse, with the largest contributions originating from China, Italy, and the United States.
- Study populations primarily included patients with metastatic disease, and many cohorts were enriched for HER2+ and/or RAS WT tumors.
- Patients were generally middle-aged to older adults (mean/median age range: 42-77 years), predominantly male, with good performance status (ECOG 0-1), left-sided primary tumors, and frequent liver metastases.

Proportion of patients with HER2+, RAS WT mCRC

HER2+ Status (n = 34 studies)

- The proportion of patients with HER2-positivity ranged from 0.69% to 100%

RAS WT Status (n = 72 studies)

- The proportion of patients with RAS WT status ranged from 1.5% to 100%

HER2+, RAS WT co-occurrence (n = 61 studies)

- Across all studies with interpretable co-occurrence data, the proportion of patients with concomitant HER2-positive and RAS WT disease ranged from 1.5%% to 100%

HER2 and RAS Testing Practices

- HER2 status was most commonly assessed using immunohistochemistry (IHC), often with confirmatory in situ hybridization (ISH) or next-generation sequencing (NGS); the most frequently reported definition of HER2 positivity was IHC 3+ or IHC 2+/ISH+
- Approximately 75% of studies specified the HER2 scoring algorithm used; among these, HERACLES was the most commonly used algorithm.
- RAS testing was primarily performed using PCR or NGS and generally defined RAS WT as the absence of KRAS and NRAS mutations; recent studies increasingly incorporated comprehensive genomic profiling and ctDNA testing.
- HER2 testing was performed primarily in metastatic disease, with 80 of 87 studies evaluating stage IV populations; limited evidence was available on testing practices in earlier disease stages.

Prognostic implications of HER2+, RAS WT mCRC

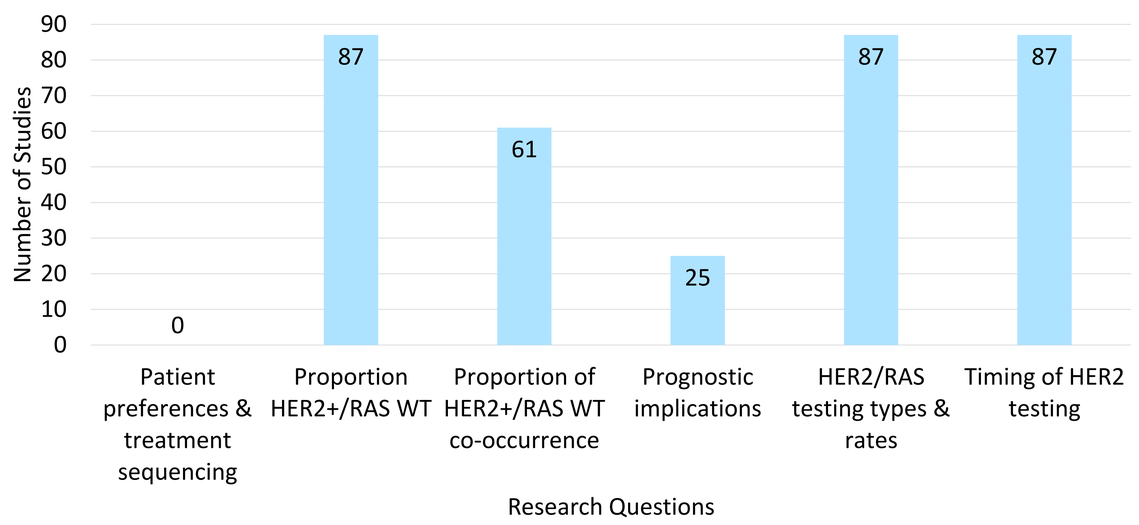
- 25 studies reported survival outcomes for HER2+/RAS WT subgroups
- 4 studies each reported overall survival and progression-free survival in HER2+/RAS WT compared to HER2-/RAS WT subgroups (**Table 1**)

Table 1. Prognostic Implications of HER2 Status

Outcome	HER2+ / RAS WT	HER2– / RAS WT
Median overall survival	~20–34 months (20: 1L FOLFIRI + cetuximab; 34: anti-EGFR monotherapy, line unknown)	~34–39 months (34: 1L chemotherapy + bevacizumab; 39: 1L+ chemotherapy and anti-EGFR–based regimens)
Median progression-free survival	~2–11 months (2: anti-EGFR monotherapy ± irinotecan, line unknown; 11: 1L FOLFIRI + cetuximab)	~1–13 months (1: 2L+ trastuzumab deruxtecan; 13: 1L chemotherapy + bevacizumab)

- Limited disease-free survival evidence (n = 3 studies) suggested increased recurrence risk and poorer long-term outcomes in HER2+ populations.
- Within HER2+ disease, RAS WT status appears prognostically favorable versus RAS-mutant disease, though HER2 positivity, amplification, and high expression remain associated with poorer outcomes.

Figure 1. Data Reported by Studies Contributing to TLR Evidence Base



Evidence Gaps Identified in the Epidemiology TLR (Figure 1)

- Treatment sequencing and patient preferences
  - No studies evaluated treatment sequencing strategies or patient treatment preferences in HER2-positive, RAS WT mCRC.
  - Additional evidence is needed to characterize real-world treatment pathways and patient-centered outcomes.
- Limited reporting of HER2+/RAS WT co-occurrence
  - Approximately one-third of studies did not adequately report dual biomarker status, limiting cross-study comparisons and interpretation of population estimates.
- Lack of standardization in HER2 testing
  - HER2 positivity estimates ranged from <1% to 100%, reflecting variability in testing methods, positivity criteria, and study populations.
- Predominance of biomarker-selected populations
  - Many studies enrolled biomarker-selected or treatment-refractory populations, which may not reflect the broader mCRC population.
- Limited prognostic evidence
  - Only 25 studies reported prognostic outcomes and interpretation of survival outcomes was confounded by small sample sizes, heterogeneous treatment regimens, varying biomarker definitions, and predominantly non-randomized study designs.

HRQoL SLR

Evidence Base and Study Characteristics

- From 28 electronic database records and 633 grey-literature records, 2 unique studies were identified; the most common reason for exclusion was no HER2+ patients (n = 8 studies.)
- Two phase 2 trials of HER2-targeted therapy assessed HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) Global Health/QoL subscale.
- Patients were heavily pretreated, predominantly ECOG performance status 0-1, with primarily left-sided tumors.

Table 2. HRQoL Findings by Trial

Trial	Treatments (N)	HRQoL outcome
MOUNTAINEER	Tucatinib + trastuzumab vs tucatinib monotherapy (n = 114)	HRQoL remained stable over time, with no clinically meaningful deterioration in global health status or functional domains
DESTINY-CRC02	Trastuzumab deruxtecan 5.4 mg/kg vs 6.4 mg/kg (n = 122)	HRQoL was maintained throughout treatment and follow-up, with no clinically significant change from baseline in either dose group

Key Takeaway

- Available evidence suggests HER2-targeted therapies maintain HRQoL while providing clinical benefit in patients with HER2-positive mCRC.

CONCLUSIONS

- Proportions of HER2-positive, RAS WT, and co-occurring HER2+ RAS WT disease were highly variable across studies, highlighting challenges in cross-study comparability.
- Variability in reported epidemiologic and clinical outcomes was driven in part by differences in testing protocols, HER2+ definitions, and selected study populations.
- Consistent HER2 testing criteria, standardized reporting of HER2+ RAS WT co-occurrence, and harmonized biomarker definitions are needed to improve comparability across studies and support future research.
- Limited HRQoL evidence suggests HER2-targeted therapies preserve quality of life in patients with HER2+ RAS WT mCRC; however, additional research with standardized reporting and greater focus on patient-reported outcomes is needed.

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