A Systematic Literature Review and Indirect Treatment Comparison Feasibility Assessment of the Comparative Efficacy of Treatments in HER2-Positive, RAS Wild-Type, Metastatic Colorectal Cancer

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INTRODUCTION

- CRC is the third most diagnosed cancer and second leading cause of cancer mortality globally.[1,2]
- HER2+, RAS wild-type (WT) mCRC is a small but clinically meaningful subgroup (~2–6% of metastatic cases).[3–5]
- mCRC is rarely curable, underscoring the need for targeted treatments, when appropriate.[6]
- Several targeted therapies show promising anti-tumor activity, informing treatment recommendations.
- Head-to-head RCTs of all options are rarely feasible; indirect treatment comparisons (ITCs) can help but require a feasibility assessment (FA) to evaluate cross-trial heterogeneity first.

OBJECTIVES

1. To systematically identify and qualitatively describe the efficacy and safety of different treatment regimens for adult patients with HER2+, RAS wild-type, locally advanced, unresectable, or mCRC, using a systematic literature review (SLR).
2. To assess the feasibility of conducting ITCs such as a network meta-analysis (NMA) for treatments used in adults with HER2+, RAS WT mCRC.

METHODS

- An SLR of systemic treatments for mCRC was conducted; the protocol was registered a priori with PROSPERO (CRD420251163361).
- Multiple databases via Ovid® (i.e., Embase, MEDLINE, Cochrane Database of Systematic Reviews) were searched October 8, 2025, supplemented by grey literature (ClinicalTrials.gov, bibliographies of relevant SLRs) and major oncology conferences (January 2023 to October 2025).
- Eligible studies included randomized (RCTs) and non-randomized trials, single-arm trials, and observational/real-world studies of adults (≥18 years) with HER2+, RAS WT locally advanced, unresectable mCRC receiving systemic therapy and reporting efficacy, effectiveness, or safety outcomes.
- ITC feasibility was assessed for RCTs only by evaluating cross-trial heterogeneity in study design, eligibility criteria, baseline patient characteristics, treatments, and outcomes.

RESULTS

- From 745 electronic database records and 633 grey-literature records, 50 unique studies were identified; the most common reason for exclusion was no HER2+ patients (n = 239).
- Of 12 RCTs, 9 were included in the FA; 3 RCT records were excluded (2 pooled analyses with insufficient trial-level biomarker and outcome data, 1 not reporting outcomes by arm)

Key Sources of Heterogeneity

The RCTs differed in biomarker composition and testing methods, treatment setting, eligibility criteria, baseline characteristics, interventions, and outcome reporting.

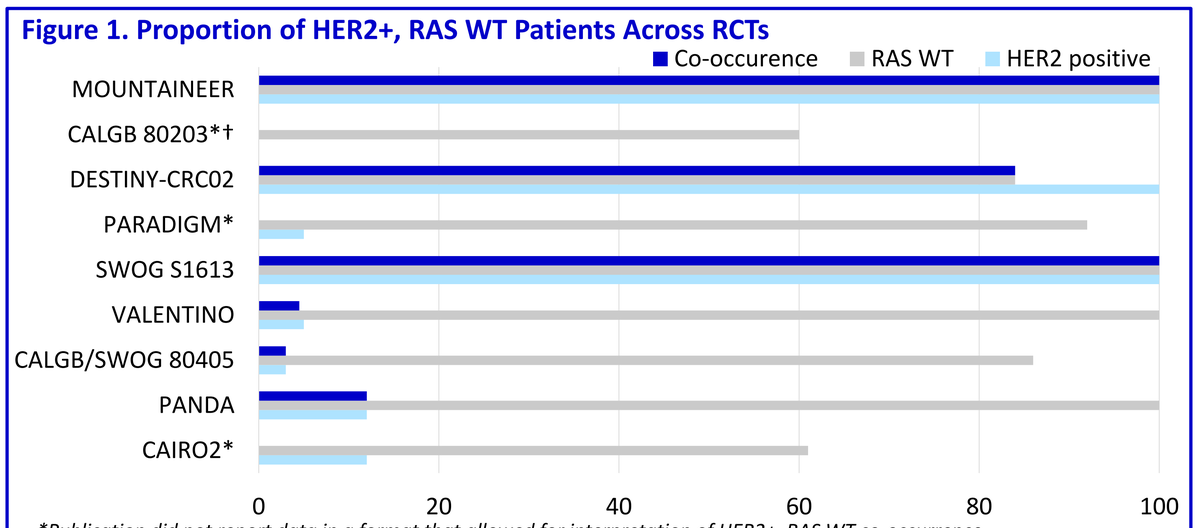
Table 1. Selected Trial Characteristics and Eligibility Criteria Across RCTs

Trial Characteristics			Eligibility Criteria			
Trial name	Phase	Sample size	HER2 status	RAS status	ECOG status	Prior therapy allowed?
MOUNTAINEER	2	117	HER2+	RAS WT	0 – 2	Yes, required
CALGB 80203	3	238*	Not specified	Not specified	0 – 1	Adjuvant chemo or radiation only
DESTINY-CRC02	2	122	HER2+	RAS WT	0 – 1	Yes, required
PARADIGM	3	823*	Not specified	RAS WT	0 – 1	No
SWOG S1613	2	53	HER2+	RAS WT	0 – 1†	≤2 prior lines required
VALENTINO	2	229	Not specified	RAS WT	0 – 1	No
CALGB/SWOG 80405	3	505*	Not specified	RAS WT	0 – 1	No
PANDA	2	183*	Not specified	RAS WT	0 – 2‡	No
CAIRO2	3	755*	Not specified	Not specified	0 – 1	No

* Studies reported separate biomarker analyses with a subset of patients; † trial used Zubrod Performance Status; ‡ if patients >75 years of age, then ECOG must be ≤1

- **Trial characteristics:** Trials varied by region, duration (10–61 months), and treatment regimen; no two RCTs evaluated identical doses, schedules, or combinations.
- **Eligibility criteria:** HER2/RAS requirements, prior therapy, and ECOG criteria varied substantially across trials (**Table 1**).
- **Baseline characteristics:** Biomarker composition varied widely (HER2+ and RAS WT, 5%–100%; **Figure 1**), alongside demographic and disease characteristics (**Table 2**).
- **Trial outcomes:**
  - **Efficacy outcomes** were reported in all trials, but definitions, assessment timing (12 weeks–64 months), and review methods varied; only two used blinded independent central review.
  - **Safety outcomes** were reported in five trials, with inconsistent definitions limiting comparability (**Table 2**).

Figure 1. Proportion of HER2+, RAS WT Patients Across RCTs



*Publication did not report data in a format that allowed for interpretation of HER2+, RAS WT co-occurrence.
† Publication did not report data in a format that allowed for interpretation of the proportion of patients with HER2+ status.

Table 2. Selected Baseline Characteristics and Outcome Reporting Across RCTs

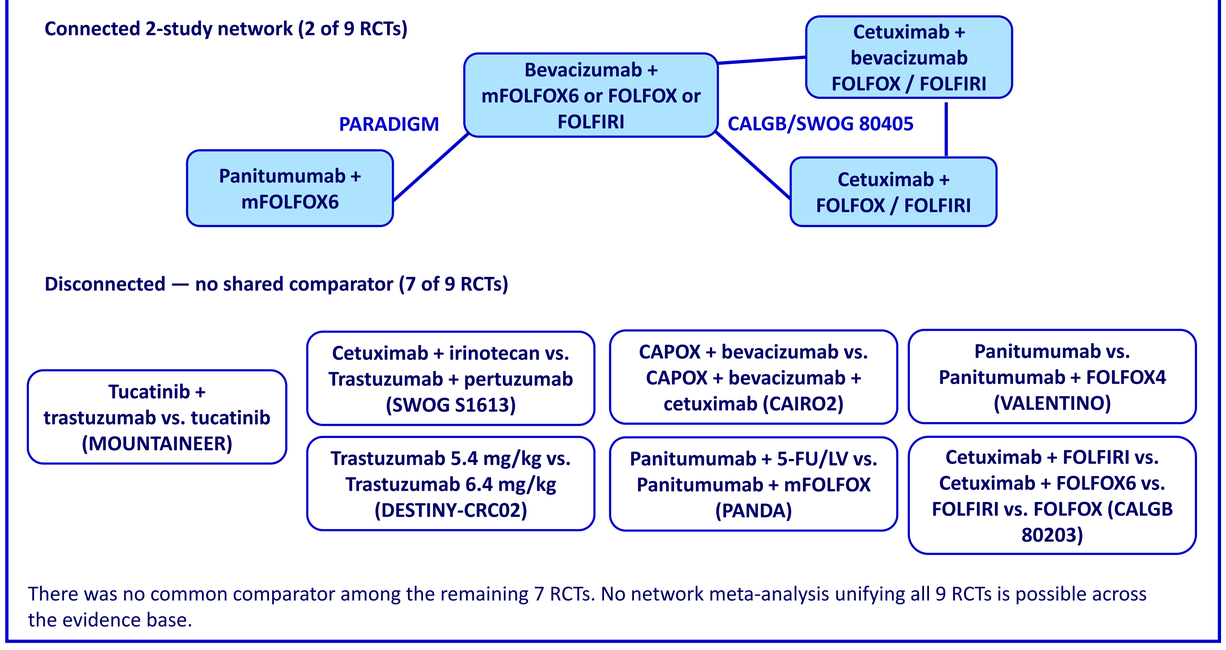
Trial Name	Sex (% male)	Liver metastases (% yes)	Primary tumor location (% left-sided)	Efficacy and safety outcomes reported*
MOUNTAINEER	57.9	64.0	92.5	ORR, OS, PFS, AE, TEAE, TRAE, SAE, tx mod, study d/c
CALGB 80203	64.5	NR	NR	OS, PFS
DESTINY-CRC02	52.5	72.0	77.9	DoR, ORR, OS, PFS, AE, TEAE, TRAE, SAE, study d/c
PARADIGM	65.3	69.0	75.6	ORR, OS, PFS, AE, TEAE, TRAE, SAE, study d/c
SWOG S1613	49.1	NR	70.4	ORR, OS, PFS, TRAE, SAE, tx mod, study d/c
VALENTINO	66.6	36.0†	85.4	DoR, ORR, OS, PFS, AE, TEAE, TRAE, SAE, tx mod, study d/c
CALGB/SWOG 80405	59.0	34.0†	56.0	ORR, OS, PFS
PANDA	64.0	33.6†	80.0	ORR
CAIRO2	64.7	NR	56.0	OS, PFS

* When biomarker-specific data was not available, outcomes were supplemented with data for the overall study population.
† Reported as "liver-only" disease so may underrepresent proportion of patients with liver metastases.
Abbreviations: AE = overall adverse events; d/c = discontinuation due to adverse events; DoR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAE = serious adverse events; TEAE = treatment-emergent adverse events; TRAE = treatment-related adverse events; tx mod = treatment modifications due to adverse events.

Network Connectivity and Feasibility of Network Meta-Analysis (Figure 2)

- No common comparator linked all 9 trials within the current evidence base.
- A 2-study network linked PARADIGM and CALGB/SWOG 80405 via bevacizumab + fluorouracil-based chemotherapy, assuming mFOLFOX6, FOLFOX, and FOLFIRI have similar efficacy profiles.

Figure 2. Evidence Network for HER2+, RAS WT mCRC



There was no common comparator among the remaining 7 RCTs. No network meta-analysis unifying all 9 RCTs is possible across the evidence base.

Data Gaps

- The evidence base was comprised of relatively few trials with notable heterogeneity among them, including highly variable proportions of patients with HER2+, RAS WT disease.
- HER2 assays and positivity thresholds were not standardized and were not harmonized across trials.
- The treatment heterogeneity among comparator arms signals a lack of standard of care for this unique population.

CONCLUSIONS

- **Comparability:** Differences in trial design, eligibility criteria, baseline characteristics, outcome definitions, and follow-up limited cross-trial comparability.
- **Feasibility:** NMA is currently infeasible because the evidence network is disconnected; unanchored population-adjusted ITCs may be possible but require clinical expert validation to determine whether reliable and valid comparative efficacy estimates can be generated. Varied comparators also reflect the lack of an established standard of care.
- **Next steps:** Population-adjusted ITCs using patient-level data may address cross-trial differences; harmonized trial designs, eligibility criteria, and outcomes are needed for robust comparative effectiveness analyses.

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