The efficacy of panitumumab plus chemotherapy as initial treatment for KRAS wild-type unresectable, metastatic colorectal cancer: A GRADE-approach systematic review and meta-analysis

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SUMMARY

OBJECTIVES

- Targeting the epidermal growth factor receptor (EGFR) either alone or in combination with chemotherapy in patients with RAS wild type metastatic colorectal cancer (mCRC) has revolutionized the treatment landscape of CRC.
- As tumour KRAS status is regarded as an important biomarker to predict the efficacy of anti-EGFRs, this study investigated the effectiveness of panitumumab plus standard of care chemotherapy treatment in treatment-naïve WT-KRAS mCRC.

METHODS

- Key biomedical databases, conference proceedings, clinical trial registries and sources for bibliographic reference checking were searched to identify relevant RCTs investigating the efficacy of panitumumab plus irinotecan or oxaliplatin-based chemotherapy for 1L WT mCRC.
- The GRADE approach was used to assess the evidence that was further assessed for feasibility and synthesised via meta-analysis in R.

FINDINGS

- 14 relevant publications which reported on 2 RCTs - PRIME (PAN + FOLFOX4) and VOLFI (PAN + mFOLFOXIRI), were identified. Efficacy data (ORR, OS, PFS) was extracted and assessed.
- Based on the meta-analysis, panitumumab is associated with a longer overall survival, a higher ORR, and no difference in PFS, compared to oxaliplatin or irinotecan-based chemotherapy. The overall certainty of evidence using GRADE was low (Table 3).

RECOMMENDATIONS

- The 1L addition of panitumumab to standard chemotherapy may be beneficial for individuals with WT mCRC based on a synthesis of published evidence.
- A subsequent meta-analysis comparing the anti-EGFR, cetuximab may strengthen the analysis and further interpretation of results.

BACKGROUND & AIMS

- Colorectal cancer (CRC) is the third most diagnosed neoplasm and second leading cause of global cancer-related mortality.[1]
- The RAS family of oncogenes, particularly the *KRAS* protein, are among the most frequently mutated protein families in cancers. *KRAS* mutation testing is indicated in adults with unresectable, metastatic colorectal cancer (mCRC).
- The non-mutant wild-type (WT) *KRAS* gene in mCRC is associated with both sensitivity and resistance to treatment with epidermal growth factors (EGFR) inhibitors.[2] This study aimed to synthesise efficacy estimates of panitumumab plus standard chemotherapy as first-line (1L) treatment in WT-*KRA*S mCRC.

METHODS

- A PRISMA-adherent systematic literature review was undertaken to identify relevant randomised controlled trials (RCTs) investigating the efficacy of panitumumab plus irinotecan or oxaliplatin-based chemotherapy for 1L WT mCRC, published in the English language before 23rd October 2024.
- Electronic database searches were conducted in Embase, MEDLINE, and the Cochrane Library via Ovid with supplementary searches undertaken in ClinicalTrials.gov, International Clinical Trials Registry Platform (WHO ICTRP), European Union Clinical Trials Register, American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR), and ASCO Gastrointestinal Symposia. Manual reference checking of the bibliographies of identified reviews and citation forward tracking via Google Scholar, was likewise conducted.
- The peer-reviewed search strategies used a combination of sophisticated subject headings, text words, synonyms and Boolean combination techniques. The protocol was registered with PROSPERO (registration number: **CRD42024607580**)
- Two reviewers independently screened the literature at title/abstract and full publication stage (Table 1), extracted data, appraised methodological quality using the Cochrane risk of bias (RoB)-2 tool, and assessed the certainty of retrieved evidence using the GRADE approach.[3]
- Retrieved studies providing clinical data were assessed for feasibility and synthesised via meta-analysis in R.

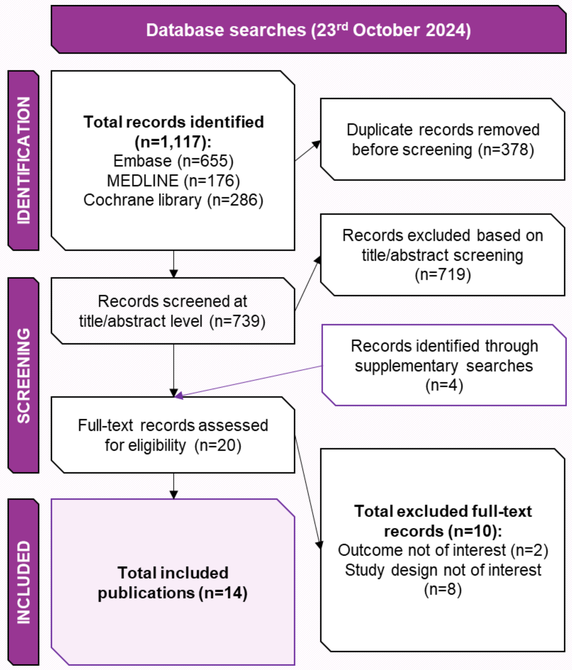
Table 1. Inclusion/exclusion criteria.

Criteria	Inclusion	Exclusion
Population	Female and male patients (≥18 years) with KRAS wild-type (WT) (non-mutated) metastatic colorectal cancer who are previously untreated with systemic or hormonal therapy for their mCRC	• Non-human • Patients previously treated with systemic therapy (i.e., second- or subsequent-line treatment)
Intervention	The epidermal growth factor receptor antagonist: panitumumab plus oxaliplatin- or irinotecan-based chemotherapy	Any other intervention
Comparator	Oxaliplatin- or irinotecan-based chemotherapy	Any other comparator
Outcomes	At least 1 of the following outcomes: • overall survival (OS) • progression-free survival (PFS) • objective response rate (ORR)	• Cost and resource use outcomes • HRQoL outcomes
Study design	Eligible study designs include prospective clinical trials (Phase 2–4)	• Observational trials • Trial protocol (without results)
Limitation(s)	English language publications or non-English language publications with an English abstract	Non-English language articles without an English language abstract

RESULTS

- Of the 739 articles identified, 14 were selected for inclusion in the review and meta-analysis (Figure 1).
- These covered two RCTs which both were judged to have a high risk of bias – PRIME study (NCT00364013)[4] compared panitumumab to FOLFOX4, whereas the comparator arm in the VOLFI trial (NCT01328171)[5] was mFOLFOXIRI.

Figure 1. PRISMA flow diagram.



- Results from the PRIME study, (Douillard, 2010)[4] and the VOLFI study (Geissler, 2019)[5] were evaluated in the feasibility assessment and included in the meta-analysis.
- The feasibility analysis found that the VOLFI study had far fewer participants (n=96), than the PRIME study (n=656), but that participants were of a similar age, and the distribution of ECOG scores of less than 2, and 2 appeared to be similar. Both studies were open-label, phase 3 RCTs.
- The hazard ratio and risk ratio data from these two studies was analysed using the metafor and meta packages in R.
- Based on the meta-analysis, panitumumab is associated with a longer overall survival (HR 0.74; 95% CI: 0.05, 11.37), a higher ORR (RR 1.25; 95% CI: 1.06, 2.60) and no difference in PFS (HR 1.00, 95% CI: 0.15, 6.77), compared to chemotherapy (Table 2).

Table 2. Meta-analysis results.

Outcome	Hazard Ratio	Lower confidence interval	Upper confidence interval
Overall Survival (OS)	0.74	0.05	11.37
Progression-free Survival (PFS)	1.00	0.15	6.77
Outcome	**Risk Ratio**	**Lower confidence interval**	**Upper confidence interval**
Objective response rate (ORR)	1.25	1.06	2.6

- This study combined the limited evidence for OS, PFS and ORR outcomes in 1L KRAS-WT mCRC.
- Only two studies were included in the meta-analysis which could be seen as a limitation in the case of heterogeneous patient populations.
- Including additional evidence from further studies on treatments for 1L KRAS-WT mCRC could improve the robustness of the meta-analysis.

Table 3. GRADE certainty assessment of the efficacy of PAN + chemo vs. chemo only for 1L KRAS-WT mCRC.

No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of evidence
Overall survival						
2 (RCT)	Very Serious[a,b]	None	Not serious[c]	Not serious	Suspected	⨁⨁⊙⊙ – Low quality
Progression-free survival						
2 (RCT)	Very Serious[a,b]	None	Not serious[c]	Not serious	Suspected	⨁⨁⊙⊙ – Low quality
Objective response rate						
2 (RCT)	Very Serious[a,b]	None	Not serious[c]	Not serious	Suspected	⨁⨁⊙⊙ – Low quality
GRADE Working Group grades of evidence:						
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.						
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.						
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.						
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.						

[A] The PRIME and VOLFI trials were open-label trials implying lack of masking in terms of assignment to intervention and outcome assessment

[B] Incomplete information on random sequencing of patients in the PRIME trial

[c] Unclear differences in population as relevant population in PRIME trial described as having wild-type KRAS tumours compared to KRAS exon 2 tumours in the VOLFI trial. The VOLFI trial was conducted across centres in Germany while the PRIME trial was conducted across Argentina, Australia, Belgium, Brazil,

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