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

The overall certainty of evidence across studies was assessed using GRADE as outlined by the GRADE Working Group. The certainty of evidence was summarised in four categories: high, moderate, low, and very low certainty. As per the GRADE criteria, reasons for certainty to be rated downward include risk of bias, inconsistency, indirectness, imprecision, and publication bias. Reasons to raise certainty include large magnitude of effect and adjustment of all plausible residual confounding.

Table 1: Comparison of the efficacy of panitumumab plus chemotherapy to chemotherapy alone as first-line therapy for KRAS wild-type unresectable, metastatic colorectal cancer

No. of studies (Design)	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[d]	Suspected[e]	⊕⊕⊙⊙ – Low quality
Progression-free survival						
2 (RCT)	Very serious[a,b]	None	Not serious[c]	Not serious[d]	Suspected[e]	⊕⊕⊙⊙ – Low quality
Objective response rate						
2 (RCT)	Very serious[a,b]	None	Not serious[c]	Not serious[d]	Suspected[e]	⊕⊕⊙⊙ – 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.

Notes:

[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 tumors compared to KRAS exon 2 tumors in the VOLFI trial. The VOLFI trial was conducted across centres in Germany while the PRIME trial was conducted across Argentina, Australia, Belgium, Brazil, Canada, Chile, Costa Rica, Czech Republic, Estonia, France, Hungary, Italy, Latvia, Mexico, Poland, South Africa, Spain, Switzerland, and the United Kingdom

[d] Few trials to inform the pairwise connection

[e] Low number of relevant studies but individual study sample sizes were sufficient to power differences within the trials, selective reporting of outcomes unlikely