Comments on Assessment Report sponsored by National Institute for Health and Clinical Excellence (NICE) on Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (CRC)

Background
The School of Health and Related Research (ScHARR), University of Sheffield, was commissioned by NICE to assess the clinical effectiveness and cost-effectiveness of bevacizumab and cetuximab in the treatment of individuals with metastatic CRC. Only trials which compared bevacizumab in combination with irinotecan and/or established fluorouracil-containing or releasing regimens given as first-line therapy were included in the review. For cetuximab, only the trials conducted on participants with epidermal growth factor receptor (EGFR)-expressing metastatic CRC who had previously failed irinotecan-including therapy, were considered.

Principal Findings
Bevacizumab: All the three trials included for the review of bevacizumab clinical efficacy were reasonably well-designed and conducted, with main concern about the inclusion of relatively younger than the UK NHS population of metastatic CRC patients in two of the three trials. The overall analysis concluded that bevacizumab in combination with 5-FU/FA or irinotecan, fluorouracil and leucovorin (IFL), is clinically effective in comparison to standard chemotherapy options for the first-line treatment of metastatic CRC. There was evidence for an increase in grade 3 / 4 adverse events which were generally manageable.

Cetuximab: None of the trials met the inclusion criteria for systemic review and no direct evidence was gathered to demonstrate whether cetuximab in combination with irinotecan improves health related quality of life or overall survival in comparison to active/best supportive care or oxaliplatin plus 5-FU/FA, although the evidence on tumour response rates suggests that the cetuximab plus irinotecan has some clinical activity. Treatment in combination with irinotecan is associated with significantly more 3 / 4 adverse events, compared to cetuximab monotherapy.

Outstanding Issues:
Bevacizumab: The true impact of bevacizumab on overall survival and disease-related symptoms within the first-line treatment setting of patients with metastatic CRC who are representative of the typical population of UK CRC patients needs to be determined.

Cetuximab: The incremental benefit of cetuximab in comparison with active/best supportive care needs to be examined in an objective randomised clinical trial setting. The predictive value of immunocytochemically detectable EGFR expression in colorectal cancer cells is uncertain. In addition there is evidence that cetuximab may be clinically active in patients with EGFR-negative CRC. On the other hand there evidence of a correlation between the presence of the acne-like rash and observed survival duration. These issues need to be evaluated critically in future clinical trials.

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