

## Recommendations and Reasons

Committee to Evaluate Drugs (CED)

# Cetuximab for metastatic colorectal cancer

**Product:**

CETUXIMAB (Erbix®)

**Class of drugs:**

anti-cancer agent; epidermal growth factor receptor (EGFR) inhibitor

**Indication:**

metastatic colorectal cancer

**Manufacturer:**

Bristol-Myers Squibb Canada

## CED Recommendation

The CED recommended that cetuximab (Erbix®) not be funded. The CED acknowledged that cetuximab provides clinical benefits in the treatment of metastatic colorectal cancer, but noted that a treatment alternative with similar benefits is available at a lower cost.

Based on the CED's recommendation and cost agreement with the manufacturer, the Executive Officer decided to fund cetuximab (Erbix®) in combination with irinotecan for the treatment of metastatic colorectal cancer through the New Drug Funding Program according to specific criteria.

## Status

Funded through the New Drug Funding Program.

**Highlights of Recommendation:**

- ◆ Cetuximab is an intravenous anti-cancer treatment that belongs to a class of drugs called epidermal growth factor receptor (EGFR) inhibitors. This review considered the use of cetuximab for the treatment of metastatic colorectal cancer (cancer of the large bowel that has spread to other organs).
- ◆ Three key studies were reviewed. In one study, cetuximab was compared against no active treatment in patients with metastatic colorectal cancer who had failed or cannot use standard chemotherapies. Cetuximab was found to improve survival by an average of one and a half months.
- ◆ In another study, cetuximab in combination with irinotecan (a standard chemotherapy used for colorectal cancer) was assessed against irinotecan alone in patients with metastatic colorectal cancer who had failed standard chemotherapies. This study found that the addition of cetuximab did not significantly prolong survival but did improve disease progression and disease response.
- ◆ The third study compared the use of cetuximab alone to cetuximab plus irinotecan in patients with metastatic colorectal cancer whose disease had progressed on irinotecan. The study found that the combination of cetuximab plus irinotecan was more efficacious than standalone cetuximab treatment.
- ◆ Cetuximab costs approximately \$7,000 per month. Based on the CED's assessment, this drug does not provide value for money. Moreover, a less expensive EGFR inhibitor for the treatment of metastatic colorectal cancer is already available.
- ◆ Overall, the CED acknowledged that cetuximab provides clinical benefits in the treatment of metastatic colorectal cancer but noted that this drug is not cost-effective and is more expensive than a comparator product.

**Background:**

Colorectal cancer refers to cancer that starts in the large intestine (colon) or the rectum (end of the colon). Metastatic colorectal cancer is cancer that has spread to other organs, such as the liver and lung.

Only a minority of patients with metastatic colorectal cancer can be cured with surgery. For others, chemotherapy can be used to improve symptoms and prolong survival. Conventional chemotherapies include fluoropyrimidines, irinotecan, and oxaliplatin. Bevacizumab can also be added to conventional chemotherapies to improve some outcomes. In most patients, resistance to chemotherapy develops over time.

Cetuximab belongs to a newer class of treatments called targeted therapies. It targets the epidermal growth factor receptor (EGFR), which is found in about 80 percent of colorectal cancers. Clinical studies have shown that cetuximab and other EGFR receptor inhibitors work best for EGFR-expressing tumors that do not have mutations in a gene called K-RAS. Testing can be done to determine whether a patient has a tumour with a non-mutated (wild-type) KRAS gene.

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## Detailed Discussion:

- ◆ Three randomized controlled studies were identified for this review.
- ◆ The CO.17 trial (*Jonker et al. New England Journal of Medicine 2007*) compared cetuximab to best supportive care (i.e. no active anti-cancer drug treatment) in patients with EGFR-expressing metastatic colorectal cancer who had previously been treated with a fluoropyrimidine, irinotecan, and oxaliplatin, or had contraindications to these treatments. The study reported that the median overall survival was 6.1 months in the patients treated with cetuximab and 4.6 months in patients who received supportive care alone. The use of cetuximab was associated with an improvement in progression-free survival and higher disease response rates.
- ◆ In the EPIC trial (*Sobrero et al. Journal of Clinical Oncology 2008*), combination cetuximab plus irinotecan was evaluated against irinotecan alone in patients with EGFR-expressing metastatic colorectal cancer who had failed a fluoropyrimidine and oxaliplatin. The study found that the median overall survival was comparable between the two treatments regimens: 10.7 months for patients treated with cetuximab plus irinotecan and 10.0 months for those treated with irinotecan alone. Patients treated with cetuximab plus irinotecan had improved progression-free survival and higher disease response rates compared with irinotecan alone.
- ◆ The BOND trial (*Cunningham et al. New England Journal of Medicine 2004*) is an open-label randomized study in patients with metastatic colorectal cancer whose disease had progressed on irinotecan therapy. This study compared the use of cetuximab alone to a combination of cetuximab plus irinotecan and found that cetuximab plus irinotecan was significantly better than standalone cetuximab treatment with respect to disease progression and disease response rate.
- ◆ As a whole, the three studies support that cetuximab provides clinical benefits in the treatment of EGFR-expressing metastatic colorectal cancer in patients who have failed standard chemotherapies and that cetuximab plus irinotecan is more efficacious than cetuximab alone.
- ◆ The CED noted that available evidence consistently support that the K-RAS status of the patient's colorectal cancer is a strong predictor of response to EGFR inhibitors, and therefore if cetuximab was to be funded, consideration should only be given to patients who have tumours with a non-mutated (wild-type) KRAS gene.
- ◆ The Ontario Public Drug Programs fund another EGFR inhibitor for metastatic colorectal cancer. There are no direct head-to-head studies comparing the efficacy and safety of cetuximab relative to the comparator product.
- ◆ Cetuximab costs approximately \$7,000 per month (the cost varies according to the patient's body size). This drug has not been shown to be cost-effective. It is also more expensive than the alternative EGFR inhibitor.
- ◆ **Overall, the Committee acknowledged that cetuximab, in combination with irinotecan, provides clinical benefits in patients with EGFR-expressing non-mutated K-RAS metastatic colorectal cancer who have failed standard chemotherapy. However, this treatment is not cost-effective and a comparator is available at a lower cost.**

*The CED worked jointly with a subcommittee involving cancer experts to review this cancer drug, as it does all other cancer drugs.*

## NDFP Funding:

Based on the CED's recommendation and cost agreement with the manufacturer, the Executive Officer decided to fund cetuximab (Erbix<sup>®</sup>) for the treatment of metastatic colorectal cancer through the New Drug Funding Program (NDFP) according to the following criteria:

- ◆ *The patient has metastatic colorectal cancer.*
- ◆ *The patient has failed chemotherapy regimens containing oxaliplatin and irinotecan.*
- ◆ *The tumour has non-mutated (wild-type) K-RAS oncogene.*
- ◆ *Cetuximab will be used in combination with irinotecan as third line therapy.*

Details of the NDFP eligibility criteria can be found at the Cancer Care Ontario website:

<http://www.cancercare.on.ca/toolbox/drugs/ndfp/>



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