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EVIDENCE BRIEFING JANUARY 2019

Encorafenib in combination with binimetinib and cetuximab for BRAF V600E mutant metastatic colorectal cancer

NIHRIO ID	12855	**NICE ID**	10078
Developer/Company	Pierre Fabre Ltd Array BioPharma Merck KGaA Ono Pharmaceuticals	**UKPS ID**	650081 (encorafenib) 650113 (binimetinib)

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Encorafenib in combination with binimetinib and cetuximab (triple therapy) is in clinical development for the treatment of patients with BRAF V600E mutant metastatic colorectal cancer (mCRC) whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. Colorectal (or bowel) cancer starts in the large bowel (colon) and the back passage (rectum) and is more common in people aged over 70 years. Its cause is unknown but various factors increase the risk of contracting it, including diet, smoking, and overweight or obesity. Around 10% of mCRC patients have the BRAF V600E mutation, and they have more than double the mortality risk of those without it.

Encorafenib in combination with binimetinib and cetuximab is one of the first regimens to target the BRAF V600E-mutation in colorectal cancer. When this mutation is present, it switches on another protein called MEK, which stimulates cell division and leads to uncontrolled cell growth. Encorafenib and binimetinib target different parts of an important signalling pathway in tumour cells with the mutation, and slows down their growth and communication. It is also one of the first combinations to simultaneously target the BRAF and MEK pathways, and encorafenib and binimetinib have the advantage of oral administration.

PROPOSED INDICATION

The treatment of adult patients with BRAFV600E mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting.[a]

TECHNOLOGY

DESCRIPTION

Encorafenib (Braftovi, LGX818) is a potent and highly selective adenosine triphosphate (ATP) competitive small molecule rapidly accelerated fibrosarcoma (RAF) kinase inhibitor.[1] The BRAF gene encodes the B-RAF protein, which plays a role in regulating the mitogen-activated protein kinases (MAPK)/ extracellular signal-related kinase (ERK) signalling pathway, which in turn impacts cell division, differentiation, and secretion. Encorafenib suppresses the RAF/MAPK /ERK signalling pathway in tumour cells expressing mutated BRAF V600E (but not wild-type BRAF), decreasing the proliferation of tumour cells.[1,2]

Binimetinib (Mektovi, MEK162) is an ATP-uncompetitive, reversible inhibitor of the kinase activity of MEK1 and MEK2, proteins which are upstream regulators of the ERK pathway, which promotes cellular proliferation. This pathway is often activated by mutated forms of BRAF, which activates MEK. Binimetinib inhibits activation of MEK by BRAF and inhibits MEK kinase activity. The addition of MEK inhibition improves anti-tumour activity for the combination of encorafenib and binimetinib.[3]

Cetuximab is a chimeric monoclonal IgG1 antibody that binds with a high affinity to the epidermal growth factor receptor (EGFR), inhibiting its function. EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis.[4]

Encorafenib in combination with binimetinib and cetuximab is in phase III clinical development for the treatment of BRAF V600E mutant metastatic colorectal cancer. The proposed dosing regimen is encorafenib (capsule) 300 mg once daily, plus binimetinib (tablet) 45 mg twice daily, plus intravenous cetuximab at the standard weekly dose – an initial dose of 400 mg/m^2, followed by 250 mg/m^2 once weekly. This is administered in a 28-day cycle.[a]

INNOVATION AND/OR ADVANTAGES

Limited treatment options are currently available for BRAFV600E mCRC patients and comprise of FOLFOX or FOLFORI.[5]

Encorafenib in combination with binimetinib and cetuximab is one of the first regimens to target BRAFV600E mCRC patients, who have a mortality risk more than double that of metastatic CRC patients without the mutation.[6] It is also one of the first combinations to target the BRAF and MEK pathway together, and has the advantage that encorafenib and binimetinib are taken orally rather than IV.[1,3,7]

[a] Information provided by Pierre Fabre Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Encorafenib in combination with binimetinib and cetuximab (triple therapy) does not currently have Marketing Authorisation in the EU/UK for any indication.

Encorafenib in combination with binimetinib is currently licensed in the UK for the treatment of adult patients with unresectable or metastatic melanoma with a BRAFV600 mutation.[1] The most common side effects from encorafenib in combination with binimetinib are tiredness, nausea, diarrhoea, vomiting, retinal detachment, abdominal pain, joint pain, muscle pain and high levels of an enzyme called creatine kinase, which may indicate muscle problems.[8]

Encorafenib in combination with binimetinib and cetuximab was designated Breakthrough Therapy for BRAF-mutant V600E metastatic colorectal cancer by the FDA in August 2018.[6]

PATIENT GROUP

DISEASE BACKGROUND

Colorectal cancer, also known as bowel cancer, is cancer that starts in the large bowel (colon) and the back passage (rectum).[9] Around 10% of metastatic colorectal cancer patients have BRAF mutations, and have a poorer prognosis than those with wild-type BRAF.[7,10]

The cause of colorectal cancer is unknown. Risk factors for colorectal cancer include overweight or obesity, smoking, drinking too much alcohol, eating processed meat, or eating too little fibre. Almost 60% of colorectal cancer cases in the UK each year are diagnosed in people aged 70 or over. [11]

Symptoms of colorectal cancer include bleeding from the back passage, blood in the faeces, changes in bowel habit, weight loss, and anaemia. If the cancer causes a bowel obstruction it may cause cramping pains in the abdomen, bloating, constipation and being unable to pass wind, or being sick.[12]

Following treatment, people may have to restrict their diet if part of the colon has been removed, and they may be more susceptible to diarrhoea. Some people may need a temporary or permanent stoma. People also experience fatigue and mood swings, and have to deal with their emotional response to having a cancer diagnosis.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Colorectal cancer is the 4th most common cancer in the UK, and accounted for 12% of all new cancer cases in 2015.[14] It is the 2nd most common cause of cancer death in the UK, and accounted for 10% of all cancer deaths in 2016.[15] The age standardised incidence rate in England in 2015 was 69.4 per 100,000.[16]

Admitted patient care statistics for colon cancer in England for 2017-18 recorded a total of 91,760 admissions, of which 68,445 were day cases (ICD-10 code C18). For cancer of the rectum there were a total of 44,896 admissions, of which 34,042 were day cases.[17]

Colorectal cancer survival is improving, and has more than doubled in the last 40 years in the UK. Five year survival is around 59% in England and Wales - 69% and 71% for men and women respectively diagnosed between 15 and 39 years, and 46% and 42% respectively for those diagnosed when they are over 80.[18,19] One year survival is around 76%.[18] In 2017 in England and Wales, there were 8,290 deaths attributed to malignant neoplasm of the colon (ICD-10 C18).[20] The risk of mortality in CRC patients with the BRAFV600E mutation is double that for those with wild-type BRAF.[6]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Metastatic colorectal cancer may be treated with a combination of surgery (if possible), chemotherapy, radiotherapy, biological therapy and supportive care. The aim of treatment is to control the symptoms and slow the spread of the tumours, and patients are usually under the care of a multidisciplinary team of specialists including a surgeon, oncologist, radiologist, and specialist nurse. Chemotherapy and radiotherapy can be used before surgery to reduce the size of the tumour for resection, instead of surgery where this is not feasible, or as a palliative procedure to control symptoms and slow the spread of the cancer.

CURRENT TREATMENT OPTIONS

For patients with advanced and mCRC, NICE recommends consideration of one of the following sequences unless contra-indicated:

- FOLFOX as first-line treatment then single-agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI as second-line treatment or
- XELOX as first-line treatment then FOLFIRI as second-line treatment.[21]

Oral therapy with capecitabine is an option for first line treatment of mCRC.[22]

Trifluridine–tipiracil is recommended, within its marketing authorisation and on a patient access scheme, as an option for treating metastatic colorectal cancer in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable.[23]

PLACE OF TECHNOLOGY

If licensed, encorafenib in combination with binimetinib and cetuximab will initially offer an additional treatment option for patients with BRAFV600E mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting.

CLINICAL TRIAL INFORMATION

Trial	BEACON CRC, NCT02928224, ARRAY-818-302, EudraCT-2015-005805-35; encorafenib + binimetinib vs encorafenib vs active comparator – either irinotecan or FOLFIRI (all arms in combination with cetuximab); phase III
Sponsor	Array BioPharma
Status	Ongoing
Source of Information	Abstracts,[10,24,25] trial registry,[26,27]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, open label, active-controlled
Participants	n=645 (planned); aged 18 years and older; BRAF V600E mutant metastatic colorectal cancer; disease has progressed after 1 or 2 prior regimens in the metastatic setting
Schedule	Patients are randomised to receive (i) triplet arm: oral encorafenib (capsule) 300 mg once-daily in combination with oral binimetinib (tablet) 45 mg twice-daily plus intravenous cetuximab 400 mg/m^2,

	followed by 250 mg/m^2 weekly; (ii) doublet arm: encorafenib 300 mg once-daily plus intravenous cetuximab 400 mg/m^2, followed by 250 mg/m^2 weekly; (iii) active comparator: investigator's choice of either irinotecan/cetuximab or FOLFIRI/cetuximab; in 28 day cycles
Follow-up	Active treatment until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent therapy, or death; follow up 6 mths
Primary Outcomes	• Safety lead-in: incidence of dose-limiting toxicities (28 days); incidence and severity of adverse events and changes in clinical laboratory parameters, vital signs, electrocardiograms (ECGs), echocardiogram (ECHO)/multi-gated acquisition (MUGA) scans and ophthalmic examinations (6 mths); incidence of dose interruptions, dose modifications and discontinuations due to adverse events (6 mths) • Phase 3: overall survival of triplet arm vs comparator arm (6 mths)
Secondary Outcomes	• Safety lead-in: overall response rate; duration of response; time to response (all 6 mths); • Safety lead-in: evaluation of the area under the concentration-time curve (AUC) for cetuximab, encorafenib, binimetinib, and a metabolite of binimetinib; evaluation of the maximum concentration (Cmax) for cetuximab, encorafenib, binimetinib, and a metabolite of binimetinib; evaluation of the time of maximum observed concentration (Tmax) for cetuximab, encorafenib, binimetinib, and a metabolite of binimetinib; evaluation of the steady-state concentration measured just before the next dose of study drug (Ctrough) for cetuximab, encorafenib, binimetinib, and a metabolite of binimetinib (all predose and 1, 2, 4 and 6 hours post-dose on Day 1 of Cycles 1 and 2); • Phase 3: overall survival in doublet arm vs comparator arm and triplet arm vs doublet arm; comparison of progression-free survival in study arms; comparison of objective response rate in study arms; comparison of duration of response in study arms; comparison of time to response in study arms; incidence and severity of adverse events (AEs) and changes in clinical laboratory parameters, vital signs, electrocardiograms (ECGs), echocardiogram (ECHO)/multi-gated acquisition (MUGA) scans and ophthalmic examinations; comparison of the quality of life in study arms (all 6 mths)
Key Results	Only results from the safety lead (n=30) are currently available.[25] The confirmed overall response rate (ORR) was 48% and median progression-free survival 8 months.
Adverse effects (AEs)	The most common grade 3 or 4 adverse events in the safety lead-in in at least 10% of patients were fatigue (13%), anaemia (10%), increased creatine phosphokinase (10%), increased aspartate aminotransferase (10%) and urinary tract infections (10%).
Expected reporting date	Study completion date reported as July 2019

ESTIMATED COST

Encorafenib in combination with binimetinib is currently licensed for the treatment of adult patients with unresectable or metastatic melanoma with a BRAFV600 mutation.

An infusion vial containing 5mg/ml of cetuximab costs £178.10 for 100mg/20ml, or £890.50 for 500mg/100ml.[28]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016
- NICE technology appraisal. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118). Last updated November 2015
- NICE technology appraisal. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (TA242). Last updated March 2015
- NICE technology appraisal. Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (TA61). Last updated June 2011
- NICE clinical guideline. Colorectal cancer: diagnosis and management. Last updated December 2014
- NICE quality standard. Colorectal cancer (QS20). Last updated in 2017

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Transanal endoscopic microsurgery (TEMS) (Adult). A08/S/e
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Distal sacrectomy (Adult). A08/S/b
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Cytoreductive surgery (Adult). A08/S/f

OTHER GUIDANCE

- Montroni, I et al. Personalized management of elderly patients with rectal cancer: expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer, 2018[29]
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