

An addendum to these minutes has been included at the end of the document.

6.04 ENCORAFENIB

**Tablet 50 mg, Tablet 75 mg,
Braftovi[®],
Pierre-Fabre Australia Pty Ltd.**

1 Purpose of Application

- 1.1 The application requested MBS listing of *BRAF* V600E testing and PBS listing of encorafenib with an EGFR inhibitor such as cetuximab for the targeted treatment of patients with *BRAF* V600E variant metastatic CRC (mCRC) who have received prior systemic therapy. The PICO Confirmation Advisory Sub-Committee (PASC) confirmed that the appropriate economic evaluation would be a cost-utility (or cost-effectiveness) analysis (Ratified PICO, Application 1617). The integrated co-dependent submission was received from Pierre Fabre Australia Pty Ltd by the Department of Health in November 2020.
- 1.2 The submission flagged a note on the terminology used to refer to mutations vs variants; that as per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016) the term “variant” should be used to replace the outdated term “mutation”; and “*BRAF* V600E” pathogenic variant refers to both class 4 (likely pathogenic) and class 5 (known pathogenic) variants. This is similar for *RAS* and other pathogenic variants. However, the term mutation was also used in the submission as it appears most often in the regulatory and clinical documents.
- 1.3 A summary of the components of the overall clinical claim addressed by the submission is presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Patients diagnosed with Stage IV metastatic colorectal cancer (mCRC). Medicine: Patients with mCRC who have received prior systemic therapy in the metastatic setting, and who have a <i>BRAF</i> V600E pathogenic variant in tumour tissue. ^a
Intervention	Test: <i>BRAF</i> V600E variant testing added to existing MBS item 73338. <i>BRAF</i> V600E variant testing ^b involves taking a biopsy of the mCRC tumour and performing DNA extraction and assay. ^c Medicine: Treatment with encorafenib [in combination with an EGFR inhibitor such as cetuximab] (also known as a doublet-therapy group). ^d
Comparator	Test: No testing, i.e. MBS item 73338 in its current format, which has no explicit inclusion of <i>BRAF</i> V600E variant testing in mCRC, and no reference to encorafenib. Medicine: FOLFIRI + cetuximab or irinotecan + cetuximab.
Outcomes	Test: Concordance between the evidentiary standard and other <i>BRAF</i> V600E variant testing methods likely to be used in Australia. Medicine: OS, ORR, PFS, health related quality of life and adverse events associated with treatment.
Clinical claim	Test: <i>BRAF</i> V600E variant testing methods likely to be used in Australia are concordant. Medicine: Encorafenib in combination with an anti-EGFR agent such as cetuximab ^d , is superior in terms of effectiveness compared with FOLFIRI + cetuximab or irinotecan + cetuximab. Encorafenib in combination with an anti-EGFR agent such as cetuximab ^d , demonstrated a manageable tolerability profile and is superior in terms of safety compared with FOLFIRI + cetuximab or irinotecan + cetuximab.

Source: Table 1-1, p 23-24 of the submission.

Abbreviations: BRAF = B-rapidly accelerated fibrosarcoma; EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = 5-fluoracil/folinic acid/oxaliplatin; MBS = Medicare Benefits Schedule; mCRC = metastatic colorectal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

^a Key exclusion criteria included no prior treatment with any rapidly accelerated fibrosarcoma (RAF) inhibitor, mitogen-activated protein kinase (MEK) inhibitor, cetuximab, panitumumab or other EGFR inhibitors.

^b Upon the amendment of MBS item 73338, to include *BRAF* V600E testing alongside *RAS* gene testing.

^c Such as polymerase chain reaction (PCR) based assays, Sanger sequencing, or next generation sequencing (NGS).

^d The clinical evidence in support of the effectiveness and safety was based on information for encorafenib + cetuximab and not in combination with any other EGFR inhibitor (such as panitumumab).

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA Delegate's Overview was available. The delegate considered the benefit-risk profile was positive. The final proposed TGA indication was:

“...in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a *BRAF* V600E mutation as detected by a validated test, who have received prior systemic therapy.”

2.2 The use of encorafenib + cetuximab for the proposed indication (or similar) was approved by the United States Food and Drug Administration (FDA) in April 2020 and by the European Medicines Agency (EMA) in June 2020.

For more detail on the PBAC's view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The submission requested an Authority Required (STREAMLINED) PBS listing for encorafenib in combination with an EGFR inhibitor, for *BRAF V600E* variant mCRC after prior systemic therapy. A Special Pricing Arrangement (SPA) was requested.
- 3.2 The requested listing is presented below. Suggested additions proposed by the Secretariat are in italics and suggested deletions are crossed out with strikethrough.

Initial

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for maximum quantity	Proprietary Name and Manufacturer	
ENCORAFENIB encorafenib 75 mg capsule, 42	3	126	3	Published: \$5313.87 Effective: \$	Braftovi®	Pierre Fabre Australia Pty Ltd
encorafenib 50 mg capsule, 28	6	168	3	Published: \$4735.32 Effective: \$		

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Severity: Metastatic
Condition: colorectal cancer
Indication: Metastatic colorectal cancer
Treatment Phase: Initial treatment
Clinical criteria: The condition must be positive for a BRAF V600E mutation <i>Patient must have BRAF V600E variant positive metastatic colorectal cancer</i>
AND
Patient must be receiving PBS subsidised EGFR inhibitor concomitantly for this condition <i>The treatment must be in combination with [cetuximab/anti-EGFR antibody therapy]</i>
AND
The condition must not have been treated previously with PBS subsidised encorafenib <i>Patient must not have been previously received PBS subsidised treatment with this drug for this condition</i>
AND
Patient must not have received prior treatment with [an anti-EGFR antibody therapy/cetuximab] for this condition
AND
The condition must have failed to respond to at least one other line of chemotherapy for their metastatic colorectal cancer
AND
Patient must have a WHO performance status of 2 or less
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Continuing

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for maximum quantity	Proprietary Name and Manufacturer	
encorafenib 75 mg capsule, 42	3	126	5	Published: \$5313.87 Effective: \$	Braftovi®	Pierre Fabre Australia Pty Ltd
encorafenib 50 mg capsule, 28	6	168	5	Published: \$4735.32 Effective: \$		

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Severity: Metastatic
Condition: colorectal cancer
Indication: Metastatic colorectal cancer
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug received PBS-subsidised treatment with this drug for this condition
AND
Patient must be receiving PBS-subsidised EGFR inhibitor for this condition. The treatment must be in combination with [cetuximab/anti-EGFR antibody therapy]
AND
Patient must not have stable or responding progressive disease while being treated with this drug for this condition
Administrative Advice: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 3.3 The broader requested restriction was inconsistent with the proposed TGA indication, the clinical evidence, the economic model and the estimated financial implications, all of which related to the use of encorafenib in combination with cetuximab specifically and not an EGFR inhibitor in general (which would include PBS-listed panitumumab).
- 3.4 The Pre-Sub-Committee Response (PSCR) stated that the broader requested listing was based on the assumption that results for encorafenib + cetuximab are a class effect, which would be seen for treatment with encorafenib + panitumumab. The ESCs were of a view that a broader listing, allowing combination use of encorafenib with any EGFR inhibitor may be clinically preferable so as not to disadvantage patients who develop sensitivity or intolerance to cetuximab. The ESCs considered that panitumumab and cetuximab are used interchangeably in clinical practice and noted that both are PBS-listed for use in patients with mCRC. The ESCs further noted that the use of encorafenib + panitumumab in this population would be consistent with the *NCCN Guidelines Version 2.2021 Colon Cancer*. However, the ESCs also noted that the requested TGA indication and all clinical trial evidence (BEACON) provided in the submission was limited to use in combination with cetuximab, and a listing on the PBS in combination with any EGFR inhibitor would represent an expansion beyond the proposed TGA indication. The pre-PBAC response proposed PBS listing in combination with cetuximab specifically, in line with the final proposed TGA indication.
- 3.5 The ESCs recalled that when PBAC recommended each BRAF inhibitor for the treatment of melanoma, reference to the V600E variant alone was omitted from the PBS restriction. The PBAC was asked to consider whether the mCRC listing should be made consistent with the melanoma listing and refer more broadly to V600 variant status (without reference to V600E specifically).
- 3.6 The analysis of drug exposure in the economic evaluation was based on time to discontinuation (TTD) in BEACON, which allowed for patients to continue to receive

therapy beyond progression if deemed to be clinically appropriate. This was not consistent with the proposed continuation criteria (see *Economic analysis*).

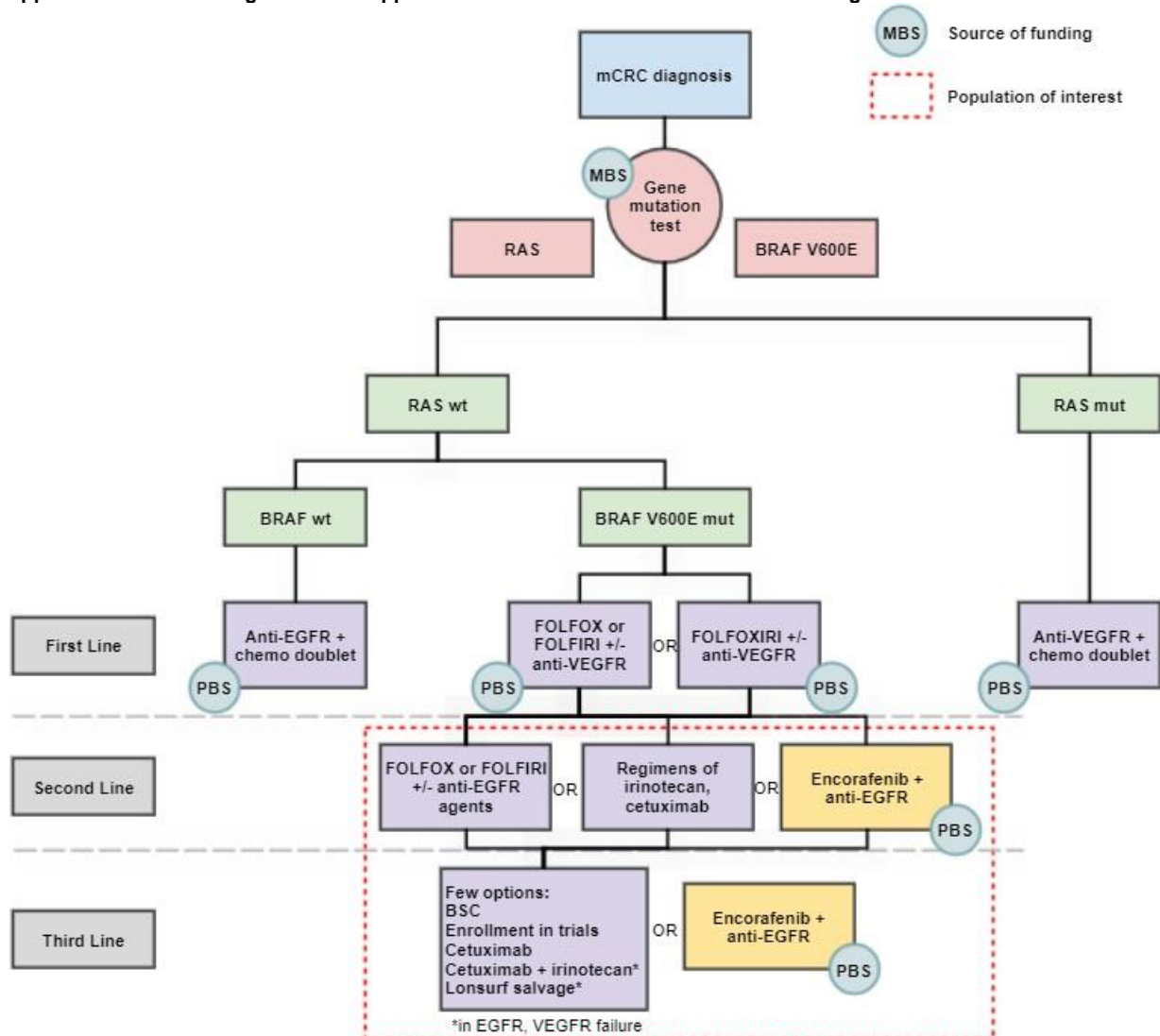
For more detail on the PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 The submission described CRC as the third most common cancer in men, and the second in women. It is also the fourth leading cause of cancer-related mortality, and 22-25% of patients are diagnosed with stage IV disease (Adam, et al., 2015; Haggard & Boushey, 2009). In 2016, CRC led to the death of 5,375 people, representing the second highest number of cancer deaths in Australia (AIHW, 2019).
- 4.2 Around 50% of new patients with CRC (stage I, II, III) will progress to a metastatic stage (stage IV) during the course of their disease. The five-year relative survival rate for patients with mCRC is 13% compared to 71% for stage III, 89% for stage II and 99% for stage I CRC. Genetic alteration of the mitogen-activated protein kinase (MAPK) signalling cascade (RAS/RAF/MEK/ERK kinase) is the most common oncogenic event in CRC tumorigenesis. Approximately 55% of mCRC patients are *RAS* wild type (WT) and 45% have a *RAS* variant.
- 4.3 The *BRAF* variant is a genetic mutation, which accounts for around 10% of patients with mCRC in clinical trials (van Cutsem, et al., 2016; Maughan, et al., 2011; Tran, et al., 2011; Tveit, et al., 2012). *BRAF* and *RAS* variants, as opposed to *RAS* WT variants, are almost mutually exclusive in mCRC (Larki, et al., 2017), with *BRAF* variants being a sub-category of *RAS* WT. Within *BRAF* variants in mCRC, *BRAF* V600E accounts for 90-95% of all *BRAF* variants (Kopetz, et al., 2015; Wan, et al., 2004). Other *BRAF* variants include V600K, V600R and V600D. Compared to other mCRC subtypes, the presence of a *BRAF* V600E variant indicates poor prognosis. The presence of a *BRAF* variant in mCRC patients predicts more than double the risk of mortality (hazard ratio; HR = 2.25, 95% CI, 1.82-2.83; Ardekani G. S., Jafarnejad, Tan, Saeedi, & Li, 2012).
- 4.4 The target population for the *BRAF* V600E genetic test was all patients newly diagnosed with mCRC. The target population for the proposed medicine, encorafenib + an EGFR inhibitor, such as cetuximab, included patients who have mCRC with a *BRAF* V600E variant and that have received prior systemic therapy. The population targeted in the submission to receive *BRAF* V600E testing and encorafenib + an EGFR inhibitor, such as cetuximab, was well described and was appropriate.
- 4.5 The submission's proposed *BRAF* testing and the place in therapy for encorafenib + an EGFR inhibitor in mCRC is presented in Figure 1. The algorithm below depicts the use of bevacizumab (an anti-VEGFR agent) in the first-line setting only, whilst the proposed clinical management algorithm presented in the submission stated that bevacizumab is sometimes used in the second-line setting (Figures 1-5 and 1-6 of the submission). The PBAC previously considered that it is standard practice to allow crossover use of an anti-EGFR (cetuximab or panitumumab) and an anti-VEGFR agent

(bevacizumab) at disease progression (paragraph 7.5, cetuximab Public Summary Document, November 2014 PBAC Meeting), which is not reflected in the reimbursement pathway in the figure below. Furthermore, the algorithm proposed the use of anti-EGFR agents (cetuximab or panitumumab) in the second- or third-line setting to be in combination with chemotherapy. However, the current PBS indication of cetuximab in the second-line setting may be either as monotherapy or in combination with chemotherapy. The ESCs agreed with the proposed algorithm that encorafenib + cetuximab would be used in patients who had failed prior systemic therapy, but disagreed that regimens including anti-EGFR agents would be used in *BRAF* V600E variant patients in the second-line setting (see *Comparator* section below).

Figure 1: Proposed gene testing and drug reimbursement pathway for patients with mCRC following MSAC approval of BRAF testing and PBAC approval of treatment with encorafenib + EGFR agent



Abbreviations: BRAF = B-Rapidly Accelerated Fibrosarcoma, BSC=best supportive care; EGFR = Epidermal Growth Factor Receptor, FOLFIRI = 5-fluorouracil/folinic acid/irinotecan, FOLFOX = 5-fluorouracil/folinic acid/oxaliplatin, FOLFOXIRI = Folinic acid, Fluorouracil, Oxaliplatin and Irinotecan; Lonsurf = trifluridine/tipiracil; MBS = Medicare Benefits Schedule, mCRC = metastatic colorectal cancer, PBS =

Pharmaceutical Benefits Scheme; RAS = Rat Sarcoma viral oncogene homolog; wt = wild type, VEGFR = Vascular Endothelial Growth Factor Receptor.

Source: Figure 1-4, p42 of the submission.

- 4.6 Cetuximab is an EGFR inhibitor that binds to the extracellular component of the EGFR and prevents the epidermal growth factor from binding to its own receptor, therefore preventing cell division. The activation of EGFR results in resistance of *BRAF* mutant CRC to RAF inhibitors, resulting in continued proliferation even in the presence of BRAF inhibition.
- 4.7 The PBAC noted that synergistic inhibition of RAF and EGFR by the combination of encorafenib and cetuximab can combat mechanisms of resistance of RAF inhibitors in BRAF mutant CRC (Corcoran, et al., 2012; Hong, et al., 2016).

For more detail on the PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated FOLFIRI (folinic acid/fluorouracil/irinotecan) + an EGFR inhibitor (cetuximab) as the main comparator for the proposed medicine. The main arguments provided by the submission in support of this nomination were:
- FOLFIRI + cetuximab represented the most commonly used second-line therapy in Australian clinical practice among patients with *BRAF* V600E mutant mCRC.
 - The FDA, the EMA and the Australian investigators in the trial endorsed the choice of FOLFIRI + cetuximab as a comparator in BEACON CRC (pivotal trial for the clinical evidence, hereafter referred to as BEACON).
 - The efficacy observed in the BEACON control arm regimens were representative of the results seen to date in trials of other second and third-line regimens.
- 5.2 The submission nominated irinotecan + an EGFR inhibitor (cetuximab) as a secondary comparator on the basis of its common use in the second and third-line setting in Australia among patients with *BRAF* V600E variant mCRC.
- 5.3 The submission claimed that the selection of these comparators was supported by Australian treatment guidelines and a survey of Australian treating oncologists (with five complete responses).
- 5.4 The ESCs did not agree with the submission's assertion that, "Given that there is no treatment specifically indicated for patients with BRAF V600E mutant mCRC, patients have been treated so far with standard of care regimens for any type of mutation status".
- 5.5 The ESCs noted that currently, and consistent with the position in the submission, the test for *BRAF* status is routinely performed and reported alongside *RAS* status as an important prognostic tool in patients with mCRC. Australian clinical practice guidelines for CRC stated that, "The preponderance of the available evidence is that response to

EGFR-targeted agents is less likely in patients whose tumours harbour a *BRAF* mutation.”¹ Furthermore, the use of FOLFIRI + cetuximab in the proposed patient population is not consistent with the *NCCN Guidelines v2.2021*, which state that patients receiving EGFR-targeted agents (cetuximab or panitumumab) should have *BRAF* WT mCRC. Therefore, the ESCs considered the appropriate main comparator in this setting was FOLFIRI alone, not FOLFIRI in combination with cetuximab.

- 5.6 The pre-PBAC response again claimed that FOLFIRI + cetuximab was the appropriate main comparator, stating that the authors of the *NCCN Guidelines v3.2015* had concluded that there were insufficient data to guide the use of anti-EGFR therapy with active chemotherapy based on *BRAF* V600E mutation status. The pre-PBAC response also cited the views of various Australian clinicians, including the clinician who presented at the sponsor hearing (see below). Generally, these clinicians suggested that FOLFIRI + cetuximab continued to be used regularly in clinical practice for *BRAF* v600E variant mCRC (despite the additional benefits being less than seen in *BRAF* WT patients) because of limited therapeutic options and the very poor prognosis for *BRAF* V600E variant mCRC.
- 5.7 The PBAC noted that, in the updated *NCCN Guidelines v2.2021*, which were published subsequent to the submission lodgement, the panel believed that, “evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely, unless given as part of a *BRAF* inhibitor regimen” (i.e. encorafenib with cetuximab or panitumumab). The NCCN panel also recommended *BRAF* genotyping at diagnosis of stage IV disease.²
- 5.8 The submission noted other treatment options recommended and available for use in the second-, third- and subsequent-line settings for *BRAF* V600E variant mCRC, including bevacizumab and trifluridine-tipiracil (Lonsurf®). Bevacizumab was not considered as a comparator because it is mostly used in the first-line setting (as evidenced by the Australian guidelines), and there are limited data supporting its continued use in the second-line setting for *RAS* WT patients. This was also evident in the 2018 DUSC report, which showed that the utilisation of bevacizumab in the second-line setting in Australia is minimal (Figure 14, Cetuximab, panitumumab and bevacizumab for mCRC - DUSC Report 2018). Trifluridine-tipiracil was not considered an appropriate comparator as it is an nth-line salvage treatment used in a different population. Trifluridine-tipiracil is restricted to patients who are not suitable candidates for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGFR agent and an EGFR inhibitor such as cetuximab. This was inconsistent with the PASC consideration of trifluridine-tipiracil as an appropriate comparator to encorafenib in its likely smaller volume of use in the third-line setting,

¹ https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Systemic_therapy_molecular_pathology

² Benson B. et al: Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* 19(3): 329-329, 2021.

given the NHMRC Guidelines for the management of mCRC (2017) included its use in patients who are refractory to all standard available therapies (Ratified PICO, Application 1617).

For more detail on the PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease and how the drug would be used in practice. The clinician emphasised the poorer prognosis for patients with *BRAF* variant mCRC compared with *BRAF* WT patients, and the clinical need for effective treatment options in this relatively small population. In terms of current treatments used in Australia, the clinician stated that while anti-EGFR inhibitors have less impact in patients with *BRAF* variant mCRC, they were nonetheless used in combination with standard chemotherapy because even a transient response was valuable in the context of the very poor survival of these patients. The clinician considered that the improved survival offered by encorafenib with an anti-EGFR inhibitor meant that this regimen would become the treatment of choice moving forward. The PBAC considered that the hearing was informative as it provided a clinical perspective of current Australian treatment approaches.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The comments, including from Bowel Cancer Australia and Rare Cancers Australia, focused primarily on the poor prognosis of *BRAF*-positive mCRC patients, the lack of effective treatment options currently available, and described benefits of treatment with encorafenib + cetuximab, including increased overall survival and improved quality of life.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the encorafenib submission. The PBAC noted that MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for encorafenib in combination with cetuximab, which was 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)³, based on a comparison with FOLFIRI + cetuximab. MOGA noted that the clinical value may be overestimated due to a questionable control arm used in BEACON. The ESMO-MCBS score was upgraded to 5 due to the QOL improvement seen in BEACON.

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

Overview of the evidence base

6.4 The approach taken in the submission was to present direct evidence of the effect of targeting *BRAF* V600E with encorafenib + cetuximab as summarised in Table 2.

Table 2: Direct evidence provided in the submission to support the use of the co-dependent technology

Study design	Extent of evidence supplied	Overall risk of bias in clinical trials
Prospective biomarker (<i>BRAF</i> V600E) stratified randomised controlled trial of encorafenib + cetuximab versus control ^a	☒ k= 1 n=665	Low

Note: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

Abbreviations: *BRAF* = B-Rapidly Accelerated Fibrosarcoma; FOLFIRI = 5-fluorouracil/ folinic acid/irinotecan; k = number of studies; n = number of patients.

Source: pp34, 115 of the submission.

6.5 Details of the trial presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Encorafenib + cetuximab – key trial		
BEACON CRC NCT02928224 ARRAY-818-302	The BEACON CRC study (Binimetinib, Encorafenib, And Cetuximab COmbiNed to Treat <i>BRAF</i> -mutant ColoRectal Cancer): A Multicentre, Randomised, Open-label, 3-Arm, Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab with a safety lead-in of Encorafenib + Binimetinib + Cetuximab in Patients with <i>BRAF</i> V600E-mutant Metastatic Colorectal Cancer.	CSR report 11 Feb 2019
	Kopetz S, Grothey A, Yaeger R, Van Cutsem E et al. Encorafenib, Binimetinib, and Cetuximab in <i>BRAF</i> V600E-mutated colorectal cancer.	<i>N Engl J Med</i> 2019; 381:1632-1643.

6.6 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Use in modelled evaluation
Encorafenib + cetuximab vs control ^a					
BEACON CRC	665 ^b	R, MC, OL 14.7 months ^c	<i>BRAF</i> V600E metastatic CRC after failure of initial therapy	OS, ORR, PFS ^d	OS, PFS, TTD

^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab.

^b BEACON CRC had three arms: encorafenib + binimetinib + cetuximab (triplet arm; n = 224), encorafenib + cetuximab (doublet arm; n = 220) or control arm (n = 221). The clinical evidence for the submission was the comparison between the doublet arm and the control arm.

^c Defined as the duration between randomisation and cut-off date in total population (N = 665).

^d These include the key secondary and secondary outcomes that are relevant to the submission.

Abbreviations: *BRAF* = B-Rapidly Accelerated Fibrosarcoma; CRC = colorectal cancer; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; TTD = time to discontinuation.

Source: compiled during the evaluation

6.7 The submission was based predominantly on one head-to-head randomised controlled trial, BEACON, comparing encorafenib + cetuximab (+/- binimetinib) to FOLFIRI + cetuximab or irinotecan + cetuximab (FOLFIRI/Ir + cetuximab) in patients with *BRAF* V600E variant mCRC. Randomisation was stratified according to Eastern

Cooperative Oncology group (ECOG) performance status (0 or 1), previous use of irinotecan (yes or no), and cetuximab formulation (United States licensed or European-approved formulation).

- 6.8 BEACON enrolled adults with histologically or cytologically confirmed mCRC; measurable disease; with the presence of *BRAF* V600E in tumour tissue as determined by a local assay or central laboratory. Patients must have had progressive disease after one or two prior regimens in the metastatic setting, ECOG ≤ 1 , and adequate haematological, hepatic and renal function. Eligible patients also needed to qualify to receive cetuximab per locally approved label with regard to tumour *RAS* status, and be able to provide a sufficient amount of representative tumour specimen for confirmatory central laboratory testing of *BRAF* and *KRAS* status.
- 6.9 Baseline patient disease characteristics were similar with respect to primary tumour location, prior cancer treatment (including number of prior systemic therapies), number of organs involved, and sites of metastases. Tumour microsatellite instability (MSI) status, was similar across the three arms. The proportion of patients classified with MSI abnormally high (MSI-H) was slightly greater in the encorafenib + binimetinib + cetuximab arm (9.8%) and encorafenib + cetuximab arm (8.6%) compared to the control arm (5.4%). The predictive value of MSI status with respect to the encorafenib treatment effect is unknown. The proportion of patients with primary tumour in the left colon (which included the rectum) was greater in the encorafenib + binimetinib + cetuximab arm (35.3%) and the encorafenib + cetuximab arm (37.7%) compared to the control arm (30.8%). The Clinical Guidelines Network (Cancer Council Australia)⁴ state the location of the primary tumour is a strong prognostic factor and that patients with left sided primary tumours have a favourable outcome compared with those with right sided tumours regardless of treatment type received. The higher proportion of patients with left colon cancer in both of the intervention arms could have potentially biased results against the control arm, although the difference was not statistically significant (RD = 0.70, 95% CI: -0.019, 0.158).
- 6.10 The overall risk of bias in BEACON was low, although potential sources of bias included:
- The Phase 3 Response Efficacy Set consisted of the first 331 patients randomised (n = 111 encorafenib + binimetinib + cetuximab arm; n = 113 encorafenib + cetuximab arm and n = 107 control arm), who had follow-up of at least 9 months. The results for objective tumour response rates at the primary analysis (data cut-

⁴ Molecular pathology and biomarkers: implications for systemic therapy, Clinical Guidelines Network, Cancer Council Australia, last modified 7 November 2017, https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Systemic_therapy_molecular_pathology#Left-sided_versus_right-sided_tumours

off 11 February 2019) could therefore be potentially subject to attrition bias as they do not consider the overall response rate in the whole trial population.

- Due to the open-label nature of the trial, investigator and patient treatment decisions may have been influenced as they were aware of the therapy to which they were assigned. Study discontinuation rates were higher in the control arm (59.3%) compared to the encorafenib + binimetinib + cetuximab arm (41.5%) and the encorafenib + cetuximab arm (44.5%).
- The control arm consisted of investigator's choice of either cetuximab + irinotecan or cetuximab + FOLFIRI. As the dose of irinotecan in both regimens was the same (i.e. the difference between the regimens was the addition of 5-fluorouracil + folinic acid), investigator's choice of one regimen over the other could have the potential to bias clinical outcomes, as well as adverse events (AEs).

6.11 Reporting of *BRAF* V600E status with respect to local and central laboratory testing was consistent between the three arms. However, there were differences in patient classification between the local and central tests. A higher proportion of mutations was detected centrally compared to locally (95.1% vs 75.4% encorafenib + binimetinib + cetuximab arm, 91.4% vs 75.5% encorafenib + cetuximab and 91.0% vs 78.3% control, respectively). For *K/RAS* testing, the same inconsistency was also evident between local (*RAS* testing) and central laboratory (*KRAS* testing) results, where a higher proportion of *RAS* WT (or no *KRAS* mutation) was detected when centrally assessed compared to locally assessed (94.6% vs 67.9% encorafenib + binimetinib + cetuximab arm, 91.4% vs 66.8% encorafenib + cetuximab arm, and 90.5% vs 71.9% control arm, respectively). The main reason for the variation between the local and central results was due to *RAS* status not being available to be assessed locally for some patients (33.2% encorafenib + cetuximab and 27.1% in the control arm). This was despite the inclusion criteria of BEACON specifying that patients needed to be eligible to receive cetuximab per locally approved label with regard to tumour *RAS* status.

Comparative effectiveness

6.12 The primary endpoint for BEACON was overall survival (OS) in the encorafenib + binimetinib + cetuximab arm compared with the control arm. The outcomes that were relevant to the submission included those that compared the efficacy and safety of encorafenib + cetuximab to the control arm. The sample size for BEACON was driven by the key secondary endpoint of OS for the encorafenib + cetuximab arm vs control arm.

6.13 The submission did not present a non-inferiority margin. However, it compared the gain in median OS for encorafenib + cetuximab vs control to the American Society of Clinical Oncology (ASCO) committee definition for clinically meaningful goals for CRC clinical trials; a stipulated improvement over current OS of 3-5 months with a target

HR = 0.67. BEACON was powered at a HR threshold greater than the recommended ASCO definition of clinical meaningfulness in CRC trials.

- 6.14 A gatekeeper hierarchical procedure was used in BEACON to control the Type I error rates in the sequential order of primary, key secondary and secondary outcomes. The effectiveness outcomes are presented as per their order in the statistical hierarchy established within BEACON. Effectiveness outcomes for the triplet therapy arm are not presented here, as the submission did not seek listing of encorafenib in combination with cetuximab and binimetinib. The applicant did not seek TGA registration for the triplet therapy. In the EMA Assessment Report, it was noted that the doublet and triplet regimens do not differ from an efficacy perspective, and that the sponsor withdrew the binimetinib part of the application for Balance/Risk reasons, applying only for doublet therapy.

OS

- 6.15 A summary of the OS results for BEACON at the three analysis time points is presented in Table 5.

Table 5: Results of overall survival in BEACON (FAS)

OS	11 Feb 2019		15 Aug 2019		5 May 2020	
	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)
Death events – n (%)	93 (42.3)	114 (51.6)	128 (58.2)	157 (71.0)	█ ⁵	█ ⁵
Median (95% CI), months	8.41 (7.46, 11.04)	5.42 (4.76, 6.57)	9.30 (8.05, 11.30)	5.88 (5.09, 7.10)	█ ⁵	█ ⁵
Difference in median OS, months ^b	2.99		3.42		█ ⁵	
Stratified HR (95% CI) ^c	0.60 (0.45, 0.79)		0.61 (0.48, 0.77)		█ ⁵	
Stratified p-value ^c	0.0002		<0.0001		█ ⁵	

Notes: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

^b calculated during the evaluation

^c Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomisation.

Abbreviations: CI = confidence interval; CETUX = cetuximab; ECOG PS = European Organization for Research and Treatment of Cancer; ENCO = encorafenib; FAS = full analysis set; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; OS = overall survival

Source: Table 2-80 p169 of the submission

⁵ OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

- 6.16 At the *post hoc* survival analysis (data cut 5 May 2020), █⁵% of patients in the encorafenib + cetuximab arm and █⁵% of the patients in the control arm had died. The median OS was longer in the encorafenib + cetuximab arm compared to the control (█⁵ vs █⁵ months; HR = █⁵, 95% CI: █⁵, █⁵). These results were consistent with the two prior OS assessments. The OS results at all three data cuts were statistically significantly different in favour of encorafenib + cetuximab. Furthermore, results from 15 August 2019 and 5 May 2020 also met the ASCO criteria for clinically meaningful goals for CRC defined as improvement of 3-5 months over

⁵ OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

current OS with target HR = 0.67. The ESCs considered that the magnitude of overall survival gain in these patients was modest.

- 6.17 The ESCs considered the efficacy of encorafenib + cetuximab versus FOLFIRI + cetuximab reported in the BEACON trial may be a reasonable estimate of the efficacy of encorafenib + cetuximab versus FOLFIRI alone in the Australian setting, given that the addition of cetuximab to the control arm is unlikely to have added significant benefit^{6,7}.
- 6.18 The Kaplan-Meier (KM) estimates for OS from BEACON at the 5 May 2020 analysis of the FAS are presented in Figure 2. The KM plots show a very early (before 2 months) and consistent separation of the two curves for all three data cut-offs.

Figure 2: Kaplan-Meier analysis of OS for BEACON (FAS; 5 May 2020)*



Abbreviations: CETUX = cetuximab; CI = confidence interval; CONTROL = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab; ENCO = encorafenib; FAS = full analysis set; HR = hazard ratio; OS = overall survival; Ref = reference

Source: Figure 2-9 p172 of the submission

*OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

- 6.19 As of the 15 August 2019 data cut-off, 45.0% of patients on encorafenib + cetuximab and 47.1% of the control arm had subsequent systemic therapy. Although the choice of drugs was similar in both arms (with the exception of oxaliplatin and cetuximab), there were some variations in the incidence of their usage. In the

⁶ Di Nicolantonio F et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; 26(35):5705-12. Available at <https://pubmed.ncbi.nlm.nih.gov/19001320/>.

⁷ Pietrantonio, F et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 2015, 51(5):587-94. Available at <https://pubmed.ncbi.nlm.nih.gov/25673558/>.

encorafenib + cetuximab arm, subsequent systemic therapy used at high incidence (>10%) included: irinotecan (26.8%), 5FU (25.9%), FA (16.4%) and bevacizumab (12.7%), whilst in the control arm these included: 5FU (19.9%), irinotecan (16.3%), cetuximab (14.5%), oxaliplatin (13.1%), FA (10.9%) and bevacizumab (10.9%; p36 BEACON Addendum CSR 15 Aug 2019). 0.5% of patients on encorafenib + cetuximab and 8.1% of patients in the control arm received a BRAF inhibitor in combination with a MEK inhibitor and EGFR inhibitor. Slight variations in the choice of subsequent therapy between the two arms of BEACON and the incidence of patients in the control arm receiving therapy similar to the triplet arm of BEACON may influence the resulting OS comparison, biasing results against encorafenib + cetuximab. However, no analysis on the effects of subsequent therapy on OS was presented.

Overall response rate (ORR) by blinded independent central review (BICR)

6.20 A summary of the ORR by BICR for BEACON is presented in Table 6.

Table 6: Results of overall response in BEACON

ORR	11 Feb 2019 ^e		15 Aug 2019 ^e				
	ENCO + CETUX (N = 113)	CONTROL ^a (N = 107)	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)	RR (95% CI) ^f	RD (95%CI) ^f	OR (95%CI) ^f
BOR – n (%) ^b							
CR	6 (5.3)	0 (0.0)	7 (3.2)	0 (0.0)	NE	0.03 (0.01, 0.06)	NE
PR	17 (15.0)	2 (1.9)	36 (16.4)	4 (1.8)	9.04 (3.27, 24.97)	0.15 (0.09, 0.20)	10.61 (3.71, 30.38)
SD	57 (50.4)	26 (24.3)	117 (53.2)	59 (26.7)	1.99 (1.55, 2.56)	0.26 (0.18, 0.35)	3.12 (2.09, 4.65)
PD	8 (7.1)	36 (33.6)	21 (9.5)	82 (37.1)	0.26 (0.17, 0.40)	-0.28 (-0.35, -0.20)	0.18 (0.11, 0.30)
Non-CR/Non-PD ^c	4 (3.5)	5 (4.7)	7 (3.2)	6 (2.7)	1.17 (0.40, 3.43)	0.00 (-0.03, 0.04)	1.18 (0.39, 3.56)
Not evaluable	21 (18.6)	38 (35.5)	32 (14.5)	70 (31.7)	0.46 (0.32, 0.67)	-0.17 (-0.25, -0.09)	0.37 (0.23, 0.59)
Confirmed ORR (CR + PR)							
n (%)	23 (20.4)	2 (1.9)	43 (19.5)	4 (1.8)	10.80 (3.94, 29.57)	0.18 (0.12, 0.23)	13.18 (4.64, 37.42)
95% CI ^d	(13.4, 29.0)	(0.2, 6.6)	(14.5, 25.4)	(0.5, 4.6)			
p-value	p < 0.0001		p < 0.0001		NA		
Confirmed disease control rate (CR + PR + SD + Non-CR/Non-PD)							
n (%)	84 (74.3)	33 (30.8)	167 (75.9)	69 (31.2)	2.43 (1.97, 3.00)	0.45 (0.36, 0.53)	6.94 (4.56, 10.56)
95% CI ^d	(65.3, 82.1)	(22.3, 40.5)	(69.7, 81.4)	(25.2, 37.8)			

Notes: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab.

^b CR and PR were confirmed by repeat assessments performed not less than 4 weeks after criteria for response were met.

^c Patients with only non-measurable disease, whose best non-target lesion response was Non-CR/non-PD and did not have any new lesions.

^d The CIs for the frequency distribution of each variable were computed using Clopper-Pearson's method.

^e The 11 Feb 2019 ORR was measured in the Response Efficacy Set (first 331 patients randomised into the Phase 3 portion). At the 15 August 2019 data cut the response evaluations were conducted in the FAS.

^f RR, RD and OR were calculated during the evaluation

Abbreviation: BOR = best overall response; CETUX = cetuximab; CI = confidence interval; CR = complete response; ENCO = encorafenib; FAS = full analysis set; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NA = not applicable; NE = not estimable; OR = odds ratio; ORR = overall response rate; PD = progressive disease; PR = partial response; RD = risk difference; RR = relative risk; SD = stable disease.

Source: Table 2-83, 2-84 pp175, 177 of the submission; p211 BEACON CSR (11 Feb 2019); p37 BEACON Addendum CSR (15 Aug 2019)

Bold text indicates a statistically significant difference.

6.21 The confirmed ORR rate was statistically significantly higher for the encorafenib + cetuximab arm compared to the control arm (19.5% vs 1.8%). Confirmed CRs were observed in patients on encorafenib + cetuximab at both data cut-offs (6 patients and 7 patients respectively) and no patients in the control arm achieved a CR at either data cut-off.

Progression-free survival (PFS) by BICR

6.22 A summary of the PFS outcomes based on BICR for BEACON is presented in Table 7.

Table 7: Results of progression-free survival in BEACON (FAS)

PFS	11 Feb 2019		15 Aug 2019	
	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)	ENCO + CETUX (N = 220)	CONTROL ^a (N = 221)
Events – n (%)	133 (60.5)	128 (57.9)	167 (75.9)	147 (66.5)
Median (95% CI), months	4.21 (3.71, 5.36)	1.51 (1.45, 1.71)	4.27 (4.07, 5.45)	1.54 (1.48, 1.91)
Difference in median PFS, months ^b	2.70		2.73	
Stratified HR (95% CI) ^c	0.40 (0.31, 0.52)		0.44 (0.35, 0.55)	
Stratified p-value ^c	< 0.0001		<0.0001	

Notes: ^a Control arm = investigator’s choice of irinotecan + cetuximab or FOLFIRI + cetuximab

^b calculated during the evaluation

^c Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomisation.

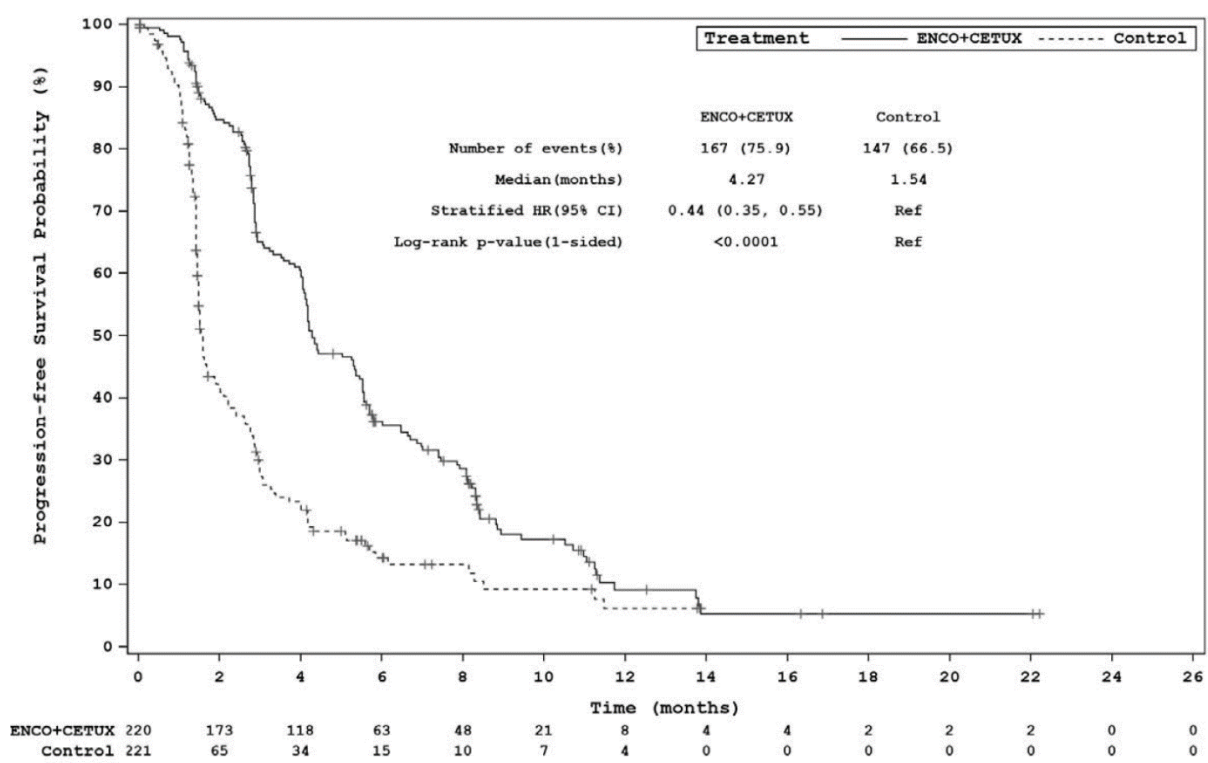
Abbreviations: CI = confidence interval; CETUX = cetuximab; ENCO = encorafenib; FAS = full analysis set; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; PFS = progression-free survival

Source: Table 2-89, p183 of the submission

6.23 The PFS results at both data cuts were similar and statistically significantly different in favour of encorafenib + cetuximab.

6.24 The KM plots for PFS in BEACON at the 15 August 2019 analysis of the FAS are presented in Figure 3. The KM plots show a very early (before 2 months) separation in favour of encorafenib + cetuximab, before the two curves start to converge from approximately 6 months.

Figure 3: Kaplan-Meier analysis of PFS for BEACON (FAS; 15 August 2019)



Abbreviations: CETUX = cetuximab; CI = confidence interval; CONTROL = investigator’s choice of irinotecan + cetuximab or FOLFIRI + cetuximab; ENCO = encorafenib; FAS = full analysis set; HR = hazard ratio; PFS = progression-free survival; Ref = reference
 Source: Figure 2-13, p185 of the submission

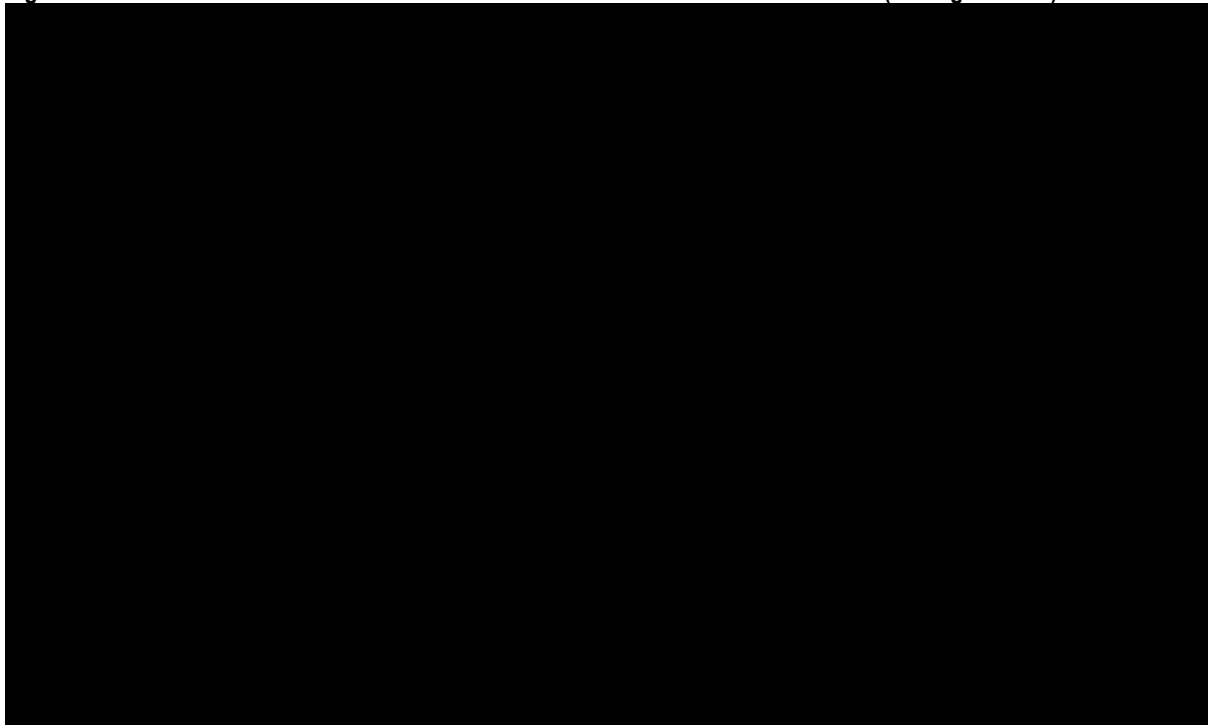
Quality of life (QoL)

EORTC QLQ-C30

6.25 The estimated median time to definitive 10% deterioration in the global health state score (Figure 4) was [redacted]⁸ months longer in the encorafenib + cetuximab arm compared to the control arm ([redacted]⁸ months and [redacted]⁸ months respectively; HR = [redacted]⁸). Similar median time to definitive 10% deterioration results were seen in the emotional functioning score ([redacted]⁸ vs [redacted]⁸ months, HR = [redacted]⁸), physical functioning score ([redacted]⁸ vs [redacted]⁸ months, HR = [redacted]⁸) and the social functioning score ([redacted]⁸ vs [redacted]⁸ months, HR = [redacted]⁸). The submission did not present the total health state scores for the EORTC QLQ-C30. Compliance for the EORTC QLQ-C30 assessment was also not provided by the submission.

⁸ QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

Figure 4: EORTC QLQ-C30 Global Health Status: time to definitive 10% deterioration (15 August 2019)*



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CONTROL = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab; ENCO = encorafenib; EORTC-QLQ = European Organization for Research and Treatment of Cancer quality of life questionnaire; HR = hazard ratio; Ref = reference

Source: Figure 2-14, p188 of the submission

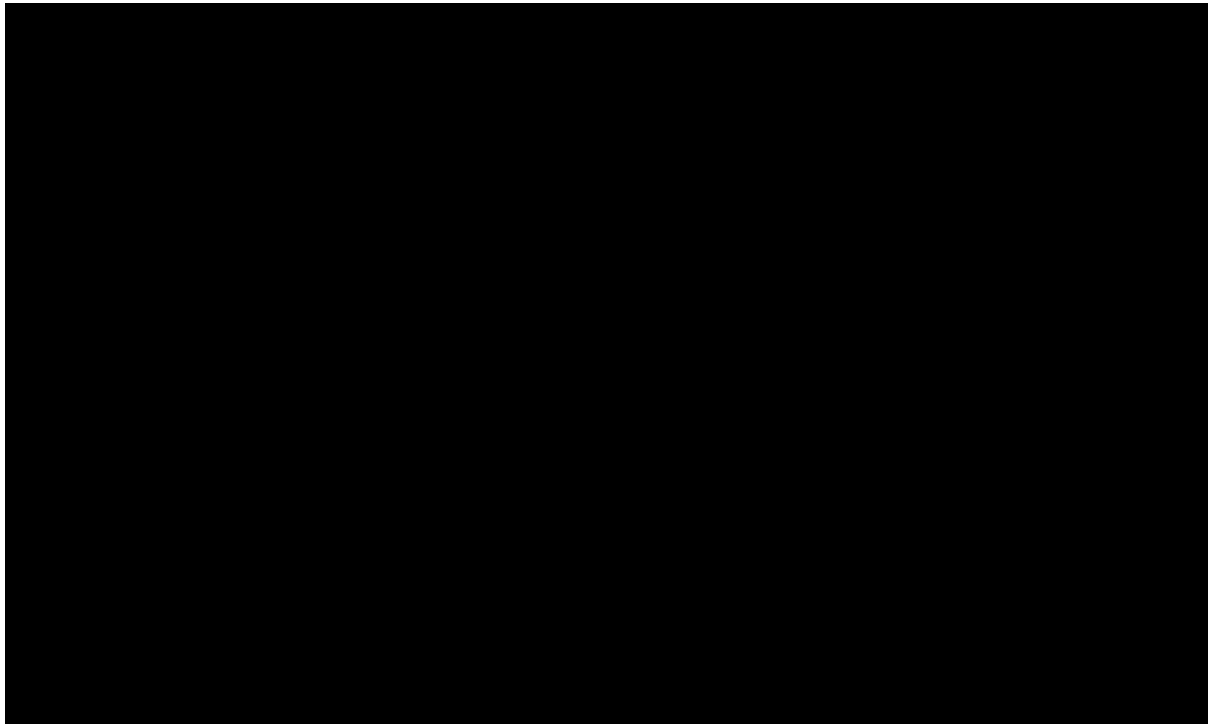
*QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

FACT-C

6.26 The estimated median time to definitive 10% deterioration in the CRC subscale score (Figure 5) was 4.10 months longer in the encorafenib + cetuximab arm compared to the control arm (■■■■⁹ months and ■■■■⁹ months respectively; HR = ■■■■⁹). Similar median time to definitive 10% deterioration results were seen in the functional well-being subscale score (■■■■⁹ vs ■■■■⁹ months, HR = ■■■■⁹), emotional well-being subscale score (■■■■⁹ months vs ■■■■⁹ months, HR = ■■■■⁹), physical well-being subscale score (■■■■⁹ months vs ■■■■⁹ months, HR = ■■■■⁹), and the social well-being subscale score (■■■■⁹ months vs ■■■■⁹ months, HR = ■■■■⁹). As was noted with the EORTC QLQ-C30 assessment, compliance with the FACT-C assessment was not provided by the submission.

⁹ QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

Figure 5: FACT-C CRC subscale score: time to definitive 10% deterioration (15 August 2019)*



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CONTROL = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab; CRC = colorectal cancer; ENCO = encorafenib; FACT-C = Functional Assessment of Cancer Therapy - Colon Cancer; HR = hazard ratio; Ref = reference

Source: August 2019 Supplementary Tables, file name 'FACTC_CCS_fas_15AUG2019_03FEB2020'

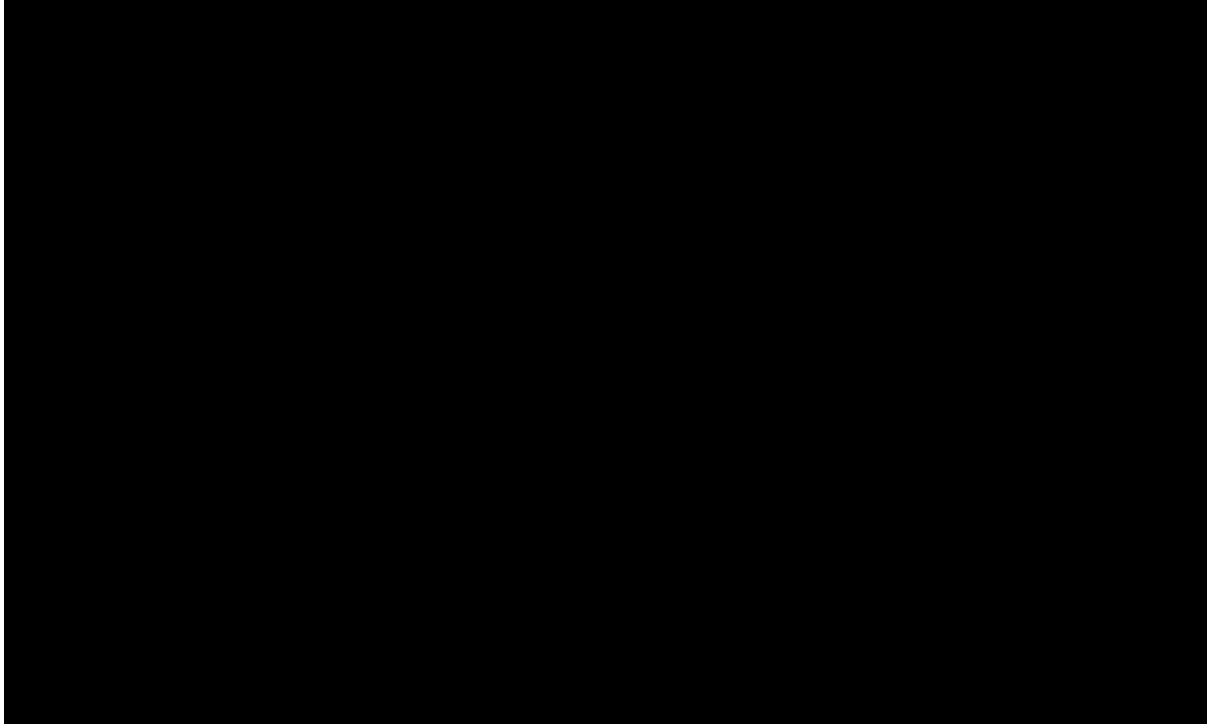
* QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

EQ-5D-5L

6.27 The estimated median time to definitive 10% deterioration in the visual analogue score (Figure 6) was █████¹⁰ months longer in the encorafenib + cetuximab arm compared to the control arm (█████¹⁰ months and █████¹⁰ months respectively; HR = █████¹⁰). Compliance with the EQ-5D-5L assessment was not provided by the submission. The submission reported the utility values arising within BEACON as part of the economic evaluation. In summary, the utility values for encorafenib + cetuximab were █████¹⁰ for patients pre-progression and █████¹⁰ post-progression; and for the control arm █████¹⁰ pre-progression and █████¹⁰ post progression. While BEACON applied the EQ-5D-5L, the resulting utility values were derived using the UK tariffs for the EQ-5D-3L and applying the crosswalk algorithm to the trial observed health related QoL ratings. This approach is addressed further in paragraph 6.52).

¹⁰ QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

Figure 6: EQ-5D-5L VAS: time to definitive 10% deterioration (15 August 2019)*



Abbreviations: BINI = binimetinib; CETUX = cetuximab; CI = confidence interval; CONTROL = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab; CRC = colorectal cancer; ENCO = encorafenib; EQ-5D-5L = EuroQol-5D-5L; HR = hazard ratio; Ref = reference; VAS = visual Analog Score

Source: Figure 2-16, p190 of the submission

* QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

Comparative harms

6.28 An analysis of safety was presented using results from the 15 August 2019 data cut-off. An overview of the adverse events (AEs) is presented in Table 8.

Table 8: Summary of adverse events in BEACON (Safety Population)

n (%)	ENCO + CETUX (N = 216)	CONTROL ^a (N = 193)	RR (95% CI) ^b	RD (95% CI) ^b
On-treatment deaths ^c	38 (17.6)	29 (15.0)	1.17 (0.75, 1.82)	0.03 (-0.05, 0.10)
On-treatment AEs leading to death	8 (3.7)	8 (4.1)	0.89 (0.34, 2.33)	0.00 (-0.04, 0.03)
Any AEs	212 (98.1)	190 (98.4)	1.00 (0.97, 1.02)	0.00 (-0.03, 0.02)
Grade ≥3 AE	124 (57.4)	124 (64.2)	0.89 (0.76, 1.04)	-0.07 (-0.16, 0.03)
Treatment related AEs	196 (90.7)	178 (92.2)	0.98 (0.93, 1.04)	-0.01 (-0.07, 0.04)
Grade ≥3 treatment related AE	46 (21.3)	82 (42.5)	0.50 (0.37, 0.68)	-0.21 (-0.30, -0.12)
Any SAEs	86 (39.8)	77 (39.9)	1.00 (0.79, 1.27)	0.00 (-0.10, 0.09)
Grade ≥3 SAE	74 (34.4)	67 (34.7)	0.99 (0.76, 1.29)	0.00 (-0.10, 0.09)
Treatment related SAE	21 (9.7)	25 (13.0)	0.75 (0.43, 1.30)	-0.03 (-0.09, 0.03)
Grade ≥3 treatment related SAE	13 (6.0)	22 (11.4)	0.53 (0.27, 1.02)	-0.05 (-0.11, 0.00)
AEs requiring additional therapy	205 (94.9)	182 (94.3)	1.01 (0.96, 1.05)	0.01 (-0.04, 0.05)
Grade ≥3 requiring additional therapy	107 (49.5)	100 (51.8)	0.96 (0.79, 1.16)	-0.02 (-0.12, 0.07)
AEs requiring dose interruption ^d	110 (50.9)	107 (55.4)	0.92 (0.77, 1.10)	-0.05 (-0.14, 0.05)
Grade ≥3 AEs requiring dose interruption ^d	72 (33.3)	72 (37.3)	0.89 (0.69, 1.16)	-0.04 (-0.13, 0.05)
AEs requiring dose reduction ^d	26 (12.0)	61 (31.6)	0.38 (0.25, 0.58)	-0.20 (-0.27, -0.12)
Grade ≥3 AEs requiring dose reduction ^d	8 (3.7)	32 (16.6)	0.22 (0.11, 0.47)	-0.13 (-0.19, -0.07)
AEs leading to discontinuation ^d	26 (12.0)	33 (17.1)	0.70 (0.44, 1.13)	-0.05 (-0.12, 0.02)
Grade ≥3 AEs leading to discontinuation ^d	24 (11.1)	24 (12.4)	0.89 (0.53, 1.52)	-0.01 (-0.08, 0.05)
AEs leading to discontinuation of all treatment	20 (9.3)	21 (10.9)	0.85 (0.48, 1.52)	-0.02 (-0.07, 0.04)
Grade ≥3 AEs leading to discontinuation of all treatment	19 (8.8)	17 (8.8)	1.00 (0.53, 1.87)	0.00 (-0.06, 0.05)

Notes: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

^b RD and RR was calculated during the evaluation

^c deaths occurring during treatment or within 30 days of the last dose due to AEs or disease progression

^d any study drug

Abbreviations: AE = adverse event; CI = confidence interval; CETUX = cetuximab; ENCO = encorafenib; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious adverse event

Source: Table 2-93 pp193-194 of the submission

Bold text indicates a statistically significant difference.

6.29 A similar proportion of patients on encorafenib + cetuximab compared with control arm in BEACON experienced AEs (98.1% vs 98.4%, respectively), but fewer Grade ≥3 AEs (57.4% vs 64.2%). Fewer patients on encorafenib + cetuximab experienced treatment-related AEs (TRAEs) and even fewer Grade ≥3 TRAEs. The difference in Grade ≥3 TRAEs was statistically significant. The incidence of serious AEs (SAEs) and Grade ≥3 SAEs was similar between the encorafenib + cetuximab and control arms. However, there were fewer treatment-related SAEs and Grade ≥3 treatment-related SAEs in the encorafenib + cetuximab arm compared to the control arm.

6.30 Eight patients in both arms experienced AEs resulting in on-treatment deaths. In the encorafenib + cetuximab arm, the causes of death included intestinal obstruction (2 patients) and aspiration (2 patients), large intestine perforation, cardio-respiratory arrest, gastrointestinal haemorrhage, and sepsis. In the control arm, the causes of death included anaphylactic reaction, cardio-respiratory arrest, cerebral ischemia, lung infection, peritonitis, pneumocystis jirovecii pneumonia, respiratory failure and subileus.

6.31 AEs of all Grades and Grade ≥ 3 that were statistically significantly different are presented Table 9. The time to onset of the first Grade ≥ 3 AE was 4.73 months (95% CI: 3.94, 6.44) in the encorafenib + cetuximab arm and 1.41 months (95% CI: 1.08, 2.07) in the control arm. No Grade ≥ 3 AEs were statistically significantly higher in the encorafenib + cetuximab arm compared to the control arm.

Table 9: Summary of AEs occurring in $\geq 10\%$ of patients or Grade ≥ 3 AEs ($\geq 5\%$ in any treatment arm) of BEACON that were statistically significant (Safety Population)

n (%)	ENCO + CETUX (N = 216)		CONTROL ^a (N = 193)		All Grades		Grade ≥ 3	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	RR (95% CI) ^b	RD (95% CI) ^b	RR (95% CI) ^b	RD (95% CI) ^b
Any AE	212 (98.1)	124 (57.4)	190 (98.4)	124 (64.2)	1.00 (0.97, 1.02)	0.00 (-0.03, 0.02)	0.89 (0.76, 1.04)	-0.07 (-0.16, 0.03)
Diarrhoea	83 (38.4)	6 (2.8)	94 (48.7)	20 (10.4)	0.79 (0.63, 0.99)	-0.10 (-0.20, -0.01)	0.27 (0.11, 0.65)	-0.08 (-0.12, -0.03)
Dermatitis acneiform	65 (30.1)	1 (0.5)	77 (39.9)	5 (2.6)	0.75 (0.58, 0.99)	-0.10 (-0.19, -0.01)	0.18 (0.02, 1.52)	-0.02 (-0.05, 0.00)
Arthralgia	49 (22.7)	3 (1.4)	3 (1.6)	0 (0)	14.59 (4.62, 46.07)	0.21 (0.15, 0.27)	NE	0.01 (0.00, 0.03)
Headache	43 (19.9)	0 (0)	5 (2.6)	0 (0)	7.68 (3.11, 19.00)	0.17 (0.12, 0.23)	NE	0.00 (0.00, 0.00)
Myalgia	33 (15.3)	1 (0.5)	4 (2.1)	0 (0)	7.37 (2.66, 20.43)	0.13 (0.08, 0.18)	NE	0.00 (0.00, 0.01)
Musculoskeletal pain	29 (13.4)	0 (0)	5 (2.6)	0 (0)	5.18 (2.05, 13.12)	0.11 (0.06, 0.16)	NE	0.00 (0.00, 0.00)
Pain in extremity	25 (11.6)	0 (0)	2 (1.0)	0 (0)	11.17 (2.68, 46.54)	0.11 (0.06, 0.15)	NE	0.00 (0.00, 0.00)
Pruritus	24 (11.1)	0 (0)	10 (5.2)	0 (0)	2.14 (1.05, 4.37)	0.06 (0.01, 0.11)	NE	0.00 (0.00, 0.00)
Stomatitis ^c	13 (6.0)	0 (0)	45 (23.3)	4 (2.1)	0.26 (0.14, 0.46)	-0.17 (-0.24, -0.11)	NE	-0.02 (-0.04, 0.00)
Hypokalaemia	13 (6.0)	2 (0.9)	27 (14.0)	6 (3.1)	0.43 (0.23, 0.81)	-0.08 (-0.14, -0.02)	0.30 (0.06, 1.46)	-0.02 (-0.05, 0.01)
Alopecia	9 (4.2)	0 (0)	21 (10.9)	0 (0)	0.38 (0.18, 0.82)	-0.07 (-0.12, -0.02)	NE	0.00 (0.00, 0.00)
Neutropenia	3 (1.4)	2 (0.9)	36 (18.7)	20 (10.4)	0.07 (0.02, 0.24)	-0.17 (-0.23, -0.12)	0.09 (0.02, 0.38)	-0.09 (-0.14, -0.05)
Neutrophil count decreased	1 (0.5)	1 (0.5)	21 (10.9)	16 (8.3)	0.04 (0.01, 0.31)	-0.10 (-0.15, -0.06)	0.06 (0.01, 0.42)	-0.08 (-0.12, -0.04)

Notes: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

^b RD and RR was calculated during the evaluation

^c added during evaluation

Abbreviations: AE = adverse event; CI = confidence interval; CETUX = cetuximab; ENCO = encorafenib; n = number of participants reporting data; N = total participants in group; NE = not estimable; RD = risk difference; RR = relative risk

Source: Table 2-94 pp195 of the submission

Bold text indicates a statistically significant difference.

6.32 The ESCs considered that, in view of the expected additional toxicity (e.g. rash) of adding cetuximab to FOLFIRI for BRAF positive patients, the comparative results of the BEACON trial may underestimate the toxicity of encorafenib + cetuximab over FOLFIRI alone.

Benefits and harms

6.33 A summary of the comparative benefits and harms for encorafenib + cetuximab versus FOLFIRI/Ir + cetuximab based on BEACON is presented in Table 10.

Table 10: Summary of comparative benefits and harms for encorafenib + cetuximab and FOLFIRI/Ir + cetuximab (control)

Benefits						
Overall survival (median duration of follow-up not defined within the submission; data cut 05 May 2020)						
Event	ENCO + CETUX n/N (%)	Control ^a n/N (%)	Absolute difference	HR (95% CI)		
Death events – n (%)	██████████ ^a	██████████ ^a			██████████	
Median OS, months (95% CI)	██████ ^{c, a}	██████ ^{c, a}	██████ ^a		██████ ^b	
% Survival estimates at 6 months (95% CI)	██████████ ^a	██████████ ^a	██████ ^a			
% Survival estimates at 18 months (95% CI)	██████████ ^a	██████████ ^a	██████ ^a			
% Survival estimates at 34 months (95% CI)	██████████ ^a	██████████ ^a	██████ ^a			
Progression-free survival (median duration of follow-up 14.7 months; data cut 15 Aug 2019)^d						
Progressed – n (%)	167/220 (75.9)	147/221 (66.5)			0.44 (0.35, 0.55)	
Median PFS, months (95% CI)	4.27 (4.07, 5.45)	1.54 (1.48, 1.91)	2.73		<0.0001 ^b	
% Progression-free estimates at 6 months	36.2 (29.5, 42.9)	14.3 (9.1, 20.6)	21.9			
% Progression-free estimates at 14 months	5.3 (1.9, 11.1)	NR (NR, NR)	NE			
Harms (median duration of follow-up 14.7 months; data cut 15 Aug 2019)^d						
Potentially clinically relevant AEs (all Grades) n	ENCO + CETUX (N = 216)	Control ^a (N = 193)	Event rate / 100 patients		RR (95% CI) ^f	RD (95% CI) ^f
			ENCO + CETUX	Control ^a		
Arthralgia	49	3	22.7	1.6	0.21 (0.15, 0.27)	14.59 (4.62, 46.07)
Headache	43	5	19.9	2.6	0.17 (0.12, 0.23)	7.68 (3.11, 19.00)
Myalgia	33	4	15.3	2.1	0.13 (0.08, 0.18)	7.37 (2.66, 20.43)
Musculoskeletal pain	29	5	13.4	2.6	0.11 (0.06, 0.16)	5.18 (2.05, 13.12)
Pain in extremity	25	2	11.6	1.0	0.11 (0.06, 0.15)	11.17 (2.68, 46.54)
Pruritus	24	10	11.1	5.2	0.06 (0.01, 0.11)	2.14 (1.05, 4.37)
Stomatitis ^e	13	45	6.0	23.3	-0.17 (-0.24, -0.11)	0.26 (0.14, 0.46)
Neutropenia	3	36	1.4	18.7	-0.17 (-0.23, -0.12)	0.07 (0.02, 0.24)
Diarrhoea	83	94	38.4	48.7	-0.10 (-0.20, -0.01)	0.79 (0.63, 0.99)
Dermatitis acneiform	65	77	30.1	39.9	-0.10 (-0.19, -0.01)	0.75 (0.58, 0.99)
Neutrophil count decreased	1	21	0.5	10.9	-0.10 (-0.15, -0.06)	0.04 (0.01, 0.31)
Hypokalaemia	13	27	6.0	14.0	-0.08 (-0.14, -0.02)	0.43 (0.23, 0.81)
Alopecia	9	21	4.2	10.9	-0.07 (-0.12, -0.02)	0.38 (0.18, 0.82)

Notes: ^a Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

^b Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomisation

^c 95% CI was not reported

^d Defined as the duration between randomisation and cut-off date in total population (N = 665)

^e added during evaluation

^f RD and RR was calculated during the evaluation

Abbreviations: AE = adverse event; CI = confidence interval; CETUX = cetuximab; ENCO = encorafenib; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable; NR = Not Reported; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = relative risk

Source: Compiled during the evaluation; Table 2-80, 2-89, 2-94 pp169,183,195 of the submission; Table 2 p12 BEACON Addendum CSR (15 Aug 2019)

Bold indicates statistically significant difference

^aOS data cut off May 2020; manuscript in preparation. To be submitted Q3 2021 to BMJ Open

6.34 On the basis of direct evidence presented by the submission from BEACON, for every 100 patients treated with encorafenib + cetuximab in comparison to FOLFIRI/Ir + cetuximab with *BRAF* V600E variant mCRC after at least one prior therapy:

- Approximately 16 additional patients will be alive for 18 months
- Approximately 22 additional patients will be alive without progression for 6 months
- Approximately 21 additional people will experience arthralgia (joint pain)
- Approximately 17 additional people will experience headaches
- Approximately 13 additional people will experience myalgia (muscle pain)
- Approximately 11 additional people will experience musculoskeletal pain (pain of the muscles/joints/bones)
- Approximately 11 additional people will experience pain in the extremities (feet/hands)
- Approximately 6 additional people will experience pruritus (itchy skin)
- Approximately 17 fewer people will experience stomatitis (inflammation of the mucous membrane of the mouth)
- Approximately 17 fewer people will experience neutropenia (low neutrophil levels, which may not result in symptoms)
- Approximately 10 fewer people will experience diarrhoea
- Approximately 10 fewer people will experience dermatitis acneiform (a skin condition that causes acne-like bumps to form)
- Approximately 10 fewer people will experience decreased neutrophil counts (low neutrophil levels, which may not result in symptoms)
- Approximately 8 fewer people will experience hypokalaemia (low potassium levels, which may not result in symptoms)
- Approximately 7 fewer people will experience alopecia (hair loss).

Interpretation of clinical evidence

6.35 On the basis of the evidence from the BEACON trial, the submission claimed encorafenib + cetuximab was superior in terms of effectiveness compared to

FOLFIRI + cetuximab or irinotecan + cetuximab, with a manageable tolerability profile and superior safety compared to FOLFIRI + cetuximab or irinotecan + cetuximab. The therapeutic conclusion presented in the submission was adequately supported by the evidence presented from BEACON, with encorafenib + cetuximab achieving statistically significantly superior outcomes (OS, PFS and ORR) compared with control. This included a difference in median PFS of 2.73 months (data cut 15 August 2019) and OS of █████¹¹months (data cut 5 May 2020) in favour of encorafenib + cetuximab. The outcome for OS was consistent with what ASCO has reported as a clinically meaningful difference (a stipulated improvement over current OS of 3-5 months). The ESCs considered the claim of superior effectiveness of encorafenib + cetuximab compared to FOLFIRI + cetuximab or irinotecan + cetuximab was reasonable, but it considered a claim of noninferior safety of encorafenib + cetuximab compared to FOLFIRI + cetuximab or irinotecan + cetuximab was more appropriate. However, as noted above, the ESCs considered that this comparison did not reflect current clinical practice in Australia (see *Comparator* section). The ESCs considered that encorafenib + cetuximab would have superior effectiveness compared with FOLFIRI alone, and may have a similar magnitude of benefit as when compared with FOLFIRI + cetuximab (see paragraph 6.17).

- 6.36 With respect to safety, the incidence of Grade ≥ 3 TRAEs, any AEs requiring dose reduction and Grade ≥ 3 AEs requiring dose reductions were statistically significantly lower for the encorafenib + cetuximab arm compared to the control. However, the data from BEACON showed that encorafenib + cetuximab was associated with statistically significantly more toxicity events than the control with respect to arthralgia, pain in extremities, headache, myalgia, musculoskeletal pain and pruritus; but fewer events than the control for decreased neutrophil count, neutropenia, stomatitis, alopecia, hypokalaemia, dermatitis acneiform and diarrhoea. The ESCs noted the safety evaluation compared encorafenib + cetuximab against FOLFIRI + cetuximab. The ESCs considered that, in view of the expected additional toxicity (e.g. rash) of adding cetuximab to FOLFIRI for *BRAF* positive patients, the comparative results of the BEACON trial may underestimate the toxicity of encorafenib + cetuximab over FOLFIRI alone.
- 6.37 In terms of patient reported outcomes, the comparison across the two arms showed greater QoL preservation for the encorafenib + cetuximab arm than the control arm. The estimated median time to definitive 10% deterioration was longer with the encorafenib + cetuximab arm compared to the control based on the EORTC QLQ-C30, FACT-C and EQ-5D-5L.
- 6.38 With respect to a main comparison between encorafenib + cetuximab and FOLFIRI with or without cetuximab:

¹¹ OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to *BMJ Open*

- The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.
- The PBAC considered that the claim of superior comparative safety was not adequately supported by the data, and considered that a claim of non-inferior comparative safety was more reasonable.

Claim of co-dependence

6.39 The submission stated that *BRAF* V600E mCRC is a distinct subtype of mCRC that has poor prognosis with no targeted therapies currently available. The submission claimed that this patient group has been treated with the standard of care regimens used for patients with *RAS*-WT mCRC. In Australia, the submission argued that EGFR treatments such as cetuximab are used in the *BRAF* V600E positive population, being indicated within *RAS*-WT. The submission did not present evidence on the treatment effect of encorafenib + cetuximab for patients who were *BRAF* V600E positive versus patients who were not *BRAF* V600E positive. Thus, an estimate of the variation in this treatment effect due to *BRAF* V600E positivity could not be established from the evidence presented and so acceptance of the predictive value of the test essentially relied on a biological plausibility argument supported by some preclinical data.

Economic analysis

6.40 The submission presented a cost-effectiveness analysis comparing encorafenib + cetuximab with FOLFIRI/Ir + cetuximab. The key components of the economic evaluation are summarised in Table 11. The ESCs noted that although the submission requested a listing of encorafenib + EGFR inhibitor, the economic analysis was limited to use of encorafenib + cetuximab only (i.e. not including encorafenib + panitumumab).

6.41 The ESCs also considered that the basis for the economic comparison was inappropriate, given that it considered FOLFIRI alone to be the relevant comparator in the Australian setting. However, the ESCs considered that the model may still be informative as the efficacy of encorafenib + cetuximab versus FOLFIRI + cetuximab reported in the BEACON trial may be a reasonable estimate of the efficacy of encorafenib + cetuximab versus FOLFIRI alone (see paragraph 6.17).

Table 11: Key components of the economic evaluation

Component	Description	Justification/comments
Type of analysis	CUA, CEA	This was appropriate.
Health outcomes	LYG and QALY gained	This was appropriate.
Time horizon	7 years	This was tested in the sensitivity analysis.
Methods used to generate results	Partitioned survival model	This was appropriate.
Health states	Three possible health states: Progression-free disease; Progressed disease; Death	This was appropriate.
Cycle length	One month	This was appropriate as encorafenib + cetuximab and FOLFIRI/Ir + cetuximab are given in 28-day cycles.
Parameters used to model the transition between health states	Disease progression (via progression-free survival) Mortality (via overall survival and all-cause mortality data)	This was appropriate.
Software package	Microsoft® Excel® 365	This was reasonable.

Abbreviations: CEA = cost effectiveness analysis; CUA = cost utility analysis; FOLFIRI/Ir + cetuximab = irinotecan + cetuximab or FOLFIRI + cetuximab; LYG = life years gained; QALY = quality adjusted life years

Source: Table 3-1, p227 of the submission

6.42 The steps taken in the submission’s economic evaluation are summarised in Table 12.

Table 12: Steps in the economic evaluation

Step	Description
Step 1	Incremental cost per progression-free LYG. BEACON based PFS period, no extrapolation beyond disease progression.
Step 2	Incremental cost per LYG. As per step 1, but cost and outcomes extended to include the period following progression and prior to death (i.e. the post-progression period is added to PFS to account for OS).
Step 3 (base case)	Incremental cost per QALY gained. As per step 2, but with the additional application of utility weights to consider the impact of HRQoL on the incremental cost-effectiveness.

Abbreviations: HRQoL = health related quality of life; LYG = life years gained; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years

Source: developed during the evaluation, pp228-229 of the submission

6.43 Costs and utility weights were assigned within each model cycle within the health state to calculate the cumulative costs and QALYs over the model time horizon. Entry into the model was at the point of primary treatment and not at the point of testing. The submission stated that no incremental cost for *BRAF* V600E testing was applied to the economic model as both *RAS* and *BRAF* status are determined using a gene panel test of the same tumour tissue. The intention was to have specific mention of *BRAF* V600E testing in the current MBS item 73338 code for gene testing for mCRC. The submission assumed that the treatment initiation cost would be equal to that of the main comparator, since such testing is required for treatment with cetuximab. This was reasonable.

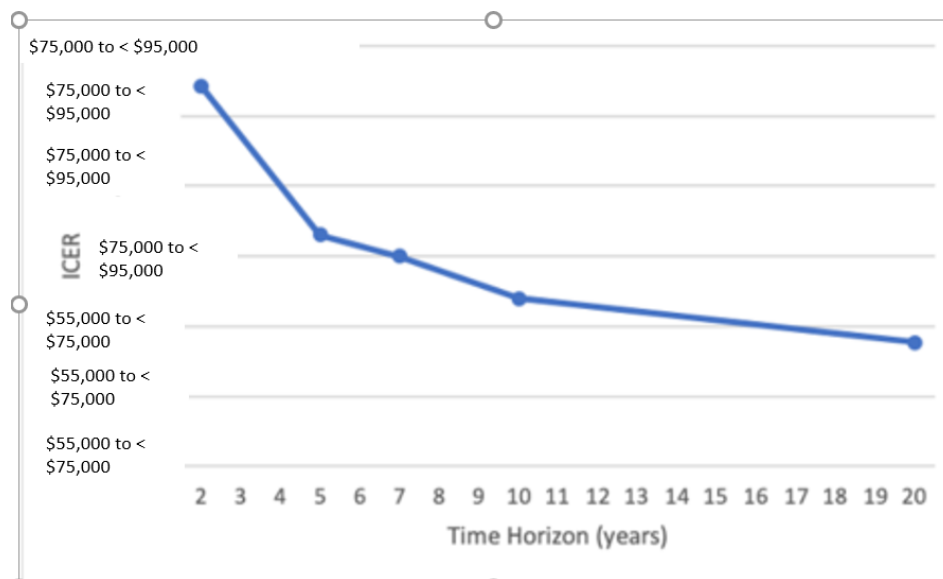
6.44 Time to discontinuation (TTD; defined as the time from first dose to the time of treatment discontinuation) was used to determine the costs associated with the primary treatment. The submission rationalised that the use of TTD allowed a more accurate estimation of the primary treatment costs than PFS because patients on

BEACON were allowed to remain on primary treatment after progression, and that some patients may have discontinued treatment pre-progression due to safety concerns. The requested PBS clinical criteria specify that “patients must have stable or responding disease” in order to continue to receive encorafenib. Thus, reliance on TTD, which includes exposure in patients beyond progression, as the basis to estimate treatment exposure did not reflect the proposed PBS listing. The submission did not present information with respect to the number of patients who remained on primary treatment beyond disease progression and therefore the effects of treatment beyond progression were difficult to interpret. The submission presented the results of a sensitivity analysis where primary treatment costs were based on PFS, which increased the ICER from the base case by 1.9% to \$75,000 to <\$95,000 per QALY. The results of this analysis may better reflect the proposed continuation criteria and the cost-effectiveness of encorafenib + cetuximab in practice. Primary treatment costs based on PFS formed the revised base case for further sensitivity analyses conducted during the evaluation (see Table 15 below).

- 6.45 The PSCR stated that using TTD to calculate the cost of primary treatment was guided by the principle that costs accrued in the model should ideally reflect the trial conditions, and argued that using PFS to calculate the cost of primary treatment should not constitute a revised base case since it introduces a disconnect between costs and outcomes. Whilst acknowledging these arguments, the ESCs considered that using PFS rather than TTD to calculate the cost of primary treatment would be more appropriate as it would reflect the PBS continuation criteria, which limits treatment to patients with at least stable disease, and the consequences of this for varying health outcomes would be comparatively small. Regardless of the outcome chosen to model primary treatment costs, the ESCs noted that the model was more sensitive to using the effective price of cetuximab and removing the assumed 25% price reduction due to generic entry.
- 6.46 The time horizon of the economic evaluation was 7 years in the base case. The KM data was used until the last model cycle prior to the median was reached, after which point the selected distribution was applied to the data to extrapolate until the 7-year time horizon. This method was appropriate. However, the extrapolation of clinical outcomes up to 7 years was based on a relatively short duration of observed data. PFS KM data were observed up to approximately 22 months for encorafenib + cetuximab and 14 months for FOLFIRI/Ir + cetuximab. The submission extrapolated the trial data for the encorafenib + cetuximab arm using log-logistic distribution for PFS and OS, and gamma models for time to treatment discontinuation (treatment continuation in PFS). The impact on the incremental cost-effectiveness ratio (ICER) of varying the time horizon was tested in sensitivity analyses. The results of these analyses are depicted graphically in Figure 7 (using published prices of cetuximab). The PSCR argued a 7-year time horizon was appropriate as it related to the life expectancy of the patient population, and reflected the time span required for nearly all of the model cohort to die (3.2% of the modelled population was alive at 7 years compared to 5% at 5 years,

and 12.5% at 34 months). The ESCs noted the proportion alive is a combination of modelled assumptions around extrapolation and the nominated time horizon, and advised that PBAC’s past considerations in this setting would also be relevant in determining the appropriate time horizon (in the context of second-line cetuximab in March 2009, the PBAC considered that, using a 5-year time horizon, the submission “likely overestimated the overall survival and that the very small number of patients alive by 14 months suggested that there may not be a need to extrapolate the treatment effect beyond the duration of the trial”).

Figure 7: Impact of time horizon on the ICER; \$ per QALY



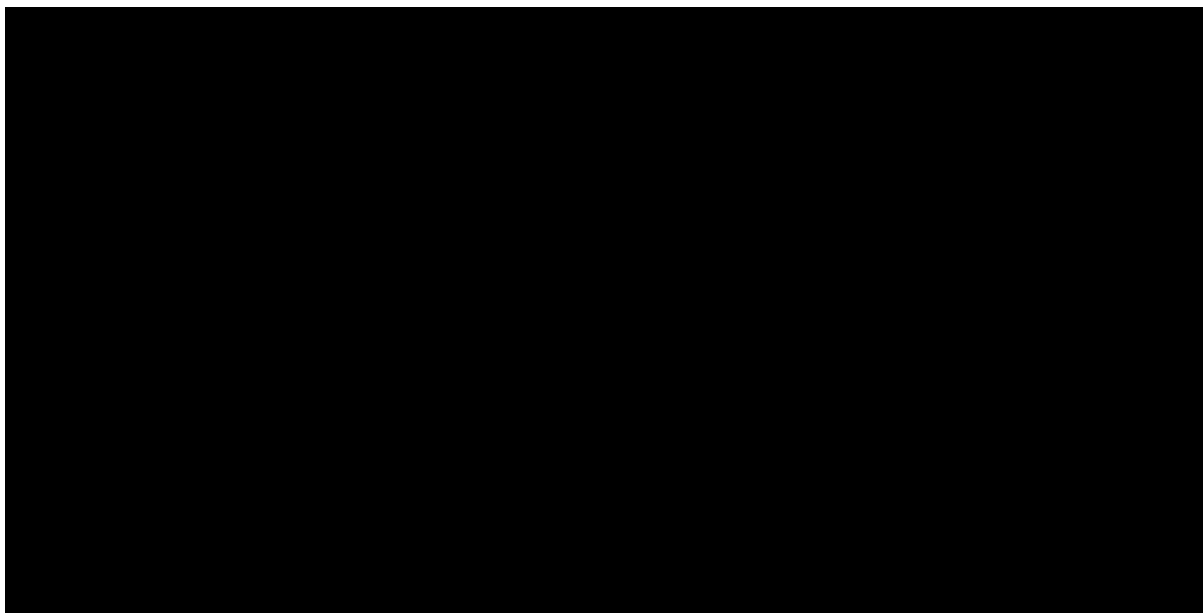
Abbreviations: ICER = incremental cost effectiveness ratio
Source: Developed during the evaluation

- 6.47 The economic model stated that 58.0% of the control arm of BEACON received FOLFIRI + cetuximab; this could not be verified during the evaluation. The BEACON CSR (11 Aug 2019; p305) stated that 107 patients (55.4%) received FOLFIRI + cetuximab. The impact on the ICER of varying the proportion of patients in the control arm who received FOLFIRI + cetuximab was tested in a sensitivity analysis (see Table 15 below).
- 6.48 The results of the traces for the comparative outcomes for PFS and OS, predicted by the model are presented in Figure 8. The submission sourced most of the inputs for the economic model from BEACON, including data for PFS, OS and TTD. The survival curve data applied to the economic evaluation were based on the latest data cut available. This meant that the data were obtained from two different data cuts: 5 May 2020 for OS and 15 August 2019 for PFS and TTD.
- 6.49 Parametric models were used to extrapolate the observed KM data from BEACON. The model was structured such that the KM curves were fitted to the data until the medianth event (PFS, OS and TTD); after the medianth point, the fitted curves were applied for extrapolation. This resulted in extrapolations being applied at different

time points for each outcome as well as between encorafenib + cetuximab and FOLFIRI/Ir + cetuximab. It may have been more appropriate to extrapolate from a single time point (median follow-up) to ensure consistency.

- 6.50 The model was sensitive to the choice of parametric function chosen for extrapolation. Applying the log-logistic distribution to TTD (consistent with the OS and PFS extrapolation) resulted in a 25.9% increase in the ICER (\$75,000 to <\$95,000/QALY gained) compared to the base case. The log-logistic distribution was the third best choice by AIC and the second-best choice by BIC (for both the encorafenib + cetuximab arm and the control arm). The PSCR argued the submission applied a standard approach to selecting the parametric models for extrapolation, which were selected based on AIC and BIC, supplemented by face-validity and plausibility. The ESCs considered that this issue was less relevant if PFS rather than TTD was used to calculate the cost of primary treatment.
- 6.51 Sensitivity analyses were conducted both by the submission and during the evaluation to test the use of alternative parametric distributions (see Table 15).

Figure 8: Trace of comparative outcome of encorafenib + cetuximab and FOLFIRI/Ir + cetuximab from the model^{*,^}



Notes: Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

Source: Developed during the evaluation based on Section 3 Workbook.xlsx

Abbreviations: EncoCetux = encorafenib + cetuximab; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TTD = time to discontinuation

^{*} OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

[^] QoL data cut off August 2019: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

- 6.52 The submission noted that minor differences in utility value were observed between treatment arms, which were not statically significant. The submission applied UK tariffs for the EQ-5D-3L to the economic model stating that Australian-specific utility weights were not available. BEACON applied the EQ-5D-5L, necessitating that a

crosswalk method (as recommended by NICE) be applied in deriving utility values using the algorithm for the 3L instrument. However, given that Australian specific tariffs are available for the 5L version of this instrument, it would have been appropriate that they be applied for this submission.

- 6.53 The model assumed no wastage in the base case analysis. It may have been appropriate for the model to consider the costs associated with wastage since both regimens are administered intravenously. Though the cetuximab doses in both the encorafenib + cetuximab and FOLFIRI/Ir + cetuximab are the same, the mean relative dose intensity (RDI) was different (92.4% encorafenib + cetuximab and 86.9% FOLFIRI/Ir + cetuximab arm; with an anticipated average dose of 413.49 mg and 388.88 mg, respectively). Thus, with weekly administration of cetuximab, there would be greater wastage for the FOLFIRI/Ir + cetuximab arm; the assumption of no wastage thus biases against encorafenib + cetuximab.
- 6.54 BEACON permitted prophylactic concomitant therapy for rash hand foot skin reaction, infection prophylaxis with antibiotics and secondary prophylactic antiemetics once patients experienced nausea and vomiting. Though the submission implied concomitant medications were considered as part of best supportive care (BSC), the cost calculation for BSC was limited to the cost of one medical oncologist consultation per cycle, and thus did not include the utilisation of prophylactic medications.
- 6.55 The economic model incorporated AEs within the model as a one-time cost during the first cycle of treatment. This is likely an underestimation of the costs associated with the management of AEs as it did not account for the potential for multiple occurrences of the same event per patient within the follow-up period and assumed resolution of Grade ≥ 3 AEs within the same model cycle in which they occurred.
- 6.56 The economic model incorporated costs associated with terminal care. The submission utilised the cost of prescription medications based on Reeve et al (2018), allocating the mean cost of medications in the last 6 months of life (\$1,840) to a per month basis (\$306.67). The submission then applied this cost to both arms of the economic evaluation to capture the post-discontinuation treatment cost. In the economic model, the cost of \$306.67 is labelled as subsequent antineoplastic treatment cost (drug cost and administration). However, the nature of the medications required in the final six months of life is likely to be different to those required for subsequent antineoplastic treatment for mCRC and thus the costs associated with these different clinical indications (subsequent antineoplastic therapy versus end-of-life) are unlikely to be substitutable as has been assumed by the submission.
- 6.57 A summary of the key drivers of the model is presented in Table 13.

Table 13: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ [redacted] /QALY gained
Extrapolation	Parametric models for extrapolation were selected based on AIC and BIC, in addition to assessment of face-validity and plausibility.	High, application of log-logistic distribution to TTD (consistent with OS and PFS parametric functions; third best fit) leads to an increase in the ICER to \$ [redacted] ¹ .
Time horizon	7 years	Moderate, favours encorafenib. Extension in the time horizon to 5 years leads to an increase in the ICER to \$ [redacted] ¹ , while restricting to the trial time horizon (34 months) produces an ICER of \$ [redacted] ¹ (with primary treatment costed on PFS).
Patient compliance	Relative dose intensity and ratio of molecule exposure duration/treatment duration were based on BEACON.	Moderate, favours encorafenib. When full patient compliance is assumed, the ICER increases to \$ [redacted] ^{a,1} .

Source: compiled during the evaluation using Section 3 worksheet

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian information criterion; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; TTD = time to discontinuation

^a The results calculated during the evaluation were different to the submission. The submission results were: incremental cost = \$ [redacted], and Incremental cost per QALY = \$ [redacted]¹, change of 8.5% from base case.

The redacted values correspond to the following ranges:

¹\$75,000 to <\$95,000/QALY gained

- 6.58 The results from the economic evaluation are summarised in Table 14. The submission assumed an SPA with an [redacted]% rebate on the published price for cetuximab and a further 25% price reduction based on the expectation that a generic formulation of cetuximab would enter the market prior to encorafenib listing (should the submission be successful). The assumed price reduction due to generic entry was not consistent with the *PBAC Guidelines* and should not be included.
- 6.59 The base case ICER per QALY was estimated at \$75,000 to <\$95,000 (\$75,000 to <\$95,000/QALY gained, based on MBS Item cost updates, July 2020).
- 6.60 The PBAC noted that the submission had applied Australian Refined Diagnosis Related Group (AR-DRG) costs for the administration of cetuximab, where the PBAC's preferred approach is to use the relevant MBS Schedule Fee for administering the medicine or preparation, where available.¹²

¹² *Manual of resource items and their associated unit costs – December 2016*, p10, available at: <https://www.pbs.gov.au/info/industry/useful-resources/manual>

Table 14: Results of the stepped economic evaluation

Step	Parameter	ENCO + CETUX	FOLFIRI/Ir + CETUX	Incremental
1	Total cost	\$ [redacted]	\$17,406	\$ [redacted]
	LYGs without progression	0.56	0.26	0.30
	Incremental cost per progression-free LYG			\$ [redacted] ¹
2	Total cost	\$ [redacted]	\$55,395	\$ [redacted]
	LYGs	1.32	0.87	0.46
	Incremental cost per LYG			\$ [redacted] ²
3	Total cost	\$ [redacted]	\$55,395	\$ [redacted]
	QALYs	0.93	0.60	0.34
	Incremental cost per QALY			\$ [redacted] ¹

Abbreviations: CETUX = cetuximab; ENCO = encorafenib; FOLFIRI/IR + CETUX = irinotecan + cetuximab or FOLFIRI + cetuximab

Source: Table 3-26 p263 of the submission.

The redacted values correspond to the following ranges:

¹\$75,000 to <\$95,000/QALY gained

²\$45,000 to <\$55,000/QALY gained

6.61 The results of the key univariate sensitivity analyses from the submission and prepared by the commentary are summarised in Table 15.

Table 15: Results of sensitivity analyses

Analysis	Incremental cost	Incremental QALY	Incremental cost per QALY	Change in ICER from base case
Base case (as per submission)	\$ [redacted]	0.335	\$ [redacted] ¹	-
Time horizon (base case 7-years)				
10-years	\$ [redacted]	0.3548	\$ [redacted] ²	-4.0%
20-years	\$ [redacted]	0.3769	\$ [redacted] ²	-8.2%
34 months (as per KM post-hoc survival analysis)	\$ [redacted]	0.253	\$ [redacted] ¹	20.1%
TTD extrapolation (base case gamma distribution)				
Log-logistic distribution (consistent with OS and PFS parametric functions)	\$ [redacted]	0.335	\$ [redacted] ¹	25.9%
PFS extrapolation (base case log-logistic distribution)				
Gamma distribution (consistent with TTD parametric function)	\$ [redacted]	0.331	\$ [redacted] ¹	1.4%
OS extrapolation (base case log-logistic distribution)				
FOLFIRI/Ir + Cetux OS curve using generalized gamma distribution (second-best fit according to AIC result)	\$ [redacted]	0.3914	\$ [redacted] ²	-13.1%
Encorafenib + cetuximab OS curve using log-normal distribution (second-best fit according to AIC result)	\$ [redacted]	0.3578	\$ [redacted] ²	-4.9%
Full compliance assumed (RDI and ratio of molecule exposure duration/treatment duration applied in the base case) ^a	\$ [redacted]	0.3350	\$ [redacted] ¹	13.3%
Survival data drawn from August 2019 data cut	\$ [redacted]	0.2809	\$ [redacted] ¹	17.0%
All medical resource utilisation for routine management, management at progression and best supportive care increased by 25% ^{b,c}	\$ [redacted]	0.3350	\$ [redacted] ¹	13.1%
Drug costs				
Decrease in effective price of encorafenib by 10%	\$ [redacted]	0.3350	\$ [redacted] ²	-5.4%
No generic drug entry discount applied to cetuximab	\$ [redacted]	0.3350	\$ [redacted] ¹	4.4%
Revised base case (with primary treatment cost based on PFS)	\$ [redacted]	0.3350	\$ [redacted] ¹	-
Time horizon (base case 7-years)				
34 months (as per n KM post-hoc survival analysis)	\$ [redacted]	0.253	\$ [redacted] ¹	13.9%
5-years	\$ [redacted]	0.310	\$ [redacted] ¹	4.2%
Proportion of patients who received FOLFIRI + cetuximab (base case 58.0%)				
55.4% as per BEACON CSR	\$ [redacted]	0.335	\$ [redacted] ¹	0.1%

Analysis	Incremental cost	Incremental QALY	Incremental cost per QALY	Change in ICER from base case
Treatment compliance (RDI and ratio of molecule exposure duration/treatment duration applied in the base case)				
Negate effects ratio of molecule exposure duration/treatment duration by making this ratio equal one	\$ [REDACTED]	0.335	\$ [REDACTED] ¹	0.5%
Ward nursing cost for encorafenib dispensation (base case \$51.06)				
Assuming no ward nursing cost associate with encorafenib dispensing	\$ [REDACTED]	0.335	\$ [REDACTED] ¹	0.0%
PFS, OS and TTD extrapolation time point (base case extrapolated from median outcome)				
PFS, OS and TTD extrapolated at the point of median follow-up ^d	\$ [REDACTED]	0.332	\$ [REDACTED] ²	-2.1%
5% discordance in test accuracy ^e	\$ [REDACTED]	0.318	\$ [REDACTED] ¹	5.3%

Note: ^a The results calculated during the evaluation were different to the submission. The submission results were: incremental cost = \$ [REDACTED], and Incremental cost per QALY = \$ [REDACTED]¹, change of 8.5% from base case.

^b this is actually a multivariate sensitivity analysis but is included here for simplicity.

^c The results calculated during the evaluation were different to the submission. The submission results were: incremental cost = \$ [REDACTED], and Incremental cost per QALY = \$ [REDACTED]¹, change of 5.6% from base case.

^d The median duration of follow-up was 14.7 months at BEACON data cut-off 15 Aug 2019, duration of median follow-up defined as the duration between randomisation and cut-off date in total population (N = 665). Cut-offs for KM estimates at median follow-up were limited to the time points depicted in the model. Values closest to the median follow-up of 14.7 months were chosen to conduct the sensitivity analysis. Details of the input are presented in Table ATT.17 in Attachment 3 of the Commentary.

^e The sensitivity analysis assumed a discordance of 5% between the test results obtained in practice and the primary clinical evidence; and further assumed that the 5% discordance would result in patients receiving FOLFIRI/Ir + cetuximab.

Abbreviations: CSR = Clinical Study Report; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; RDI = relative dose intensity; PFS = progression-free survival; OS = overall survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Source: Developed during the evaluation

The redacted values correspond to the following ranges:

¹\$75,000 to <\$95,000/QALY gained

²\$55,000 to <\$75,000/QALY gained

6.62 The submission presented a scenario analysis which investigated the structural uncertainty relating to the comparator applied in the economic model, where the FOLFIRI/Ir + cetuximab was replaced with FOLFIRI + bevacizumab. In forming this analysis, the submission used an indirect treatment comparison (naïve comparison) between BEACON and the FIRE-3 trial (FOLFIRI + cetuximab vs FOLFIRI + bevacizumab). The analysis resulted in an incremental cost per QALY of \$55,000 to <\$75,000 (15.1% reduction to the base case ICER; based on the published price of bevacizumab; assuming an SPA with an [REDACTED]% rebate on the published price). However, the FIRE-3 trial population is different to that of BEACON and the requested PBS listing of encorafenib in this submission, as it compared FOLFIRI + cetuximab vs FOLFIRI + bevacizumab as first-line treatment for patients with mCRC. The ESCs considered that the relevance of the scenario was limited given that the utilisation of bevacizumab in the second-line Australian setting is minimal (see Figure 14 of the Commentary; Cetuximab, panitumumab and bevacizumab for mCRC - Drug Utilisation Subcommittee Report 2018).

Drug cost/patient/course: \$ [REDACTED]

6.63 The mean duration on encorafenib + cetuximab treatment for the model was 6.57 months, which resulted in a drug cost/patient/course of \$ [REDACTED] for encorafenib and \$ [REDACTED] for the encorafenib + cetuximab combination (based on the effective

price of encorafenib and the published price for cetuximab). The drug cost per patient for the proposed drug combination and its nominated comparator are summarised in Table 16.

Table 16: Drug cost per patient for encorafenib + cetuximab and FOLFIRI/Ir + cetuximab

	ENCO + CETUX			FOLFIRI/Ir + CETUX ^a		
	Trial dose and duration	CUA ^b	Financial estimates	Trial dose and duration	CUA	Financial estimates
Mean dose intensity	ENCO: 87.6% CET: 86.9%	ENCO: 84.5% CET: 86.0%	ENCO: 100% CET: 100%	CET: 77.3% IRIN: 72.5% 5FU: 67.3% FA: 71.6%	CET: 71.0% IRIN: 69.7% 5FU: 67.3% (bolus) 64.0% (CIV) FA: 67.7%	CET: 100% IRIN: 100% 5FU: 100% FA: 100%
Cost per patient per month ^c	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$4,940 CET: \$4,617 IRIN: \$176 5FU: \$50 (bolus) \$73 (CIV) FA: \$25	Total: \$4,552 CET: \$4,240 IRIN: \$169 5FU: \$50 (bolus) \$69 (CIV) FA: \$24	Total: \$6,432 CET: \$5,972 IRIN: \$243 5FU: \$74 (bolus) \$108 (CIV) FA: \$35
Mean duration	6.30 months ^d	6.57 months ^e	5.75 months ^e	3.00 months ^d	3.02 months ^e	2.68 months ^e
Average cost per patient ^d	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$ ██████ ENCO: \$ ██████ CET: \$ ██████	Total: \$14,820 CET: \$13,850 IRIN: \$528 5FU: \$149 (bolus) \$218 (CIV) FA: \$75	Total: \$13,747 CET: \$12,806 IRIN: \$511 5FU: \$150 (bolus) \$209 (CIV) FA: \$71	Total: \$17,237 CET: \$16,006 IRIN: \$650 5FU: \$197 (bolus) \$289 (CIV) FA: \$93

Note: ^a 55.4% of the cost of 5FU and FA was used to calculate the cost of FOLFIRI/Ir + cetuximab. The BEACON CSR (11 Aug 2019; p305) stated that 107 patients (55.4%) received FOLFIRI and the dose of irinotecan in both regimens was the same (i.e. the difference between the regimens was the addition of 5FU + FA).

^b the economic model also considered the ratio of molecule treatment duration to treatment duration, however these values could not be verified during the evaluation. The values presented in the CUA are calculated based on the mean RDI * by the ratio of molecule treatment duration to treatment duration applied in the submission. Sourced from the Section 4 worksheet

^c The cost of cetuximab was assumed to be 250 mg/m² i.e. the additional 150 mg (to make up the total initial dose of 400 mg/m²) was not considered in the cost calculation.

^d The duration of treatment (exposure) was reported in weeks in the Study report, this was converted to months during the evaluation by dividing the duration in weeks by 4.

^e As per p289 of the submission

Abbreviations: 5FU = 5-fluorouracil; CET = cetuximab; CETUX = cetuximab; CIV = continuous intravenous infusion; CUA = cost utility analysis; ENCO = encorafenib; FA = folinic acid; IRIN = irinotecan

Source: Table 3-16, p 251 of the submission; Table 3,4 p14,15 BEACON Addendum CSR (15 Aug 2019); Section 4 worksheet

Estimated PBS & financial implications

6.64 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the market size and the associated financial impact of listing

encorafenib + cetuximab on the PBS. This approach was consistent with the primary clinical evidence but inconsistent with the requested PBS listing, which was for encorafenib + an EGFR inhibitor (i.e. not including combination use with panitumumab).

- 6.65 The submission assumed that encorafenib + cetuximab would draw █████% of its market share from FOLFIRI/Ir + cetuximab and possibly the remaining █████% from FOLFIRI + bevacizumab. The submission did not provide any justification for the proposed market share, and replacement of FOLFIRI + bevacizumab was not consistent with the comparator section or clinical evidence presented. Furthermore, the utilisation of bevacizumab in the second-line Australian setting is minimal. The ESCs considered this approach did not reflect the appropriate comparator for this intervention.
- 6.66 The sources of data and methods applied by the submission to derive the financial estimates are summaries in Table 17.

Table 17: Data sources used to calculate the financial impact of encorafenib + cetuximab

Data	Value	Source	Comment
Epidemiological data (estimation of eligible population)			
Incident rate	0.08%	AIHW, 2019 (AIHW, 2019). Calculated from the 2019 data using the total adult population and the estimated number of incident colorectal cancer cases, 16,398.	The source was appropriate.
Incidence of colorectal cancer	Yr 1: [REDACTED] ¹ Yr 2: [REDACTED] ¹ Yr 3: [REDACTED] ¹ Yr 4: [REDACTED] ¹ Yr 5: [REDACTED] ¹ Yr 6: [REDACTED] ¹	Calculated as a product of the incident rate and the projected number of adult population for a particular year.	This was appropriate.
Rate of colorectal cases to develop metastatic disease	26.4%	Luo et al, 2017	The source appears to be appropriate.
Incident of mCRC	Yr 1: [REDACTED] ² Yr 2: [REDACTED] ² Yr 3: [REDACTED] ² Yr 4: [REDACTED] ² Yr 5: [REDACTED] ² Yr 6: [REDACTED] ²	Calculated as a product of estimated incident cases of CRC and rate of metastatic disease.	This was appropriate.
Rate of mCRC patients that have a <i>BRAF</i> V600E variant	10%	Tie et al, 2011	The source appears to be appropriate.
Incident patients (i.e. proportion mCRC patients with a <i>BRAF</i> V600E variant)	Yr 1: [REDACTED] ³ Yr 2: [REDACTED] ³ Yr 3: [REDACTED] ³ Yr 4: [REDACTED] ³ Yr 5: [REDACTED] ³ Yr 6: [REDACTED] ³	Calculated as a product of the number of mCRC patients and the rate of mCRC patients that have a <i>BRAF</i> V600E variant.	This was appropriate.
Treatment utilisation			
Uptake rate	70%	Assumption	This appears reasonable, however, the submission did not provide any justification for its assumption.
Estimated number of patients to uptake encorafenib + cetuximab	Yr 1: [REDACTED] ³ Yr 2: [REDACTED] ³ Yr 3: [REDACTED] ³ Yr 4: [REDACTED] ³ Yr 5: [REDACTED] ³ Yr 6: [REDACTED] ³	Calculated as a product of incident mCRC patients with a <i>BRAF</i> V600E variant and uptake rate.	This was appropriate.
Dispensed packs per treatment	5.56	Calculated using the treatment duration (months) in BEACON: 5.75, equivalent to 175 days and the dose per maximum quantity: 31.5 (estimated as maximum quantity units-126/capsules per day-4, assuming use of 75 mg capsule). That is, 175/31.5.	The approach used in estimating the dispensed packs per treatment was conservative and reasonable.

Public Summary Document – March 2021 PBAC Meeting with May 2021 Addendum

Data	Value	Source	Comment
Estimated number of packs dispensed	Yr 1: [REDACTED] Yr 2: [REDACTED] Yr 3: [REDACTED] Yr 4: [REDACTED] Yr 5: [REDACTED] Yr 6: [REDACTED]	Calculated as a product of the number of mCRC patients with a <i>BRAF</i> V600E variant likely to uptake encorafenib + cetuximab and the dispensed packs per treatment.	This was reasonable.
Treatment duration (months)	Encorafenib + cetuximab = 5.75 - Encorafenib = 5.72 - Cetuximab = 5.75 FOLFIRI or irinotecan + cetuximab = 2.68 - Irinotecan = 2.68 - Folinic acid = 2.68 - Fluorouracil bolus = 2.68 - Infusional 5-Fluorouracil = 2.68 - Cetuximab = 2.68 FOLFIRI + bevacizumab = 2.68 - Irinotecan = 2.68 - Folinic acid = 2.68 - Fluorouracil bolus = 2.68 - Infusional 5-Fluorouracil = 2.68 - Bevacizumab = 2.68	Observed BEACON results without extrapolation.	The mean duration of treatment used for the financial estimates was not consistent with the mean duration of treatment in the economic model; 5.75 vs 6.57 months in the encorafenib + cetuximab arm and 2.68 vs 3.02 months in the comparator arm for FOLFIRI/Ir + cetuximab and 2.68 vs 3.32 months for FOLFIRI + bevacizumab. Assuming the treatment duration of 6.57 resulted in an 18% increase in the overall net financial implications to the health budget for all the years (published prices).
Treatment compliance	Full compliance	BEACON	This was not reasonable as compliance in clinical practice will not be the same as for clinical trials, BEACON.
Costs			
Encorafenib (DPMQ, effective price)	75 mg = \$ [REDACTED]	Proposed effective price	Consistent with the price proposed.
Cetuximab (listed price)	550 mg = \$1,835.12 550 mg = \$1,900.24	4731B 7273T	An SPA with an [REDACTED]% rebate on the published price was assumed.
Bevacizumab (listed price)	900 mg = \$2,821.22 900 mg = \$2,900.15	4400N 7243F	An SPA with an [REDACTED]% rebate on the published price was assumed.
Irinotecan (listed price)	800 mg = \$150.66 800 mg = \$192.17	4451G 7249M	This was appropriate.
Folinic acid (listed price)	1000 mg = \$59.11 1000 mg = \$43.80 500 mg = \$38.90 500 mg = \$53.84 500 mg = \$53.85 500 mg = \$38.90 1200 mg = \$42.12 1200 mg = \$57.30	1704Q 1904F 5890B 8740B 1610R 1899Y 5870Y 9041W	This was appropriate.
Fluorouracil bolus (listed price)	1000 mg = \$92.87 1000 mg = \$133.60	4431F 7239B	This was appropriate.

Public Summary Document – March 2021 PBAC Meeting with May 2021 Addendum

Data	Value	Source	Comment
Fluorouracil infusion (listed price)	5500 mg = \$165.96 5500 mg = \$124.78	7234R 4394G	This was appropriate.
PBS co-payment	PBS = \$23.08 RPBS = \$6.14	A single patient co-payment calculated on the basis of observed distribution from PBS 2019 statistics (for public setting), for all medicines used to estimate the financial impact for PBS and RPBS setting.	Estimates were appropriately sourced and calculated based on utilisation of the medicines involved.
Specialist follow up (for medical oncologist, radiation oncologist, psychology specialist and surgeon consultations)	\$45.00 ^a	MBS item 105	This was appropriate.
Oncology nurse visit	\$9.90 ^a	MBS item 82200	This was appropriate.
Level C GP consultation	\$75.50 ^a	MBS item 36	This was appropriate.
Brain MRI	\$403.20	MBS item 63001	This was appropriate.
Brain CT-scan	\$198.00 ^a	MBS item 56001	This was appropriate.
Chest radiograph	\$299.40 ^a	MBS item 56301	MBS item 56341 which was nominated by the submission was deleted as of May 2020 (MBS Online, May 2020). Instead, MBS item 56301 had a similar description and was applied in the evaluation.
Blood test	\$16.95	MBS item 65070	This was appropriate.

Note: ^a Updated based on MBS item prices from July 2020.

Abbreviations: *BRAF* = B-Rapidly Accelerated Fibrosarcoma; CT = computed tomography; Dispensed price maximum quantity; FOLFIRI = 5-fluorouracil + folinic acid + irinotecan; GP = general practitioner; MBS = Medicare Benefits Schedule; mCRC = metastatic colorectal cancer; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SPA = Special Pricing Arrangement.

Source: Table 4-2, p273; Table 4-3, p274; Table 4-4, p274; Table 4-5, p274; Table 4-6, p275; Table 4-7, p275 and Encorafenib mCRC Financial Table Workbook, sheets '1.Overview' and '4b. Impact-affected (pub)' of the submission.

The redacted values correspond to the following ranges:

¹10,000 to <20,000

²500 to 5,000

³<500

⁴500 to 5,000

- 6.67 The submission did not consider potential use by prevalent mCRC patients, arguing that mCRC patients with a *BRAF* V600E variant have a short survival period. While this may be the case, it is likely that some mCRC patients diagnosed with a *BRAF* V600E variant in the year before encorafenib is listed will be alive post-listing. As a result, the evaluation considered it likely that the submission had underestimated the number of patients eligible to receive encorafenib + cetuximab in the first year of listing. However, given the short survival period of patients with mCRC, the ESCs considered this underestimate in eligible patient numbers would mainly impact the first year of listing.
- 6.68 The costs of *BRAF* V600E testing were not included in the financial estimates. The submission noted that there would be no additional cost to the MBS due to *BRAF* testing as it is already done as part of routine testing for *RAS* status and that the

request is for the formal inclusion and reporting of existing *BRAF* V600E testing into the existing MBS item 73338.

- 6.69 The submission requested an SPA for encorafenib. The financial impact of encorafenib presented in the submission was estimated using the encorafenib effective price. The submission also applied SPAs assumed for cetuximab and bevacizumab (an assumed ■% rebate) as well as a 25% reduction to the price of cetuximab under the assumption of generic entry, to the base case. As with the economic model, the assumed price reduction due to generic entry was not consistent with the *PBAC Guidelines*.
- 6.70 The estimated numbers of patients treated, scripts dispensed and financial implications of the proposed listing are summarised in Table 18. At year 6, the estimated number of patients was <500 and the net cost to the PBS would be \$0 to <\$10 million. The net cost would increase once the assumption of a price reduction due to generic entry for cetuximab is removed. Applying the effective price of cetuximab will also impact on the net cost.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of encorafenib						
Incident mCRC patients with a BRAF V600E variant, eligible, who will receive encorafenib	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated total volume of scripts dispensed	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Estimated financial implications of encorafenib to the PBS/RPBS (effective encorafenib price)						
Cost to PBS/RPBS	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Copayments	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³
Cost to PBS/RPBS less copayments	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Estimated financial implications of BRAF V600E testing to the MBS						
Net cost to the MBS budget	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Estimated financial implications for affected medicines (effective price associated with SPA assumptions) ^a						
Cost to PBS/RPBS	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³
Copayments	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Cost to PBS/RPBS less copayments	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³	-\$■ ³
Estimated financial implications from changes to MBS items						
Net cost to MBS budget ^b	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Net financial implications						
Net cost to the PBS	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Net cost to RPBS	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Net cost to MBS ^b	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³
Net cost to government ^b	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³	\$■ ³

^a The submission applied the SPAs assumed for cetuximab and bevacizumab (an assumed ■% reduction) as well as a 25% reduction to the price of cetuximab under the assumption of generic entry, to the base case.

^b Updated based on MBS item prices from July 2020.

Abbreviations: BRAF = B-Rapidly Accelerated Fibrosarcoma; MBS = Medicare Benefit Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4-7,4-10,4-17,4-23, 2-24, pp275,277,282,285,286 of the submission.

The redacted values correspond to the following ranges:

¹<500

²500 to <5,000

³\$0 to <\$10 million

6.71 The submission stated that a range of factors such as number of patients who would be treated with encorafenib + cetuximab, accounts for uncertainty in the financial estimates. As such, sensitivity analyses were presented to examine the impact of uncertainty inherent in the base case results. The financial estimates were most sensitive to the mean duration of treatment and compliance rate; resulting in an overall increase in the net financial estimates. The mean duration of treatment used for the financial estimates was as reported within BEACON and not subject to extrapolation. This resulted in the application of shorter mean durations of therapy across all therapies for the financial estimates compared with the economic model as

follows: 5.75 vs 6.57 months for encorafenib + cetuximab; 2.68 vs 3.02 months for FOLFIRI/Ir + cetuximab; and, 2.68 vs 3.32 months for FOLFIRI + bevacizumab. The ESCs noted the submission presented the results of a sensitivity analysis which assessed the impact of the longer mean duration of treatment (as seen in the economic model), resulting in an 18% increment in the overall net financial implications to the health budget for all the years. A reduction in the treatment compliance rate led to a reduction in the net financial estimates.

- 6.72 Overall, the absolute impact on government expenditure in all instances of the sensitivity analyses conducted was 10% or less in either direction in the first year of listing, from the base case (based on the proposed effective price of encorafenib, and the published prices of cetuximab and bevacizumab with █% SPA rebate assumptions applied).

For more detail on the PBAC's view, see section 7 PBAC outcome.

7 PBAC outcome

- 7.1 The PBAC deferred its consideration of encorafenib in combination with cetuximab for the targeted treatment of patients with *BRAF* V600E variant mCRC who have received prior systemic therapy until an MSAC intention to support the co-dependent *BRAF* V600 testing in mCRC via the MBS is available. The PBAC foreshadowed its support for recommending that encorafenib in combination with cetuximab be listed and stated that, if MSAC subsequently decided to support the MBS listing of *BRAF* V600 testing in mCRC, it would support an expedited process for reconsideration to align any PBAC recommendation for listing encorafenib aligned with the circumstances supported by MSAC.
- 7.2 The PBAC acknowledged there was a high clinical need for effective treatments for patients with *BRAF* V600E positive mCRC, noting that the presence of a *BRAF* V600E variant indicates very poor prognosis, and that currently available therapies have limited effectiveness in this patient population. The PBAC considered that the sponsor hearing and consumer comments received confirmed this high unmet need.
- 7.3 The PBAC agreed with the submission that encorafenib with cetuximab would be used as a second-line treatment after prior systemic therapy, noting this was consistent with the key clinical evidence (the BEACON trial), the proposed TGA registration, and the *NCCN Guidelines v2. 2021*. The submission claimed that FOLFIRI + cetuximab was the most commonly used second-line regimen among patients with *BRAF* V600E variant mCRC, and was thus the appropriate main comparator. However, the PBAC noted the ESCs' advice that this regimen was not recommended in Australian or recent international guidelines since response to EGFR inhibitors was unlikely in this patient population (unless given with encorafenib, owing to the combination's synergistic mechanism of action). Despite this, the clinician views in the pre-PBAC response and at the sponsor hearing suggested that FOLFIRI + cetuximab continues to be used in

Australian clinical practice as even a transient response was clinically meaningful in the context of the very poor survival of these patients. On balance, the PBAC considered that FOLFIRI + cetuximab was the therapy most likely to be replaced in current practice, although the extent of cetuximab use remained uncertain (and other therapies including irinotecan-based regimens may be used in some patients). Importantly, as discussed further below, the clinical trial evidence was supportive of superior effectiveness over FOLFIRI given with or without cetuximab.

7.4 In terms of the requested PBS listing, the PBAC:

- Noted that the submission had initially requested encorafenib be used in combination with any EGFR inhibitor (i.e. cetuximab or panitumumab on the PBS). However, the proposed TGA approval, the clinical evidence, the economic model and the financial estimates were based on use with cetuximab specifically. Although the PBAC agreed with the ESCs that a broader listing may be clinically preferable so as not to disadvantage patients who develop sensitivity or intolerance to cetuximab, it was mindful of the proposed TGA indication, and stated that, should the sponsor seek regulatory alignment in future, the PBAC would welcome a submission to list encorafenib in combination with panitumumab.
- Considered that the listing should refer more broadly to V600 variant status (without reference to V600E specifically), noting that this would be consistent with the encorafenib melanoma listing and that *BRAF* V600E variant accounts for more than 90-95% of *BRAF* variants.
- Noted that the submission requested listing for both 50 mg and 75 mg strengths of encorafenib, with the 50 mg strength intended for dose modification purposes. The PBAC noted that the recommended dose modifications in the proposed TGA Product Information are in 75 mg increments, and considered that the 50 mg strength may not be required on the PBS.

7.5 The PBAC considered that BEACON, the head-to-head randomised controlled trial presented in the submission, had an overall low risk of bias. Although the control arm included cetuximab, which as mentioned above, is not recommended in current guidelines for patients with *BRAF* V600E variant mCRC, the PBAC considered that this regimen is nonetheless still used in current Australian practice. Furthermore, the PBAC agreed with the ESCs that the results of BEACON would provide supportive clinical evidence even where FOLFIRI were used alone, since the addition of cetuximab to the control arm was unlikely to result in a smaller incremental benefit.

7.6 The submission claimed superior comparative effectiveness with respect to a main comparator of FOLFIRI + cetuximab. The PBAC noted that OS, ORR, and PFS results were statistically significantly in favour of encorafenib + cetuximab. The PBAC noted that the OS and QoL improvement for encorafenib in combination with cetuximab represented a score of 5 (out of a maximum of 5, where 5 and 4 represent the grades

with substantial improvement) on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS).¹³ Thus, the PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data (compared with FOLFIRI ± cetuximab).

- 7.7 The submission claimed superior comparative safety with respect to a main comparator of FOLFIRI + cetuximab. The PBAC noted that the incidence of Grade ≥3 TRAEs, any AEs requiring dose reduction and Grade ≥3 AEs requiring dose reductions were statistically significantly lower for the encorafenib + cetuximab arm compared to the control. However, the data from BEACON also showed a mix of different toxicity events across the regimens. Additionally, the comparative safety relative to FOLFIRI alone was even less clear since this was not the control regimen. The PBAC noted the ESCs' advice that BEACON may underestimate comparative toxicity in this situation, in view of additional toxicity expected when adding cetuximab to FOLFIRI. On balance, therefore, the PBAC considered that a claim of non-inferior safety with respect to FOLFIRI + cetuximab (or FOLFIRI alone) was more reasonable than a claim of superiority.
- 7.8 The submission presented a cost-effectiveness analysis comparing encorafenib + cetuximab with FOLFIRI/Ir + cetuximab. The PBAC considered that this analysis reflected the appropriate main comparator. The PBAC noted a range of issues raised by the evaluation and the ESCs (see paragraphs 6.44 to 56 and Table 13 for details). The PBAC considered that the impact of many of these structural concerns and inputs was relatively minor, noting that the ICER was most sensitive to applying the effective price of cetuximab, and to a 25% price reduction applied due to an assumed generic entry for cetuximab.

Committee-In-Confidence Start

- 7.9 The PBAC noted that the ICER presented in Table PBAC.20 of the Committee-In-Confidence section of the ESCs' advice was \$75,000 to < \$95,000/QALY when the effective DPMA for cetuximab and the MBS fee for the administration of cetuximab were both applied (and without assumptions around generic entry of cetuximab). The PBAC, noting the relatively small variation across the other sensitivity analyses, considered this ICER to be a more reliable base case result, although relatively high. The PBAC further noted that cetuximab has limited clinical benefit when used alone and when the incremental cost of encorafenib only was considered the ICER reduced to \$30,000 to <\$45,000/QALY. In this context, the PBAC considered the ICER of \$75,000 to < \$95,000/QALY to be acceptable, together with the high clinical need and low estimated financial implications, and hence that encorafenib would be cost-effective at the price proposed in the submission.

¹³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

Committee-In-Confidence End

- 7.10 The PBAC noted the associated net cost to the PBS of listing encorafenib reported in the financial estimates was approximately \$0 to <\$10 million per year, based on published prices for medicines substituted. The PBAC noted that an assumed price reduction for cetuximab due generic entry should not be included in the estimates. The PBAC noted the financial estimates were most sensitive to the mean duration of treatment and compliance. The PBAC considered the duration of treatment used in the financial estimates should be consistent with the economic model, rather than the shorter duration observed in BEACON (6.57 vs 5.75 months respectively), and that use by prevalent mCRC patients should be included in the estimates. With regard to other sensitivities of the estimates, the PBAC noted that the impact on expenditure was 10% or less in either direction in the first year of listing (based on published prices).

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Pierre Fabre welcome the opportunity to work with PBAC and MSAC to expedite availability of Braftovi® (encorafenib) in combination with cetuximab for Australian patients with BRAF V600E variant mCRC.

Addendum to the March 2021 PBAC Minutes:

4.02 ENCORAFENIB

**Tablet 50 mg, Tablet 75 mg,
Braftovi[®],
Pierre-Fabre Australia Pty Ltd.**

10 Background

- 10.1 At its March 2021 meeting, the PBAC deferred its decision about the PBS listing of encorafenib in combination with cetuximab for the targeted treatment of patients with *BRAF* V600E variant mCRC who have received prior systemic therapy. The decision was deferred until an MSAC intention to support the co-dependent *BRAF* V600 testing in mCRC via the MBS was available. The PBAC foreshadowed its support for recommending that encorafenib in combination with cetuximab be listed for this population.
- 10.2 At its 31 March – 1 April 2021 meeting, the MSAC supported an amendment to the descriptor for MBS item 73338 to include *BRAF* V600 testing, noting that this amendment would not be associated with any change in the fee for this item.
- 10.3 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration on 7 May 2021, the TGA Delegate’s Overview was available.

11 PBAC outcome

- 11.1 The PBAC recommended the listing of encorafenib in combination with cetuximab for the treatment of patients with *BRAF* V600 variant mCRC, who have received prior systemic therapy. The PBAC is satisfied that encorafenib in combination with cetuximab provides, for some patients, a significant improvement in efficacy over 5-fluorouracil/folinic acid/irinotecan (FOLFIRI) in combination with cetuximab. The PBAC recalled that it had considered encorafenib to be cost-effective at the price proposed in the submission.
- 11.2 The PBAC noted that MSAC supported an amendment to the descriptor for MBS item 73338 to include *BRAF* V600 testing. The PBAC also re-affirmed its previous advice concerning the clinical need for this combination, the submission’s comparator, clinical evidence, clinical claim, economic model and financial estimates. The PBAC reiterated that: combination therapy should be available with cetuximab only (not any EGFR inhibitor); the listing should refer broadly to V600 status (without reference to V600E specifically); and the 75 mg strength of encorafenib was sufficient for dose modifications in mCRC according to its draft Product Information.

- 11.3 The PBAC advised that a new PBS listing for cetuximab would be required to allow for combination therapy with encorafenib for this mCRC indication. The PBAC noted that existing PBS listings for cetuximab continuing therapy for RAS wild-type mCRC (first-line: 10262D/10265G and second-line: 4731B/7273T) currently include the note that, “The treatment must not exceed a single course of therapy with this drug for metastatic colorectal cancer in a patient's lifetime.” Any *BRAF* V600 positive patients taking cetuximab via existing PBS listings for *RAS* wild-type mCRC may therefore potentially be excluded from switching to cetuximab with encorafenib. Given the poor prognosis for *BRAF* V600 positive mCRC, the PBAC considered that these patients should be able to switch to treatment with encorafenib and cetuximab (if they have not progressed whilst taking cetuximab), and that existing PBS cetuximab listings should clarify this intent.
- 11.4 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for encorafenib:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over FOLFIRI in combination with cetuximab in terms of overall survival;
 - b) The treatment is expected to address a high and urgent unmet clinical need in patients with *BRAF* V600E positive mCRC, noting that the presence of a *BRAF* V600E variant indicates very poor prognosis;
 - c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.
- 11.5 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

12 Recommended listing

Encorafenib

Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ENCORAFENIB					
Encorafenib 75 mg capsule, 42	NEW	3	126	3	Braftovi
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
9624	Indication: Metastatic colorectal cancer				
	Treatment Phase: Initial treatment				
NEWCC1	Clinical criteria: Patient must have BRAF V600 variant positive metastatic colorectal cancer,				
	AND				
	Clinical criteria:				
New CC2	The treatment must be in combination with cetuximab,				
	AND				
	Clinical criteria:				
NEWCC3	Patient must not have received prior treatment with cetuximab for this condition; OR				
NEWCC4	Patient must not have developed disease progression while receiving cetuximab for this condition,				
	AND				
14393	Clinical criteria:				
14392	Patient must not have previously received PBS-subsidised treatment with this drug for this condition,				
	AND				
	Clinical criteria:				
New CC5	The condition must have failed to respond to at least one other line of chemotherapy,				
	AND				
7601	Clinical criteria:				
7600	Patient must have a WHO performance status of 2 or less.				
7606	Administrative advice: No increase in the maximum quantity or number of units may be authorised.				
7607	Administrative advice: No increase in the maximum number of repeats may be authorised.				
7608	Administrative advice: Special Pricing Arrangements apply.				

Public Summary Document – March 2021 PBAC Meeting with May 2021 Addendum

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ENCORAFENIB					
Encorafenib 75 mg capsule, 42	NEW	3	126	5	Braftovi
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
9624	Indication: Metastatic colorectal cancer				
	Treatment Phase: Continuing treatment				
11365	Clinical criteria:				
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition,				
	AND				
	Clinical criteria:				
NEW CC2	The treatment must be in combination with cetuximab,				
	Clinical criteria:				
22669	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.				
7606	Administrative advice: No increase in the maximum quantity or number of units may be authorised.				
7607	Administrative advice: No increase in the maximum number of repeats may be authorised.				
7608	Administrative advice: Special Pricing Arrangements apply.				

Cetuximab

Add new item:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
CETUXIMAB Injection	NEW	880 mg	0
Available brands			
Erbitux cetuximab 500 mg/100 mL injection, 100 mL vial cetuximab 100 mg/20 mL injection, 20 mL vial			
Restriction Summary [new] / Treatment of Concept: [new]			
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners		
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]		
9624	Indication: Metastatic colorectal cancer		
	Treatment Phase: Initial		
	Clinical criteria:		
New CC6	The treatment must be in combination with PBS-subsidised encorafenib for this condition.		
7606	Administrative Advice: Special Pricing Arrangements apply.		

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
CETUXIMAB Injection	NEW	550 mg	11
Available brands			
Erbitux cetuximab 500 mg/100 mL injection, 100 mL vial cetuximab 100 mg/20 mL injection, 20 mL vial			
Restriction Summary [new] / Treatment of Concept: [new]			
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners		
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]		
9624	Indication: Metastatic colorectal cancer		
	Treatment Phase: Continuing		
	Clinical criteria:		
New CC6	The treatment must be in combination with PBS-subsidised encorafenib for this condition.		
7606	Administrative Advice: Special Pricing Arrangements apply.		

This restriction may be subject to further review. Should there be any changes made to the restrictions, the sponsors will be informed.

13 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

14 Sponsor's Comment

Pierre Fabre welcomes the decision of PBAC and MSAC and will work with the Department to expedite availability of Braftovi® (encorafenib) in combination with cetuximab for Australian patients with BRAF V600 variant mCRC.