****

RATIFIED PICO

Application 1617:

*BRAF* *V600* testing to help determine eligibility for PBS access to Braftovi® (encorafenib), in patients with metastatic colorectal cancer (stage IV)

## Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

| **Component** | **Description** |
| --- | --- |
| Patients | **Test:** Patients diagnosed with Stage IV metastatic colorectal cancer (mCRC).**Drug:** Patients with mCRC who have progressed following one or two previous lines of treatment in the metastatic setting, and who have a B-rapidly accelerated fibrosarcoma (*BRAF*) *V600E* pathogenic variant in tumour tissuea. |
| Prior tests | Clinical or biochemical suspicion of metastatic disease is confirmed by radiological imaging.Routine histology, cytology and immunohistochemical tests used to confirm if the CRC is metastatic. |
| Intervention | **Test:** *BRAF V600E* variant testingb involves taking a biopsy of the mCRC tumour (stage IV) and performing DNA extraction and assayc.**Drug:** Treatment with encorafenib [in combination with an epidermal growth factor receptor (*EGFR*) inhibitor such as cetuximab] (also known as a doublet-therapy group), in patients with *BRAF V600E*-variant mCRC as second and subsequent lines of therapyd. |
| Comparator | **Test:** No testing, i.e. Medicare Benefits Schedule (MBS) item 73338 in its current format, which has no explicit inclusion of *BRAF V600E* variant testing in CRC, and no reference to encorafenib.**Drug:** Standard of care for second-line therapy (FOLFOX or FOLFIRI+/- biologics, such as bevacizumab, cetuximab, panitumumab) and third-line therapy (cetuximab, other chemo regimens, trifluridine/tipiracild, experiments treatments and Best Supportive Care*)* |
| Outcomes | * Safety: adverse events associated with testing and subsequent treatment, rate of re-biopsy, impact on patients of false positives and false negative results
* Test-related: diagnostic accuracy, prognostic accuracy, change in clinical management, test turn-around time
* Clinical/therapeutic effectiveness: overall survival (OS), objective response rate (ORR), progression-free survival (PFS)
* Health-related quality of life
* Healthcare resources: cost of testing, cost of treatment, and cost related to treating adverse events
* Cost-effectiveness: cost per life-year gained, cost per quality-adjusted life-year (QALY) gained
 |

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 It is unclear if the applicant wishes encorafenib + cetuximab to be considered as third-line therapy for mCRC. If so, the
proposed algorithm needs to align with this.

***PICO or PPICO rationale for therapeutic and investigative medical services only***

**Please note: As per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016):**

* **The term ‘variant’ should be (and has been) used to replace the outdated term ‘mutation’; and**
* **‘*BRAF* *V600*’ pathogenic variant refers to both class 4 (likely pathogenic) and class 5 (known pathogenic) variants. This is similar for RAS and other pathogenic variants.**

**POPULATION**

The population includes patients who have stage IV metastatic colorectal cancer (mCRC). These patients would receive a publicly funded **REDACTED** to detect B-rapidly accelerated fibrosarcoma (*BRAF*) *V600* variant positivity, in order to determine eligibility for treatment with encorafenib, in combination with binimetinib and an epidermal growth receptor (EGFR) inhibitor, such as cetuximab.

Colorectal cancer (CRC), or bowel cancer, is a cancer of the colon or rectum, caused by an accumulation of variants, leading to transformation of cells lining the colon or rectum, or to polyps, which, upon further variation and growth, result in cancerous adenocarcinoma cells (1). There are four stages of CRC, detailed in Table 1. The diagnosis can be made through colonoscopy, biopsy and imaging (2).

Table 1: Stages and locations of colorectal cancer

| TNM stage | Location | Definition |
| --- | --- | --- |
| I | Local | Cancer is located in the innermost lining of the bowel |
| II | Local | Cancer has grown through the muscle layer of the bowel |
| III | Regional | Cancer has spread to at least one lymph node close to the bowel |
| IV | Metastatic | Cancer has spread in the body |

Source: p15 of MSAC Application 1617

TNM = Tumour, Node, Metastasis

Globally, CRC is the third most common cancer, comprising more than 9% of all cancer incidence (3, 4). It is also the fourth leading cause of cancer-related mortality, and 22-25% of patients are diagnosed at the most extended cancer stage (IV) (5, 6).

Around 50% of non-metastatic patients develop mCRC within three years of diagnosis (7-9). In 2016, CRC led to the death of 5,375 people, representing the second highest number of cancer deaths in Australia (10). It has been estimated to cost over $427 million to the Australian healthcare system (2008-09 figure) (11). This figure is equivalent to around 10% of all cancer expenditure. CRC accounts for the highest proportion of cancer costs, with most of the expenditure occurring in patients aged 55 years and over (11).

Life expectancy of patients with CRC depends on the cancer stage (12, 13). Australian cancer data revealed that the five-year relative-survival rate for patients with local CRC (stage I) is 99% (13). Patients with local CRC (stage II) have a survival rate of 89%. When CRC is likely to spread to at least one of the regional lymph nodes (stage III), patients have a five-year survival rate of 71%. When the cancer reaches the metastatic stage (i.e. mCRC, stage IV), the five-year survival rate reduces to 13%.

Without treatment, the median survival for stage IV mCRC is approximately 9 months (14). Even patients with limited metastatic disease, such as liver metastases, have a poor five-year survival rate. Patients with hepatic (i.e. liver) cancer have a median survival of 5-20 months without treatment (15). mCRC is therefore the most crucial stage of CRC, because of its impact on survival time and other patient-related outcomes (16).

Testing population

mCRC patients can have either a rat sarcoma oncogene (*RAS*) wild type (occurring in 55% patients) - or *RAS* variant (occurring in 45%) (17).

A *BRAF* variant is a different genetic variant, which accounts for around 10% of patients with mCRC in clinical trials, ranging from 8% to 12% (18-21). While the same mean estimate (10%) is quoted, a much wider range of estimates are provided in pivotal trial Kopetz et al 2019 (5-21%, page 1633 of publication) [original sources: 10 publications]. However, of these, it would need to be checked which measures might apply to the Australian context.

A *BRAF V600* variant is characterised by increased kinase activity in the *BRAF* gene, an important constituent in the EGFR-mediated mitogen-activated protein kinase (MAPK) pathway, where a valine-to-glutamate change occurs at position 600 (22). *BRAF* and *RAS* variants occur nearly always mutually exclusively (23).

Compared to other mCRC subtypes, the presence of a *BRAF V600* variant indicates poor prognosis, with no targeted therapies currently available (18, 20). The presence of a *BRAF* variant in mCRC patients predicts more than double the risk of mortality [hazard ratio = 2.25 (95% CI, 1.82-2.83)] (24). The Application Form stated that: “*BRAF* positivity in CRC may influence choice and timing of therapy more effectively than therapies allocated on the basis of *RAS* variant status alone, and highlights the importance of testing for *BRAF* concurrently, to identify patients with poorer prognosis”.

A *BRAF V600*E variant is the most common type of *BRAF* variant, constituting about 90-95% of all *BRAF* variants (25, 26). The Application Form states that patients with a “BRAF *V600* variant” (in general) is the targeted population of interest, and did not make a distinction between subtypes of *V600*, such as *V600E*, *V600K*, *V600R* and *V600D*. Since the Application Form used evidence from the BEACON trial (that only considered patients with a *V600E* variant), the targeted population can be clearly distinguished as *V600E* type.

Alternatively, use of the generic term “*V600*” should be justified, including with reference to use of this generic term (for this biomarker) in relevant melanoma-related MBS and PBS items.

Although still controversial, evidence is accumulating that patients with *BRAF*-variant mCRC do not benefit from anti-EGFR antibodies alone, or in combination with cytotoxic chemotherapy (27). Doublet chemotherapy is therefore the current standard of care in this patient population.

Estimates for size of the testing population

Estimates of the size of the testing population provided in the Application Form were based on total services used under Medicare Benefits Schedule (MBS) item 73338, from July 2015 to June 2019 (detailed in Table 2). The Application Form estimated an average of 2,466 *RAS* variant testing services have been performed per year under MBS item 73338 (over five years, from July 2015 to June 2019). This number was similar[[1]](#footnote-1) to the average of the actual number of *RAS* tests (MBS item 73338) identified in the utilisation report for the Medical Services Advisory Committee (MSAC), considered at the July 2018 MSAC meeting. *PASC confirmed the proposed population, noting that the test population is the same as described in MBS item 73338 with metastatic colorectal cancer (stage IV).*

**Table 2: Number of patients who received *RAS* variant testing services under MBS item 73338**

| **Financial Year** | **Total Services** |
| --- | --- |
| 2015/2016 | 2,844 |
| 2016/2017 | 2,397 |
| 2017/2018 | 2,187 |
| 2018/2019 | 2,434 |
| Total | 9,862 |
| Mean (July 2015-June 2019) | 2,466 |

Source: Page 24 of MSAC Application Form 1617
MBS = Medicare Benefits Schedule, RAS = Rat Sarcoma Oncogene
Note: The Application Form also presented figures for 2013/2014 (n = 52) and 2014/15 (n = 1,462), but did not use them to calculate the mean. Given MBS item 73338 was used for the first time in 2013/2014, it is justified not to use numbers from those financial years in the mean computation. The Application Form stated that the mean of 2,466 patients receiving *BRAF V600* variant testing in year 1 would be refined and validated in the assessment report/submission.

***Rationale***

The rationale for this co-dependent submission is primarily based on evidence outlined in the BEACON trial (28, 29). The BEACON trial is a phase III randomised controlled trial (RCT) evaluating the efficacy and safety of encorafenib + binimetinib + cetuximab, for patients aged ≥ 18 years with histologically or cytologically confirmed mCRC with the *BRAF* *V600E* variant, who had disease progression after one or two prior regimens in the metastatic setting. Key exclusion criteria included no prior treatment with any rapidly accelerated fibrosarcoma (*RAF*) inhibitor, mitogen-activated protein kinase (*MEK*) inhibitor, or cetuximab, panitumumab or other *EGFR* inhibitors.

The Application Form stated that all mCRC patients in Australia undergo a test of tumour tissue, to identify if a gene variant has appeared. This gives both a prognosis for the patient, and helps to determine their targeted treatment.

Existing MBS item 73338 allows for testing to determine *RAS* variant status to help determine the patient’s eligibility for cetuximab or panitumumab. The applicant stated that “most of the colorectal RAS testing is done with next generation sequencing (NGS) panels” and that *BRAF* *V600* variant status is routinely reported, based on the same test panel. The Application Form stated that both *RAS* and *BRAF* variant status are determined using a gene panel test of the same tissue sample. Consequently, the proposed treatment algorithm assumes no change in utilisation of MBS item 73338.

The MBS Explanatory Note (PN.0.26) associated with MBS item 73338 states that: “For a Medicare benefit to be payable, the test must be conducted for all clinically relevant variants on KRAS exons 2, 3, and 4, and NRAS exons 2, 3, and 4, **or until a clinically relevant *RAS* variant is found**” (PN.0.26, MBS March 2020)**.**

The MBS does not currently require pathologists to continue testing for other clinically relevant variants once a clinically relevant *RAS* variant is found. If patients need to be shown to be both *RAS* wild type (to be eligible for cetuximab or panitumumab) and also *BRAF* *V600*-positive (to be eligible for encorafenib), then adding *BRAF* testing to this MBS item should not reduce the extent of use of MBS item 73338.

**Prior test**

The Application Form stated that clinical or biochemical suspicion of metastatic (stage IV) disease is confirmed by radiological imaging (computed tomography [CT] scan; magnetic resonance imaging [MRI]; ultrasound). A PET scan can be useful in determining malignant characteristics of tumoural lesions, and the extent of metastatic disease.

Diagnostic pathology of the primary tumour or metastases is conducted prior to treatment. Prior tests would consist of routine histology, cytology and immunohistochemical tests, to confirm mCRC status (30).

**INTERVENTION**

Testing

The requested intervention would be the formal inclusion of *BRAF V600* variant testing (among mCRC patients) into existing MBS item 73338. The purpose of *BRAF V600* variant testing is to improve prognostic information and guide the use of the triplet-therapy group, consisting of encorafenib plus binimetinib and cetuximab.

The BEACON trial showed this has superior performance, especially in terms of overall survival (OS) and response rate, compared with standard therapy (29). As discussed above, the BEACON trial only included patients with a *BRAF V600E* variant, which is inconsistent with the Application Form’s request for all *BRAF V600* variant sub-types. Information on the effectiveness of encorafenib in other *BRAF V600* variant sub-types should be presented in the assessment report. Alternatively, PASC may wish to restrict MBS testing to only identify a *BRAF V600E* variant, and with this, the PBS restriction for encorafenib. *PASC advised that, as per the evidentiary standard testing for the pivotal trial, the relevant BRAF variant should be specified as BRAF V600E, unless there is a basis to conclude that other BRAF variants are similarly predictive of improved effectiveness of encorafenib.*

MBS item 73338 is currently used for testing *RAS* variant status in patients with mCRC, to facilitate access to PBS-subsidised treatment with *EGFR* inhibitors (cetuximab and panitumumab), in patients with no *RAS* variant. The Application Form proposed that *BRAF* *V600* testing (among mCRC patients) be added to the existing MBS item descriptor (73338), stating it is currently routinely used for NGS tumour panels. *PASC noted the current international guidelines recommending BRAF, KRAS and NRAS genetic testing for all mCRC tumour specimens individually or part of a next generation sequencing (NGS) panel (National Comprehensive Cancer Network [NCCN] Guidelines v2.2020). PASC also noted that some laboratories in Australia could be testing separately for BRAF V600E and the clinically relevant variants in the RAS genes.*

The Application Form stated that Sonic is Australia’s largest pathology provider, and the NGS panel its laboratories use is called Find-It™. This is a focused panel for colorectal testing, including four genes: *RAS, BRAF, NRAS and PIK3CA*. *BRAF* *V600* variant testing protocols in Australia are presented in Table 3. **REDACTED**

Evidentiary standard

In the pivotal trial (BEACON), which provided the key evidence for encorafenib [in combination with binimetinib and cetuximab], the presence of a *BRAF* *V600E* variant in tumour tissue was previously determined by a local assay (at any time prior to screening) by the central laboratory. The Application Form stated that validation of the test used in the pivotal trial, versus test(s) commonly used in Australia, will be presented in the assessment report/submission.

Table 3: REDACTED

The European Society for Medical Oncology (ESMO’s) recommendation 5 for *BRAF* testing states that: “tumour BRAF mutation *[variant]* status should be assessed alongside the assessment of tumour RAS mutational *[variant]* status for prognostic assessment (and/or potential selection for clinical trials)” (18).

The National Institute for Health and Care Excellence (NICE) in the UK recommends routine testing of all patients with colorectal cancer for the *BRAF* *V600E* mutation [variant], if they have either an abnormal MLH1[[2]](#footnote-2) or a positive microsatellite instability test[[3]](#footnote-3) (31). NICE clinical guidelines for rectal cancer also recommend this (under principles of pathologic review, REC-B B 5/9). These oncology guidelines are widely used.

*BRAF V600* variant testing involves taking a biopsy of the mCRC tumour and performing DNA extraction and assay. Examples of assays include fluorescent in situ hybridisation (FISH), polymerase chain reaction (PCR), and NGS. The procedure is similar to conducting *RAS* testing in patients with mCRC, as prescribed in MBS item 73338.

The Application Form stated that *BRAF* *V600* variant testing is usually requested by the patient’s surgeon or oncologist, once a diagnosis of mCRC is confirmed. The surgeon or oncologist is typically responsible for collection of a biopsy (or cytological sample) from the patient. The biopsy sample used to establish a diagnosis can also be used to perform *BRAF* *V600* variant testing.

Biopsy samples are normally processed into formalin-fixed, paraffin-embedded (FFPE) tissue blocks, followed by sectioning, staining and mounting onto glass slides. An anatomical pathologist then investigates the mounted samples and marks the tumour. Subsequently, a scientist performs a dissection of the tumour cells (sample enrichment). This aids in identifying an appropriate sample for DNA extraction. The DNA extract is used to perform an assay by a molecular scientist or technician, under the supervision of a senior scientist or pathologist, following National Pathology Accreditation Advisory Council (NPAAC) laboratory supervision standards. It is not clear whether further pathologist training and quality assurance programs are required to be developed to assist in the interpretation of the test results based on genetic panel tests for *BRAF* *V600* variant positivity in mCRC following its inclusion in MBS item 73338. Further details should be provided.

*BRAF V600* variant testing is carried out in National Association of Testing Authorities (NATA) accredited laboratories (32). The Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP) monitors the competency of technicians involved in performing the test.

Treatment

The proposed treatment is encorafenib, in combination with binimetinib and cetuximab, as second-line therapy for patients with *BRAF V600*-variant mCRC. Encorafenib is a BRAF inhibitor that works by targeting key enzymes in the MAPK signalling pathway. *PASC noted that the applicant revised its proposed drug intervention to use encorafenib in doublet therapy, rather than triplet therapy (by dropping the proposed concomitant addition of the MEK inhibitor, binimetinib).*

At its 74th Meeting in November 2018, MSAC considered Application 1543, supporting the amendment to MBS item 73336 for *BRAF* testing in patients with metastatic melanoma, to also determine access to encorafenib under the PBS.

On 1 April 2020, MBS item 73336 was subsequently amended to include reference to encorafenib. Encorafenib was listed on the Pharmaceutical Benefits Scheme (PBS) on the same day. The current application (1617) is the first to request MBS funding for *BRAF* *V600* testing in patients with mCRC to determine access to encorafenib.

Internationally, NICE recommends the combination of encorafenib and binimetinib for the treatment of *BRAF V600E* variant-positive unresectable or metastatic melanoma but not for mCRC (31). The USA’s National Comprehensive Cancer Network (NCCN) clinical guidelines, and Australia’s Cancer Institute (NSW) EviQ clinical guidelines, should also be used as sources for establishing parameters (31). They will also be useful for considering/validating the proposed/edited algorithms.

The NCCN clinical guidelines importantly provide recommendations for encorafenib (cetuximab or panitumumab) in *BRAF V600E*-variant mCRC patients. Recommendations for these double therapy regimens are included throughout the clinical guidelines. However, recommendations for proposed triple therapy do not appear to be in these guidelines. Pivotal trials provided in Application 1617 are included in the references section of the guidelines. The algorithm is very complex, and dependent on previous treatment, in line with EviQ guideline recommendations.

NICE is currently considering encorafenib in dual or triple therapy for previously treated *BRAF V600E*-variant mCRC (NICE application ID 1598), with an expected publication in October 2020) (31).

The Application Form stated that “an application for **REDACTED** will be lodged with PBAC soon **REDACTED**, seeking PBS listing of these medicines, in combination, for the treatment of *BRAF V600*-variant mCRC”. PBAC may wish to restrict the treatment population to patients with *BRAF V600E*-variant only.

The applicant also stated that it intends to submit to the Therapeutic Goods Administration (TGA) in the near future **REDACTED**, to extend registration of encorafenib to include mCRC. The proposed TGA indication is: “encorafenib in combination with cetuximab for the treatment of patients with metastatic colorectal cancer who have received prior systemic treatment and whose tumours harbour a *BRAF V600* mutation [variant]”.

The BEACON trial will provide the main clinical evidence to support the safety, effectiveness and cost-effectiveness of encorafenib + binimetinib + cetuximab, in patients with *BRAF V600*-variant mCRC. In this trial, the standard of care was the investigator’s choice of either cetuximab and irinotecan, or cetuximab and FOLFIRI (a chemotherapy doublet, including folinic acid, fluorouracil and irinotecan).

***Rationale***

If encorafenib is recommended by PBAC only for patients with *BRAF* variant-positive mCRC, *BRAF V600* variant testing would be used to direct treatment to encorafenib. In this case, patients with *BRAF* *V600*-variant mCRC, who had progressed following one or two previous lines of therapy, would be eligible.

It was uncertain whether the applicant intended for encorafenib + binimetinib + cetuximab to be considered as third-line treatment for mCRC (i.e. following two previous lines of therapy). The Application Form proposed “second and subsequent lines of treatment”.

A subsequent (additional) document provided by the applicant included third-line treatment, and nominated regorafenib or trifluridine + tipiracil as comparators. A further (subsequent) document provided by the applicant indicated that third-line treatment and comparators are not relevant to this application (1617). The applicant was requested to clarify if third-line treatment should be considered in the evaluation.

*The Applicant clarified that third line treatment will be considered in the submissions. The comparators for the economic evaluations will be expanded on and supported in the submissions. Also the proposed TGA indication is likely to be modified to “encorafenib, in combination with cetuximab, is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by a validated test, who have received prior systemic treatment.”*

The Royal College of Pathologists of Australasia (RCPA) advised that confirming the presence of “*BRAF* mutations [variants] can be useful in helping to distinguish between sporadic tumours arising through hypermethylation, and Lynch syndrome-associated tumours arising from a germline mutation [variant]”. The absence of *BRAF V600E* variant in identifying tumours is not helpful, because the tumour could be either sporadic or familial.

In its consideration of MSAC Applications 1362.1 and 1363 (relating to MBS item 73338), MSAC noted that genetic testing would reach a point where gene panel testing (and possibly exome sequencing) would be clinically appropriate and more cost-effective than reimbursing testing on a gene by gene basis. MSAC advised that applications for additional somatic genetic testing for CRC should also trigger a review of cost-effectiveness of *RAS* testing (33, 34).

In a utilisation review of MBS item 73338, MSAC advised that if panel-based testing for predictive biomarkers is introduced, the ongoing need for MBS item 73338 will need to be considered (33, 34). MSAC Application 1495 proposed a single somatic tumour gene panel test that would replace existing tests associated with MBS items 73336 (*BRAF V600* for melanoma), 73337 (*EGFR* for non-small cell lung cancer), 73338 (*RAS* for colorectal cancer) and 73341 (anaplastic lymphoma kinase (*ALK*) for non-small cell lung cancer). MSAC Application 1495 has been placed on hold by its applicant.

MBS item 73338 currently only requires a test to rule out *RAS* mutation [variant], which may or may not be conducted using a gene panel test. Adding the *BRAF V600* variant test to the current MBS item may restrict utilisation to testing sites (pathology laboratories) that only use NGS panels.

During preparation of the PICO for Application 1617, the applicant indicated that approximately 20-30% of laboratory sites still use non-panel testing (e.g. sequential or simultaneous single-gene sequencing). However, these were not included in the proposed clinical management algorithms.

The exact proportion of sites using NGS versus single gene-sequencing methods is currently not known to any certainty. The applicant also indicated that it would “further refine” this data. Further data and details to support the availability and accessibility of testing devices and testing sites should be included in the assessment report.

Additional information is needed regarding whether the amendment to MBS item 73338 would lead to separate tests for *RAS* and *BRAF* variants. If the applicant believes this to be the case, the applicant should provide further advice on whether this would lead to duplication of tests, delay in producing test results, and deciding and administering appropriate treatments.

The Application Form proposed triplet-therapy group (encorafenib + binimetinib + cetuximab) as the treatment intervention, based on its superior performance in the BEACON trial. The trial also included a doublet therapy group that received a combination of encorafenib and cetuximab.

Several findings from the BEACON trial for the doublet-therapy group suggest it could be considered as one of the treatment strategies. While a head-to-head comparison of the doublet- and triplet-therapy groups was not conducted in the BEACON trial (as it was not powered to make a direct comparison), their performances were compared with a common control group. Table 4 outlines the effectiveness, safety and quality of life outcomes reported for patients receiving encorafenib + cetuximab in the BEACON trial, compared with a common control group.

Table 4: Effectiveness, safety, and quality of life for patients receiving encorafenib + binimetinib + cetuximab and encorafenib + cetuximab in the BEACON trial

|  | **Doublet therapy(encorafenib + cetuximab)** | **Triplet therapy(encorafenib + binimetinib + cetuximab)** |
| --- | --- | --- |
| **Effectiveness** |
| Overall survival in months (median, 95% CI) | 8.4 (7.5,11.0) | 9.0 (8.0, 11.4) |
| Progression-free survival in months (median, 95% CI) | 4.2 (3.7, 5.4) | 4.3 (4.1, 5.2) |
| Objective response rate (complete or partial response) | 20% | 26% |
| Risk of disease progression or death(hazard ratio, 95% CI) | 0.40 (0.31, 0.52) | 0.38 (0.29, 0.49) |
| Patients maintaining response for > 6 months | 43% | 24% |
| **Safety** |
| Adverse events, any | 98% | 98% |
| Adverse events, ≥ grade 3 | 50% | 58% |
| **Quality of life** |
| **REDACTED** |  |  |
| **REDACTED** |  |  |

Source: Kopetz et al. (2019) (29) and Kopetz et al. (2020) (35)

CI = Confidence Interval, EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- 30, FACT-C = Functional Assessment of Cancer Therapy – Colorectal, QoL = Quality of Life

Although median overall survival (OS) in the triplet-therapy group was numerically longer than the doublet-therapy group **REDACTED**. OS in both therapy groups was significantly higher than the control group (5.4 months), and no direct comparison between the doublet- and triplet-therapy groups was conducted. The observed difference in OS between the two therapy groups may not be statistically significant. Since both therapy groups achieved similar results in most other outcomes, the applicant should explain why the doublet-therapy should not be considered as an intervention to treat *BRAF V600-*variant mCRC patients.

*The Applicant confirmed the intended drug intervention is to use encorafenib in doublet-therapy*.

**COMPARATOR**

The proposed comparator for the formal inclusion of *BRAF* V600 variant testing (to determine the eligibility for BRAF inhibitor encorafenib) is MBS item 73338 with its current item descriptor (Table 5). Current MBS item 73338 allows testing for *RAS* variant status of a patient to determine eligibility for cetuximab or panitumumab. If *BRAF V600* variant testing is not explicitly stated in the item descriptor for MBS item 73338 (i.e. the intervention), then patients will continue to receive standard of care as per clinician’s choice. Access to encorafenib based on *BRAF* status will not be possible. *PASC confirmed the comparator for the test.*

Table 5: Current MBS item 73338

| Category 6– Pathology Services |
| --- |
|  Group P7 - Genetics**MBS item 73338**A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene *(RAS)* gene mutation *[variant]* status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:(a) the test is conducted for all clinically relevant mutations *[variants]* on *KRAS* exons 2, 3 and 4and *NRAS* exons 2, 3, and 4; or(b) a [clinically relevant] *RAS* mutation *[variant]* is found.MBS Fee: $362.60 Benefit: 75% = $271.95 85% = $308.25 |

Source: Page 26 of MSAC Application Form 1617
KRAS = Kirsten Rat Sarcoma Oncogene, NRAS = Neuroblastoma Rat Sarcoma Oncogene, RAS = Rat Sarcoma Oncogene, PBS = Pharmaceutical Benefits Scheme

The key randomised trial (BEACON) cited in the Application Form indicates the clinical evidence will consist of a comparison of encorafenib + binimetinib + cetuximab to investigator’s choice of cetuximab + FOLFIRI or cetuximab + irinotecan. Patients in the BEACON trial had mCRC, which had progressed following one or two previous lines of treatment in the metastatic setting.

The Application Form (page 21) proposed FOLFOXIRI or anti-VGFR (e.g. bevacizumab) + chemo-doublet (FOLFOX or FOLFIRI) as the treatment comparator. During preparation of the PICO, the applicant clarified these were first-line treatments for *BRAF*-variant mCRC. The applicant nominated chemotherapy doublet (FOLFOX or FOLFIRI) as the second-line treatment comparator for *BRAF*-variant mCRC (36).

If encorafenib + binimetinib + cetuximab is considered a third-line treatment for BRAF-variant mCRC, the proposed comparator is trifluridine + tipiracil (under certain conditions, e.g. ECOG 0 to 1 only, based on the [EviQ guidelines for this combination drug](https://www.eviq.org.au/medical-oncology/colorectal/metastatic/1940-colorectal-metastatic-trifluridine-tipiracil#indications-and-patient-population) (31).

*After the PASC meeting, PASC noted that, in addition to references provided by the applicant, the HTA group reviewed the DUSC report (Cetuximab, panitumumab and bevacizumab for metastatic colorectal cancer, February 2018), previous PBAC advice, and current PBS restrictions for potential 2nd and 3rd line comparators to encorafenib.*

*Cetuximab is currently PBS listed for metastatic colorectal cancer as:*

* *First-line treatment (in combination with chemo)*
* *After failure of first-line chemo (either as monotherapy or in combination with chemo)*

*The HTA group’s conclusion was that cetuximab is not PBS listed as third-line therapy. For a PBAC submission, the comparator needs to be a current PBS listed medicine, hence proposing only trifluridine/tipiracil in third-line. The PASC noted that while the comparator in a PBAC submission is not always a PBS-listed treatment, it agreed with the assessment group that cetuximab is not an appropriate comparator, given the NHMRC Guidelines for management of mCRC (2017) position cetuximab as a third-line treatment option for patients with RAS and BRAF wild-type tumours. Given the patient population included in this application have BRAF V600E positive tumours and noting the NHMRC Guidelines include the use of trifluridine/tipiracil as third-line treatment in patients refractory to all standard available therapies, the PASC agreed that trifluridine/tipiracil is the appropriate comparator in the third-line setting.*

*With regard to treatment comparators for the proposed doublet, the Applicant confirmed that the treatment comparators for second and third line treatment will be expanded on in the PBAC submission. While it is beyond the scope of this process to expand on the role of cetuximab, it is of note that cetuximab is included in the NHMRC Guidelines as an agent that could be considered to be used in the third line setting, along with other chemo regimens, trifluridine/tipiracil, experiments treatments and Best Supportive Care. As such, the Applicant noted that the submission will show that trifluridine/tipiracil is a possible comparator, not the sole comparator.*

### *The Applicant noted the NHMRC Guidelines comment the following on cetuximab and panitumumab:*

*“In patients with RAS wild-type metastatic colorectal cancer, both cetuximab and panitumumab have shown efficacy in the third-line/salvage-therapy setting, and are equally active as single agents. Combination therapy with cetuximab and irinotecan appears more active than cetuximab alone in patients with irinotecan-refractory tumours.”*

***Rationale***

The Application Form suggested the comparator would be the test detailed in current MBS item 73338, plus treatment with standard of care.

The Application Form stated the majority of *BRAF V600* variant tests are currently conducted as part of NGS tumour gene panels, but considered that all patients in the proposed population would receive a tumour gene panel (see Figure 1). There could be pathology laboratory sites where non-NGS testing methods are adopted, such as FISH, PCR, or Sanger sequencing (37). In such a scenario, concordance between the testing methods should be demonstrated. *PASC supported the applicant’s proposal to assess the analytical performance of test options available in Australia compared with the evidentiary standard test.*

Standard of care treatment in the BEACON trial was the investigator’s choice of either cetuximab and irinotecan or cetuximab and FOLFIRI (29). This is not consistent with the second-line treatment comparator proposed by the applicant (FOLFOX or FOLFIRI).

**OUTCOMES**

*Patient-relevant outcomes*

The applicant listed the following patient-relevant outcomes:

* Safety: Toxic effects from subsequent treatment, adverse events associated with biopsy, rate of re-biopsy, impact on patients of false positive and false negative test results
* Clinical/therapeutic effectiveness: overall survival (OS), objective response rate (ORR), progression-free survival (PFS)
* Analytic validity: The applicant advised it could present data to demonstrate analytic accuracy of Australian tests in colorectal specimens, and a comparison of test methodology between Australian laboratories with test methodology used in phase 3 of the BEACON pivotal clinical trial. This information should be provided in the assessment report.

More outcomes may be required to understand the full benefit of the intervention; for example:

* Diagnostic accuracy: Sensitivity, specificity, concordance (between NGS and other tests), reliability, positive and negative predictive values, positive and negative likelihood ratios
* Prognosis: prognostic effect of BRAF V600-variant mCRC patients treated with standard of care
* Change in management: Percentage change in management plan (such as changes in the treatment plan as a result of introducing the test). Change in management plan could also be induced by test turn-around time
* Predictive validity: Treatment effect modification predicted across test results.

Health-related quality of life should be included as an outcome. A recent publication based on the BEACON trial states that quality of life (QoL) outcomes were assessed as secondary endpoints in the trial (35). The QoL of patients was assessed by administering the instruments - European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- 30 (EORTC QLQ C30), Functional Assessment of Cancer Therapy- Colorectal (FACT-C), EuroQoL 5D 5L, and Patient Global Impression of Change (35). Only preliminary results regarding the endpoints concerning the QoL are available. Thus, additional evidence will need to be presented to better understand the QoL of patients following the treatment.

*Healthcare system outcomes*

Healthcare system-related outcomes have not explicitly been discussed in the Application Form. However, introduction of a new intervention will have an impact on the Australian healthcare system, and should be investigated. The following financial outcomes should be included: total number of mCRC patients tested, number of patients receiving treatment with encorafenib, cost of treatment with encorafenib, cost of treating adverse events, and cost per QALY.

The Application Form stated that most mCRC patients already receive *BRAF* *V600* variant testing, along with RAS testing under MBS item 73338 (via panel tests, such as NGS). It goes on to argue that explicit inclusion of *BRAF* testing in MBS item 73338 will not change delivery pathways or increase MBS costs*.* The proportion of patients currently receiving a *BRAF V600* gene test under MBS item 73338 should be determined by the applicant, in consultation with a designated body, such as the RCPA. Any claim there is a possibility that utilisation of MBS item 73338 may decrease if the proposed item descriptor change is approved, would need clarification. The possibility that there would be a decrease may be based on the assumption that some providers are currently billing the item to test for somatic markers, then billing the same item again to test for another set of markers.

While the cost to the MBS would be minimal, the cost to the PBS may be substantial. This is because it could lead to a change in treatment regimen, as patients become eligible for encorafenib. This depends on the difference in cost of treatment between the intervention (encorafenib + binimetinib + cetuximab) and comparators (FOLFOX or FOLFIRI).

*PASC confirmed the proposed outcomes.*

***Rationale***

This Application Form proposed the introduction of co-dependent technologies. Therefore, the treatment effect modification and/or prognostic impact of *BRAF V600* variant testing among mCRC patients and encorafenib needs to be explained. Currently, this is not clear from the BEACON trial, because the trial was not stratified by this biomarker. Specifically, all patients enrolled in the BEACON trial were known to be *BRAF* *V600E*-variant.

## Current and proposed clinical management algorithms for identified population

## Current clinical management algorithm

Encorafenib + binimetinib + cetuximab is intended as second-line treatment for patients with *BRAF-*variant mCRC. The current and proposed treatment algorithms have been amended to reflect second-line treatment of mCRC. Clarification is needed about whether these changes have been influenced by clinical guideline(s), and if so, they should be referenced.

*The Applicant confirmed that the intended treatment is encorafenib as doublet therapy in the second and third line settings. The submissions to MSAC and PBAC will reference the guidelines and expert input that have guided the clinical management algorithm.*

It is unclear if the applicant intends encorafenib + binimetinib + cetuximab to be considered as third line therapy for mCRC. Therefore, the treatment algorithms have not been extended to consider third-line treatment.

*The Applicant noted that while it is anticipated that the majority of use of the doublet will be in the second line setting (64% of patients in the key BEACON trial received the treatment in the second line setting), the Applicant acknowledged that the doublet will also be used in the third line setting and will present algorithms accordingly.*

The current management algorithm of mCRC is illustrated in Figure 1. Following mCRC diagnosis, genetic testing is conducted to establish *RAS* variant status. The Application Form stated that the use of somatic gene panels would minimise the cost of testing for multiple tumour markers, and decrease the risk of treatment with inappropriate therapies. Although Figure 1 states that: “gene variant panel testing” is the diagnostic test performed, gene panel testing is not currently required to determine *RAS* variant status. If possible, more information on the availability, acceptability and trend of gene variant panel testing should be substantiated by the applicant.

A patient with a *RAS* variant is highly unlikely to have a *BRAF* variant, because *RAS* and *BRAF* variants are nearly always mutually exclusive (23). The presence of a *RAS* variant rules out the presence of a *BRAF* mutation. Those with *RAS* wild type could have either *BRAF* wild type or *BRAF* variants, leading to the current treatment regimen.

Figure 1: Edited version of the current gene variant testing and treatment pathway for patients
 with mCRC


Source: Compiled during PICO preparation using Application Form 1617 (page 21) and applicant feedback
BRAF = B-Rapidly Accelerated Fibrosarcoma, EGFR = Epidermal Growth Factor Receptor, FOLFOXIRI = FOLinic acid, Fluorouracil, OXaliplatin and IRInotecan, 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
Note: Chemo doublet therapy is either FOLFOX or FOLFIRI. Patents who fail first-line treatment with FOLFOXIRI or chemo doublet will receive the alternate chemo doublet as second-line treatment.

## Proposed clinical management algorithm

The proposed testing and treatment algorithm is presented in Figure 2. In the proposed treatment algorithm, a gene panel test will be required to determine both *RAS* and *BRAF* status. In this scenario, testing sites not currently using gene panel tests would no longer be eligible for MBS item 73338.

This view needs to be clarified, because the test method is not specified in proposed MBS item descriptor. It may be more likely that non-panel testing methods are not included in algorithm, because NGS panels would be the main testing method. *PASC confirmed the clinical management algorithms, noting that the gene mutation panel test specified in the algorithms is not specified in MBS item 73338, which also allows for sequential testing.*

Figure 2, compiled during preparation of the PICO, demonstrates the place of encorafenib + binimetinib + cetuximab as second-line therapy for patients with *BRAF V600*-variant mCRC. The comparator in second-line treatment is chemo doublet (FOLFIRI or FOLFOX) (Figure 1). It is difficult to ascertain this from the diagram below (which needs to be addressed). The current diagram (below) implies that the only second-line option is proposed triplet therapy.

Changes made from the applicant’s original proposed algorithm (in its Application Form) should be explained/cross-referenced against the amended version.

*PASC noted that the applicant’s response to the draft PICO provided further details of first-, second- and third-line treatment options for mCRC from the National Health and Medical Research Council (NHMRC)-approved guidelines, and considered that these should be appropriately incorporated into the proposed clinical management algorithms.*

*The Applicant reiterated that the submission to the PBAC will expand on the Australian treatment algorithms and the place of the proposed therapy in the second and third line settings, with reference to the NHMRC and other Australian Guidelines.*

Figure 2: Edited version of the proposed gene variant testing and treatment pathway for mCRC
patients – second-line treatment



Source: Compiled during PICO preparation for Application 1617 (page 22 of Application Form) to denote encorafenib + binimetinib + cetuximab as the second-line treatment among those who had already received the first-line treatment
BRAF = B-Rapidly Accelerated Fibrosarcoma, EGFR = Epidermal Growth Factor Receptor, FOLFOXIRI = FOLinic acid, Fluorouracil, OXaliplatin and IRInotecan, 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
Note: chemo doublet therapy is either FOLFOX or FOLFIRI.

The proposed algorithm implies 100% uptake of encorafenib + binimetinib + cetuximab in patients with *BRAF* variant mCRC. However, the rationale for this assumption was not provided in the Application Form.

*The Applicant acknowledged that the algorithm’s assumptions regarding uptake were simplistic and confirmed that detailed projected uptake rates will be included in the forthcoming submissions. They further confirmed that only the doublet therapy will be submitted for consideration.*

The proposed algorithm does not reflect doublet-therapy group, comprising encorafenib + cetuximab in the treatment pathway. However, the BEACON trial revealed that effectiveness of the doublet- and triplet-therapy groups was similar in terms of several outcomes, including PFS, ORR, and quality of life (29).

Additionally, patients in the doublet-therapy group had lower incidence of adverse events (grade 3 or higher) (29). The applicant should therefore substantiate reasons why the doublet-therapy intervention should not be considered for treatment of *BRAF V600*–variant mCRC patients. The NICE [final scope](https://www.nice.org.uk/guidance/gid-ta10496/documents/final-scope) considered doublet therapy and triplet therapy as intervention options in the same proposed population.

*The Applicant provided the following clarification around the place of the therapy in the treatment of mCRC (Figure 3):*

Figure 3: Place of the proposed therapy in the treatment of mCRC.

| Confirmed mCRC |
| --- |
|  |
| Most common treatment:First-line and second-line treatment options for patients with mCRC include doublet or triplet chemotherapy plus a targeted biologic |
|  |
| RAS wt treatment options | (RAS wt- not relevant to this application) |
| *Note: the decision on treatment for RAS wt patients is based on BRAF status, patient prognosis, prior treatment, left or right sided CRC.**Because BRAF status is now widely done routinely, patients are already being given either anti-EGFR + chemo doublet for BRAF wt and FOLFOXIRI or anti-VEGFR+chemo doublet for BRAF variant (see below)* |
|  |
| BRAF wt | BRAF variant |
|  | First line |
| *An epidermal growth factor receptor (EGFR) inhibitor + chemo doublet**(cetuximab or panitumumab, in combination with chemotherapy for patients with*RAS*and*BRAF*wild-type mCRC)* |  | FOLFOXIRI +Anti-VEGFROR |  |  |
|  | Anti VEGFR + chemo doublet(ie fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (FOLFOX or FOLFIRI) , an anti-vascular endothelial growth factor (anti-VEGF) therapy  |
|  |  | Second line  |  |
|  |  | Once patients progress, they would be rechallenged, with either FOLFOX or FOLFIRI +/- biologics (bevacizumab, cetuximab, panitumumab). Similarly, if they receive the doublet + bevacizumab 1st line, then 2nd line is whatever doublet they did not receive in 1st line (FOLFOX then FOLFIRI, or FOLFIRI then FOLFOX +/- biologics (bevacizumab, cetuximab, panitumumab). |  |  |
|  |  | Third line |  |  |
|  |  | 3rd line setting are a few options: BSC, enrolment in trials, cetuximab, cetuximab+irinotecan. Trifluridine-tipiracil is used in a more narrow patient population of those who have either previously received or are not suitable candidates for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent. |  |  |
| Source: Provided by Applicant as post-PASC Outcomes comment. BRAF = B-Rapidly Accelerated Fibrosarcoma, EGFR = Epidermal Growth Factor Receptor, FOLFOXIRI = FOLinic acid, Fluorouracil, OXaliplatin and IRInotecan, mCRC = metastatic colorectal cancer, PBS = Pharmaceutical Benefits Scheme, RAS = RAt Sarcoma viral oncogene homolog, wt = wild type, VEGFR = Vascular Endothelial Growth Factor ReceptorNote: chemo doublet therapy is either FOLFOX or FOLFIRI. |

*The Applicant further clarified, the treatment of mCRC in Australia is as summarised by the NHMRC-approved guidelines[[4]](#footnote-4):*

*The Australian guidance places the most commonly used comparators for encorafenib regimens as:*

* *Second line setting: FOLFOX or FOLFIRI +/- biologics such as bevacizumab, cetuximab, panitumumab*
* *Third line setting: try BSC, enrolment in trials, cetuximab, cetuximab+irinotecan. Trifluridine-tipiracil is used in a more narrow patient population of those who are have previously received or not suitable candidates for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent*

***THIRD LINE TREATMENT OF mCRC:***

*Patients in the third-line setting have limited therapeutic options. If patients retain adequate performance and after failure of all conventional agents/combinations, enrolment into a clinical trial testing novel agents/combinations should be considered.*

1. Cetuximab and panitumumab:

*In patients with RAS wild-type metastatic colorectal cancer, both cetuximab and panitumumab have shown efficacy in the third-line setting, and are equally active as single agents. Combination therapy with cetuximab and irinotecan appears more active than cetuximab alone.*

1. *Trifluridine-tipiracil:*

*Trifluridine-tipiracil has been shown to be effective in patients with refractory metastatic colorectal cancer. The PBS restriction for this agent is limited to patients who have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent for this condition; or patients who are not suitable candidates for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent.*

## Proposed economic evaluation

The Application Form stated: “it will be claimed that, in the subset of patients shown to be *RAS* wild type and *BRAF V600*-variant, treatment with encorafenib + binimetinib with cetuximab is superior to the current standard of care”. These clinical claims are based on interim analyses of phase 3 of the BEACON trial (29). Doublet-therapy with encorafenib + cetuximab could be considered an alternative intervention in the economic evaluation.

The following claims could be proposed, based on the BEACON trial (28, 29, 35):

1. Encorafenib (+ binimetinib + cetuximab) or (+ cetuximab) prolongs progression-free survival compared with the control group (i.e. standard care chemotherapies)
2. Encorafenib (+ binimetinib + cetuximab) or (+ cetuximab) improves ORR compared with the control group
3. Encorafenib (+ binimetinib + cetuximab) or (+ cetuximab) prolongs OS compared with the control group
4. Encorafenib (+ binimetinib + cetuximab) or (+ cetuximab) has non-inferior safety and tolerability profile compared with the control group
5. Encorafenib (+ binimetinib + cetuximab) or (+ cetuximab) improves the QoL of patients compared with the control group

Based on the above claims, the appropriate type of economic evaluation would be a cost-utility (or cost-effectiveness) analysis. *PASC confirmed that the appropriate economic evaluation would be a cost-utility (or cost-effectiveness) analysis*.

## Proposed MBS item descriptor and MBS fee

MBS item 73338 currently describes the tumour tissue test that determines *RAS* gene status and therefore eligibility for cetuximab or panitumumab in patients with mCRC (see Table 5). The Application Form stated that “*BRAF V600* gene variant status is reported routinely with *RAS* gene variant status, using next-generation sequencing panels”. Based on this argument, the applicant is seeking an amendment to the existing MBS item, so *BRAF V600* variant testing is included for access to encorafenib. *PASC advised that the descriptor should also include an ‘E’ after BRAF V600 in Table 6 (i.e. it should read BRAF V600E). This change has been made to Table 6 as per PASC’s advice.*

The Application Form did not propose a change to the MBS fee for item 73338. **REDACTED**. Additional information, including an average cost from all mCRC genetic panel test providers, should be provided if possible. *PASC noted that there was no proposal to increase the fee for this item.*

The Application Form anticipated that patients would require only one test per lifetime. However, the Application Form also stated that “re-testing may be required in a small minority of patients, if insufficient DNA is retrievable from biopsy cells; if the biopsy sample is not considered satisfactory (due to deterioration or formalin-associated artefacts); or if DNA testing is inconclusive.”

The proposed change to MBS item descriptor 73338 (Table 6) does not clearly define the link between components 1 and 2 of the proposed descriptor change. For clarity, and because cetuximab or panitumumab could be used without encorafenib (but encorafenib could not be used without cetuximab or panitumumab), the following text could be considered to link these two item descriptor components: “and, when also requested”.The proposed change (without clarity) could possibly widen the number of medicines accessed through item 73338 (i.e. eligibility for encorafenib + binimetinib, in addition to current eligibility for cetuximab or panitumumab). It could be that genetic panel tests would also be needed to determine eligibility for cetuximab, panitumumab, and/or encorafenib. However, the testing method is not stipulated in proposed MBS item descriptor update, so this is unlikely.

The Application Form stated that most testing is currently done using NGS panels, under the existing item descriptor (which does not specify test method). This is probably because somatic gene panels minimise the cost of testing for pathology laboratories (page 18 of Application Form). It is likely that, with the proposed descriptor expansion, non-panel testing methods will not be used.

To assist clarity on wording of the proposed item amendment, MSAC’s reasoning in Public Summary Document (PSD) 1363 should be considered (i.e. “MSAC considered the most cost-effective way of implementing an extension of *RAS* mutation [variant] testing would be to allow pathology laboratories to determine the most efficient approach to testing multiple exons, and to develop a simple single MBS item for expanded *RAS* mutation [variant] testing”. *PASC agreed with the proposed additional text and changes (in red in Table 6). PASC also advised that a restriction is required for the MBS item to allow for only one billing of the item, which is addressed by the text ‘when also requested’ (in blue in Table 6).*

Table 6: Proposed new descriptor for MBS item 73338 (edits in red and strikethrough)

| Category 6 – Pathology Services |
| --- |
| A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if:1. requirements relating to rat sarcoma oncogene ~~(RAS)~~ (*RAS*) gene ~~mutation~~ variant status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:
2. the test is conducted for all clinically-relevant ~~mutations~~ variants on KRAS exons 2, 3 and 4, and NRAS exons 2, 3, and 4; or
3. a clinically-relevant RAS ~~mutation~~ variant is found;

**and, when also requested**1. requirements relating to *BRAF* V600E gene variant status for access to encorafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

**MBS Fee: $362.60 Benefit: 75% = $271.95 85% = $308.25** |

Source: Page 26 of MSAC Application Form 1617

BRAF = B-Rapidly Accelerated Fibrosarcoma, KRAS = Kirsten Rat Sarcoma Oncogene, NRAS = Neuroblastoma Rat Sarcoma Oncogene, RAS = Rat Sarcoma Oncogene, PBS = Pharmaceutical Benefits Scheme

**Consultation feedback**

*PASC noted the consultation feedback from the Medical Oncology Group of Australia Inc., which supports the application, with the following clarifications:*

* *BRAF variants are estimated to occur in around 10% of mCRC patients; BRAF V600 is the most common variant identifying a subtype of mCRC that has a poor prognosis and no available targeted therapies*
* *Supported the applicant’s claim that BRAF V600 testing is routinely performed and reported as part of NGS tumour panels, even though it is not specified in MBS item 73338.*

**Next steps**

*PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process. PASC agreed that the following clinical questions would need to be resolved by ESC at that time:*

* *While the cost to the MBS would be minimal, the cost to the PBS may be substantial. What is the difference in cost of treatment between the intervention and comparators?*
* *What BRAF* V600E *test methodologies were used in the BEACON trial?*
* *What is the diagnostic accuracy (sensitivity, specificity) and the concordance between BRAF* V600E *test methodologies (NGS vs non-NGS PCR-based assays)?*

*PASC noted the applicant elected to progress its application as an ADAR (applicant-developed assessment report) in the form of an integrated codependent submission.*

**References**

***(Please note: Where publication titles include ‘mutation’, ‘mutations’, ‘mutant’ or ‘mutated’, these have been retained, noting the current correct terms are ‘variant’ or ‘variants’)***

1. Goel A, Boland CR. Recent insights into the pathogenesis of colorectal cancer. Current opinion in gastroenterology. 2010;26(1):47.
2. Rutter MD, Beintaris I, Valori R, Chiu HM, Corley DA, Cuatrecasas M, et al. World endoscopy organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. Gastroenterology. 2018;155(3):909-25. e3.
3. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer. 2018.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
5. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer treatment reviews. 2015;41(9):729-41.
6. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clinics in colon and rectal surgery. 2009;22(04):191-7.
7. Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. International journal of colorectal disease. 2015;30(2):205-12.
8. van der Geest LG, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. Clinical & experimental metastasis. 2015;32(5):457-65.
9. Van der Pool A, Damhuis R, Ijzermans J, de Wilt J, Eggermont A, Kranse R, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population‐based series. Colorectal Disease. 2012;14(1):56-61.
10. Australian Institute of Health and Welfare 2019. Cancer in Australia 2019. Cancer series no.119, Cat. no. CAN 123. Canberra: AIHW.
11. Morris G, Shukla S, Bennetts R, Harvery J, McGlynn L, Ellis M. Health System Expenditure on Cancer and Other Neoplasms in Australia 2008–09. 2013.
12. Classification IUaCCoT. TNM classification of malignant tumours: International Union Against Cancer; 1974.
13. Health AIo, Welfare. Cancer data in Australia. Canberra: AIHW; 2019.
14. Rodriguez-Bigas M, Lin E, Crane C. Stage IV colorectal cancer. Holland-Frei Cancer Medicine Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF and Frei E. 2003;2.
15. Valderrama-Treviño AI, Barrera-Mera B, Ceballos-Villalva JC, Montalvo-Javé EE. Hepatic metastasis from colorectal cancer. Euroasian journal of hepato-gastroenterology. 2017;7(2):166.
16. Riihimäki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Scientific reports. 2016;6(1):1-9.
17. Raimondi C, Nicolazzo C, Belardinilli F, Loreni F, Gradilone A, Mahdavian Y, et al. Transient disappearance of RAS mutant clones in plasma: A counterintuitive clinical use of EGFR inhibitors in RAS mutant metastatic colorectal cancer. Cancers. 2019;11(1):42.
18. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken J, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology. 2016;27(8):1386-422.
19. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. The Lancet. 2011;377(9783):2103-14.
20. Tran B, Kopetz S, Tie J, Gibbs P, Jiang ZQ, Lieu CH, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011;117(20):4623-32.
21. Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. Journal of clinical oncology. 2012;30(15):1755-62.
22. Barras D. BRAF Mutation in Colorectal Cancer: An Update: Supplementary Issue: Biomarkers for Colon Cancer. Biomarkers in cancer. 2015;7:BIC. S25248.
23. Larki P, Gharib E, Yaghoob Taleghani M, Khorshidi F, Nazemalhosseini-Mojarad E, Asadzadeh Aghdaei H. Coexistence of KRAS and BRAF Mutations in Colorectal Cancer: A Case Report Supporting The Concept of Tumoral Heterogeneity. Cell J. 2017;19(Suppl 1):113-7.
24. Ardekani GS, Jafarnejad SM, Tan L, Saeedi A, Li G. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. PloS one. 2012;7(10).
25. Kopetz S, Desai J, Chan E, Hecht JR, O'Dwyer PJ, Maru D, et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. Journal of clinical oncology. 2015;33(34):4032.
26. Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004;116(6):855-67.
27. Luu L-J, Price TJ. BRAF mutation and its importance in colorectal cancer. Advances in the Molecular Understanding of Colorectal Cancer: IntechOpen; 2019.
28. Van Cutsem E, Huijberts S, Grothey A, Yaeger R, Cuyle P-J, Elez E, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E–mutant metastatic colorectal cancer: safety lead-in results from the phase iii Beacon colorectal cancer study. Journal of Clinical Oncology. 2019;37(17):1460-9.
29. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019;381(17):1632-43.
30. Cancer diagnosis: Histopathology, cytology and tumour markers [Internet]. Cancer Council Australia. [cited 6 March 2020]. Available from: [https://wiki.cancer.org.au/oncologyformedicalstudents/Cancer\_diagnosis:\_Histopathology,\_cytology\_and\_tumour\_markers](https://wiki.cancer.org.au/oncologyformedicalstudents/Cancer_diagnosis%3A_Histopathology%2C_cytology_and_tumour_markers).
31. Naional Institute for Health and Care Excellence. Draft scope for the appraisal of encorafenib with binimetinib and cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer. 2019.

- NICE's **Final scope** is at https://www.nice.org.uk/guidance/gid-ta10496/documents/final-scope.

- Current NICE application for encorafenib in dual or triple therapy for previously treated *BRAF V600E*-variant mCRC is at https://www.nice.org.uk/guidance/indevelopment/gid-ta10496

- USA National Comprehensive Cancer Network (NCCN) guidelines are at:
<https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/rectal_blocks.pdf>

- Australia’s Cancer Institute (NSW) EviQ clinical guidelines are at: <https://www.eviq.org.au/medical-oncology/colorectal>).
32. NATA procedures for accreditation [Internet]. National Association of Testing Authorities, Australia. [cited 6 March 2020]. Available from: <https://www.nata.com.au/phocadownload/gen-nata-docs/NATA-procedures-for-accreditation.pdf>.
33. Medicare Services Advisory Committee. Public Summary Document: Application No. 1362.1 – Cetuximab and KRAS mutation testing under MBS 73330. 2014.
34. Medicare Services Advisory Committee. Public Summary Document: Application 1363 – RAS (KRAS and NRAS) mutation testing for eligibility to access panitumumab. 2014.
35. Kopetz S, Grothey A, Cutsem EV, Yaeger R, Wasan HS, Yoshino T, et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC). Journal of Clinical Oncology. 2020;38(4\_suppl):8-.
36. Systemic options for second-line treatment [Internet]. 2017 [cited 10 March 2020]. Available from: [https://wiki.cancer.org.au/australia/Guidelines:Colorectal\_cancer/Systemic\_options\_second-line\_treatment](https://wiki.cancer.org.au/australia/Guidelines%3AColorectal_cancer/Systemic_options_second-line_treatment).
37. Genomics in general practice [Internet]. 2019 [cited 7 March 2020]. Available from: <https://www.racgp.org.au/FSDEDEV/media/documents/Clinical%20Resources/Guidelines/Genomics-in-general-practice.pdf>.
1. Average number of patients utilising MBS item 73338 over two-year period (2015-16 and 2016-17) = (2,654+2,287)/2 = 2,471 [Source: Public Summary Document Report to the Medical Services Advisory Committee on utilisation of MBS item 73338 following Applications 1362 and 1363: RAS variant testing for

eligibility for panitumumab and cetuximab in previously untreated metastatic colorectal cancer patients. [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/3AB4337273F7E5D7CA25801000123BE0/$File/PvA%201362-1363%20Final%20PSD.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/3AB4337273F7E5D7CA25801000123BE0/%24File/PvA%201362-1363%20Final%20PSD.pdf), accessed 21 February 2020] [↑](#footnote-ref-1)
2. MLH1 is one among four DNA mismatch repair (MMR) proteins (along with MSH2, MSH6 and PMS2) that play part in DNA replication. MMR deficiency results in a cancer due to increased rate of mutation (by up to 10- to 100-fold) [↑](#footnote-ref-2)
3. Microsatellite instability tests are short tandem DNA repeat sequences of 1- 6 bases present along the coding/non-coding regions of the genome. They are prone to replication errors which would otherwise be repaired by the MMR process. [↑](#footnote-ref-3)
4. Clinical Guidelines network: Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 October 2017 under section 14A of the National Health and Medical Research Council Act 199 [↑](#footnote-ref-4)