

## **MSAC Application 1779**

**Testing of tumour tissue to detect *FGFR2* fusions or rearrangements in people with cholangiocarcinoma, to determine eligibility for treatment with PBS subsidised futibatinib**

**Applicant: Taiho Pharma Oceania Pty Ltd**

# **PICO Confirmation**

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

Table 1 PICO for *FGFR2* fusions or rearrangements testing in patients with cholangiocarcinoma (CCA)

Component	Description
Population	<p><b>Test:</b> Adult patients with cholangiocarcinoma (CCA)</p> <p><b>Treatment:</b> Adult patients with locally advanced or metastatic CCA who have disease progression following at least one line of systemic therapy</p>
Prior tests	Histological confirmation of CCA
Intervention	<p><b>Test:</b> Tumour tissue testing for <i>fibroblast growth factor receptor 2 (FGFR2)</i> gene fusions or rearrangements using ribonucleic acid (RNA) with next-generation sequencing (NGS)</p> <p><b>Alternate test (for comparison with NGS on RNA):</b> Tumour tissue testing for <i>fibroblast growth factor receptor 2 (FGFR2)</i> gene fusions or rearrangements using fluorescence <i>in situ</i> hybridisation (FISH) testing on deoxyribonucleic acid (DNA)</p> <p><b>Treatment:</b> Futibatinib as second- or subsequent line treatment in patients with locally advanced or metastatic CCA harbouring a <i>FGFR2</i> fusion or rearrangement</p>
Comparators	<p><b>Test:</b> No testing for <i>FGFR2</i> fusions or rearrangements</p> <p><b>Treatment:</b> Second- or subsequent line treatment with standard of care chemotherapy or palliative care with active symptom control</p>
Clinical utility standard	NGS for detection of <i>FGFR2</i> fusions or rearrangements in DNA from tumour tissue
Outcomes	<p><b>Test-performance related outcomes:</b></p> <ul style="list-style-type: none"> <li>• Treatment effect modification for futibatinib based on presence/absence of <i>FGFR2</i> fusions or rearrangements (predictive validity)</li> <li>• Prognostic implications of <i>FGFR2</i> fusions or rearrangements</li> <li>• Concordance between the proposed test (on RNA), and FISH on DNA and the clinical utility standard (on DNA) (overall, positive percent agreement and negative percent agreement) and implications of cases of discordance</li> <li>• Comparative test performance of NGS RNA testing, NGS DNA testing and FISH testing on DNA</li> <li>• Comparative reliability of the test methods (proportion of failed and equivocal test results, inter-rater reliability, inter-laboratory variability/agreement)</li> <li>• Stability of the biomarker in tissue samples</li> </ul> <p><b>Other test-related considerations:</b></p> <ul style="list-style-type: none"> <li>• Number estimated to be tested &amp; diagnostic yield of each method</li> <li>• Number needed to test (to identify one case eligible for futibatinib), taking into account the proportion of patients whose CCA does not progress to being locally advanced or metastatic</li> </ul>

Component	Description
	<ul style="list-style-type: none"> <li>• Test turn-around times</li> <li>• Rate of re-biopsy (including due to test failure for <i>FGFR2</i> testing, and inadequate sample rate)</li> <li>• <i>FGFR2</i> test failure rate</li> <li>• Safety of re-biopsy</li> </ul> <p><b>Treatment-related outcomes:</b></p> <ul style="list-style-type: none"> <li>• Critical outcomes (GRADE): Progression-free survival (PFS) Overall survival (OS) Objective response rate (ORR)</li> <li>• Important outcomes (GRADE): Time from randomisation to discontinuation or death (TDT) Health-related quality of life (HRQoL)</li> <li>• Safety and tolerability: Treatment-emergent adverse events (TEAEs) Physical examination and laboratory findings</li> </ul> <p><b>Health care system:</b></p> <ul style="list-style-type: none"> <li>• Cost of testing and associated re-biopsies per patient</li> <li>• Cost-effectiveness of testing and treatment</li> <li>• Financial implications</li> </ul>
<p>Assessment questions (<i>for the full list see 'Assessment framework'</i>)</p>	<ul style="list-style-type: none"> <li>• What is the safety, effectiveness, cost-effectiveness and total costs of testing for <i>FGFR2</i> fusions or rearrangements and targeted treatment with futibatinib versus no testing and standard of care chemotherapy or palliative care in patients with locally advanced or metastatic CCA who have disease progression following at least one line of systemic therapy?</li> <li>• Do results from the testing for <i>FGFR2</i> fusions or rearrangements using (i) NGS testing and (ii) FISH testing predict a treatment effect modification with futibatinib? Is this distinguishable from the variation in prognosis following the results of <i>FGFR2</i> fusions or rearrangements testing?</li> <li>• Do the methods proposed for <i>FGFR2</i> fusion or rearrangement testing detect the same cases as the clinical utility standard? If not, what are the implications of the additional cases detected (will they respond to futibatinib to the same degree as those detected by the clinical utility standard?)</li> </ul>

ECOG PS = Eastern Cooperative Oncology Group performance status

Note: Standard of care chemotherapy refers to 5-Fluorouracil (FU) and oxaliplatin (FOLFOX) (recommended) or 5-FU and irinotecan (FORFIR)

## Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of tumour tissue testing for *fibroblast growth factor receptor 2 (FGFR2)* gene fusions or rearrangements for the determination of patient eligibility for treatment with futibatinib.
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of futibatinib (Lytgobi®) for the treatment of patients with locally advanced or metastatic cholangiocarcinomas (CCAs) who have an *FGFR2* fusion or rearrangement and have disease progression after first or subsequent-line treatment.

Clinical claim:

Testing of tumour tissue to detect *FGFR2* fusions or rearrangements, followed by targeted therapy with futibatinib results in superior health outcomes compared to no testing and standard of care chemotherapy or palliative care with active symptom control in patients with locally advanced or metastatic CCAs.

## PICO criteria

### **Population**

The population proposed for *FGFR2* variant testing is patients with CCA. The proposed population for futibatinib is patients with locally advanced or metastatic CCA who have disease progression following first- (or later) line systemic therapy and have *FGFR2* fusions or rearrangements.

CCA is a rare cancer arising from the epithelial cells of the bile ducts, a group of small tubes that convey the bile (a digestive fluid produced in the liver) to the gallbladder and eventually to the small intestine. CCA can arise from bile ducts that are within the liver (i.e., intrahepatic CCA, or iCCA) or from bile ducts outside of the liver (i.e., extrahepatic CCA, or eCCA). iCCA is the second most common primary liver tumour after hepatoma (Banales et al. 2016).

CCAs comprise approximately 3% of all gastrointestinal cancers. The incidence of CCA has been reported to be 0.3-6 cases per 100,000 people per year worldwide, and 0.43 cases per 100,000 in Australia (Banales et al. 2016). In areas where there is endemic liver fluke infection caused by *Opisthorchis viverrine* and *Clonorchis sinensis*, such as China, Thailand, Vietnam, Cambodia, and Korea, the incidence can be much higher (incidence of 85 per 100,000 has been reported in northeast Thailand and where CCA represents approximately 85% of total primitive liver cancers) (Banales et al. 2016; Poomphakwaen et al. 2009). eCCA has been reported to account for more than 80% of all CCAs in the United States (Banales et al. 2016). In Australia, the true incidence of iCCA and eCCA is unknown.

The incidence of CCA has been rising in the past few decades as a global trend, with the increase of incidence in iCCA being more obvious, likely owing to a growing population with conditions such as cirrhosis, hepatitis B and C, excess alcohol, obesity, and diabetes that result in chronic liver inflammation (Forner et al. 2019). Primary sclerosing cholangitis (PSC), a rare condition characterised by long-term inflammation and scarring

of the bile ducts and most commonly affects people with inflammatory bowel disease, has been found to account for a 240-fold increased risk for development of CCA and its related deaths in an Australian retrospective cohort study (Tan et al. 2022). People with rare congenital abnormalities of the biliary tree such as choledochal cyst and Caroli disease (which has a higher incidence among Asians) also carry an increased risk for the development of CCA (Forner et al. 2019).

CCA is diagnosed in around 1,300 people in Australia each year<sup>1,2</sup>. The cancer typically affects individuals aged between 50 and 70 years, and males are slightly more affected than females (Van Dyke et al. 2019). Patients with CCA are frequently asymptomatic early in the disease trajectory and therefore, the cancer frequently has a dismal prognosis because it tends to be diagnosed in advanced stages (Banales et al. 2016). Early stage CCAs are detected in approximately 35% of patients (Li, Y, Song & Liu 2022). However, even among patients who are diagnosed with early stage CCA and qualify for surgery for tumour resection (the only potentially curative treatment), the relapse rate is high (range 42% to 70%), with most cancer relapses occurring in the form of distant metastases, with the liver being the most prevalent site of cancer recurrence (Ebata et al. 2018; Horgan et al. 2012; Koerkamp et al. 2015; Lamarca, Angela et al. 2020). The presence of underlying liver diseases such as PSC, viral hepatitis, and cirrhosis, are major risk factors for both development of iCCA and for increased recurrence after surgical resection, with recurrence rate up to 70% (Bekki et al. 2021). The presence of underlying liver disease also limits patients' likelihoods of qualifying for major resection, which is often necessary for an optimal long-term survival (Bekki et al. 2021). For patients diagnosed with localised iCCA who have undergone surgical resection, most recurrences occur within 2 years of resection, which is defined as early recurrence (Doussot et al. 2016). For those whose CCAs recur within 6 months of resection, (defined as the very early recurrence (VER) and accounts for approximately one quarter of patients with localised iCCAs who underwent surgical resection), survival was dismal compared to those without VER (5-year overall survival 8.9% vs. 49.8%;  $p < 0.001$ ) (Bekki et al. 2021; Tsilimigras et al. 2020).

The five-year survival rate in patients diagnosed with localised CCA was reported to be 23% in 2018<sup>3</sup>. The overall 5-year relative survival rate for eCCA reported by the American Cancer Society<sup>4</sup> was 11% between 2012 and 2018, and the 5-year survival rates for eCCA that has spread to the regional lymph nodes (locally advanced) and metastatic eCCA were reported to be 18% and 2%, respectively. The Australian Cancer Research Foundation reported the 5-year survival rate for eCCA in Australia to be 15% in 2018. For iCCA, the American Cancer Society reported the 5-year survival rates for overall, localised, locally advanced, and metastatic iCCA to be 9%, 23%, 9%, and 2% respectively. No Australian survival data specific for iCCA were identified.

Signs and symptoms of CCA depend upon the location of the tumour lesion. Jaundice (yellowish or greenish pigmentation of the skin and the mucous membranes) is the common manifestation in patients with eCCA

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<sup>1</sup> Australian Institute of Health and Welfare URL: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/stage> [Accessed 19 June 2024]

<sup>2</sup> Cholangiocarcinoma Foundation Australia URL: <https://cholangiocarcinomaaustralia.org/key-statistics/> [Accessed 19 June 2024]

<sup>3</sup> The Australian Cancer Research Foundation: Bile Duct Cancer URL: <https://www.acrf.com.au/support-cancer-research/types-of-cancer/bile-duct-cancer/> [Accessed 19 June 2024]

<sup>4</sup> American Cancer Society: Survival Rates for Bile Duct Cancer URL: <https://www.cancer.org/cancer/types/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html>. [Accessed 19 June 2024]

due to the obstruction of the bile outflow. Other signs and symptoms indicating bile outflow obstruction include pale stools, dark urine, and pruritus (Forner et al. 2019). Patients with iCCA can also present with jaundice but usually at a later stage, while a significant proportion of iCCA cases are incidental findings, especially in early stages (Cardinale et al. 2018). Apart from jaundice, CCA can associate with other non-specific symptoms including abdominal pain, nausea, weight loss, night sweats, or fatigue. Liver function testing may show abnormalities in early stages of the disease. Clinically, iCCA remains a diagnostic challenge. (Forner et al. 2019).

The usually late diagnosis of CCA, the high cancer relapse rate in patients with localised CCA who undergo surgery, and the limited systemic treatment options for patients with locally advanced or metastatic CCA are the main reasons for the poor prognosis. At present, there are no PBS-listed targeted treatments available in current practice in the Australian setting for this patient population.

*PASC noted that CCA is a very rare cancer (approximately 1300 per year in Australia), with a very low survival rate (only 2% in metastatic disease).*

*PASC noted that the applicant had sought clinical advice that suggested that the population to be tested should be those diagnosed with CCA. The test results can take 2-3 weeks for a small RNA fusion panel or 6-8 weeks for a large panel to be returned, so results usually become available while the patient is receiving first-line systemic treatment. PASC supported testing for FGFR2 gene fusion at the point of diagnosis, regardless of stage, as CCA is a rapidly progressive disease. Testing at point of diagnosis would also streamline the diagnostic process and allow more efficient use of diagnostic tissue. PASC also noted applicant's clinical expert advice that performing testing at diagnosis would ensure use of high-quality nucleic acids which would be crucial especially if RNA testing is performed.*

*Management of CCA patients in the lead up to testing for FGFR2 fusions or rearrangements of tumour tissue*  
Symptomatic patients are assessed by general practitioners to evaluate the presence of jaundice and to look for signs of chronic liver dysfunction through physical examination (Fargo, Grogan & Saguil 2017). When necessary, laboratory investigations (including liver function tests and serum bilirubin level) and imaging studies (likely to be ultrasound or computed tomography (CT)) are organised to further evaluate the presence of cholestasis (caused by bile outflow obstruction) and its possible aetiology. Patients with specific findings are referred to specialists' services, where further imaging studies are arranged to confirm the presence of a tumour causing the biliary obstruction and for staging purposes in case of a malignancy. These studies can include magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cholangiography (endoscopic or percutaneous), or positron emission tomography (PET). The cancer is staged according to the TNM classification system developed by the American Joint Committee on Cancer (AJCC), where T reflects the extent of the primary tumour, N is the extent of regional lymph node infiltration and M indicates the presence of distant metastases (American Cancer Society 2022).

Once the presence of a tumour is confirmed, the investigation typically proceeds to a biopsy of the tumour for a histological confirmation of CCA to be made by a pathologist. Where feasible and safe, core biopsy is recommended, in order to obtain sufficient tissue for further detection of genomic alteration in the tumour such as *FGFR2* fusions or rearrangement, as recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) as part of the routine diagnostic procedure for patients with CCA, particularly for those with confirmed locally advanced or metastatic CCA and will receive systemic therapy as their first-line treatment (Lamarca, A., Edeline & Goyal 2022; NCCN Guidelines Version

2. 2023 ; Vogel et al. 2023). Fine needle aspiration is an alternative for obtaining CCA tumour tissue (Forner et al. 2019).

#### *Biological rationale for targeting FGFR2 fusions or rearrangements with futibatinib*

FGFR2 is a member of the family of fibroblast growth factor receptors (FGFRs) that play a critical role in signal transduction within cells. Four FGFRs (FGFR 1-4) function as receptor tyrosine kinase and are responsible for the phosphorylation (i.e., transferring a phosphate group from adenosine triphosphate (ATP)) of their fibroblast growth factor (FGF) ligands, the polypeptide growth factors that regulate a number of cellular activities including proliferation and differentiation (Teven et al. 2014). The binding of an FGF ligand at the cell surface results in FGFR dimerisation, which subsequently triggers the intracellular FGF-FGFR signalling pathway. Aberrant FGF-FGFR signalling has been shown to have the role of oncogenic driver by enhancing cellular proliferation, migration, survival, and invasion, as well as angiogenesis (Babina & Turner 2017).

FGFR2 is encoded by the *FGFR2* gene located on chromosome 10 (Normanno 2021). *FGFR2* fusions have been classified as level I genomic alteration according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) (Mosele et al. 2020). *FGFR2* fusions or rearrangements have also been classified as Tier I variants (i.e., variants with strong clinical significance) in CCA, according to the Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists (Li, MM et al. 2017). As one of the most prevalent actionable molecular targets found in CCA, between 9% and 15% of iCCAs are expected to harbour one or more *FGFR2* fusion genes, and this form of genomic alteration has been found to occur nearly exclusively in iCCA (Arai et al. 2014; Goyal et al. 2021; Kendre et al. 2023). *FGFR2* fusions in iCCA have also been associated with younger age and female gender at diagnosis, as well as a better prognosis (Graham et al. 2014; Jain et al. 2018; Niu et al. 2024). *FGFR2* gene fusions originate by chromosomal rearrangements, and approximately 50% of the rearrangements occur within the same chromosome (i.e., intrachromosomal), with many of other fusion partner genes fuse at a consistent breakpoint with the *FGFR2* gene (Borad et al. 2014; Goyal et al. 2021). *FGFR2-BICC1* fusion is the most common *FGFR* gene aberration (Arai et al. 2014; Jain et al. 2018). The two most common actionable molecular targets in iCCA, *FGFR2* fusions or rearrangements and *IDH1* R132X variants, have been found to be mutually exclusive (Murugesan et al. 2022).

*FGFR2* fusions encode fusion proteins with oncogenic ability which can be suppressed by a FGFR inhibitor, such as futibatinib. Futibatinib selectively and irreversibly inhibits FGFR 1-4 by forming a covalent adduct with a conserved cysteine residue in the FGFR kinase domain P-loop structure (Sootome et al. 2020). Despite the considerable number of fusion partner genes described, recent evidence supports that the presence of the *FGFR2* fusion itself is responsible for the sensitivity to FGFR inhibitor, regardless of the fusion partner identified (Silverman et al. 2019).

*PASC noted that FGFR2 gene fusions were a relevant biomarker, regardless of the fusion gene partner.*

Note: Niu et al. (2024) report on a meta-analysis of studies assessing overall survival and disease-free survival in iCCA patients with and without *FGFR2* alterations, undergoing either systemic therapy or surgical resection, showing a non-statistically-significant trend favouring patients with *FGFR2* alterations in the context of overall survival (HR 1.31, 95%CI 1.00, 1.72, k=6). Rizzato et al. (2022) reported the median overall survival from start of second line therapy for iCCA was 24.7 months in those with *FGFR2* fusions, and 10.0 months in those without *FGFR2* fusions (HR 0.37, 95%CI 0.12, 1.19, p=0.08).

## Intervention

### Tests

Currently, no testing for *FGFR2* fusions or rearrangements is publicly funded in Australia. The applicant has proposed a new MBS items for testing patients for the presence of fusions or rearrangements in the *FGFR2* gene using NGS on RNA, in CCA tumour tissue obtained via biopsy. If inadequate tumour sample is available, a re-biopsy would be required to provide a tissue sample for testing. This would likely be a liver biopsy, as the majority of cancers spread to the liver (Lamarca, Angela et al. 2020). The testing is proposed to be once in a patient's lifetime. The applicant proposed testing of RNA using next generation sequencing (NGS), with fluorescence *in situ* hybridisation (FISH) of DNA as an alternative method. The test results will serve to determine the patients' eligibility for PBS-subsidised futibatinib treatment either when diagnosed with, or on progression to, locally advanced or metastatic CCA.

NGS is a high-throughput DNA and/or RNA sequencing method that allows sequencing of many target genes at the same time. NGS typically involves 4 steps: (1) Constructing the DNA "library"; (2) amplifying the library clonally; (3) sequencing the library, and (4) analysing data<sup>5</sup>. The method can be used on formalin-fixed, paraffin-embedded (FFPE) tissue, and Carrick et al (2015) have demonstrated the feasibility and reliability of conducting NGS on older FFPE tumour tissue samples in their study, regardless of storage time. In the key study (FOENIX-CCA2), the confirmation testing for *FGFR2* fusions or rearrangements was carried out on either fresh or archival FFPE tumour tissue samples (Goyal et al. 2023). Tumour tissue samples are often minimal and gene panels may provide a more efficient use of the limited tissue available. However, as per previous MSAC Executive advice, CCA gene panel testing should provide prognostic information for clinical decision-making for it to be appropriate under MBS funding arrangements.

When detecting *FGFR2* fusions using DNA sequencing, detection can be limited by the presence of intronic regions (i.e., the non-coding DNA regions) within the fusion gene (De Luca et al. 2020). ESMO recommends RNA sequencing to be included for detection (Normanno 2021). For RNA-based method, the level of fusion expression can affect the method's sensitivity (De Luca et al. 2020). RNA is also less stable than DNA, especially when FFPE samples are used (De Luca et al. 2020). In combination of cytogenetics (i.e., the study of the structure and properties of chromosomes), FISH employs fluorescently labelled probes that bind to specific complementary target DNA sequences. Signals are then detected using the fluorescence microscopy (Speicher & Carter 2005). The break-apart FISH assay, in particular, uses two differently labelled (usually red and green) DNA probes specific for loci that are physically close in the wild-type configuration to allow identification of gene translocations. Since rearrangements increase the distance between the loci, an orange signal (derived from overlapping red and green) indicates wild-type (unaltered gene), whereas a separate red and green signal pattern indicates gene rearrangements (Cheng et al. 2017). FISH using dual colour probe is also capable of detecting cryptic chromosomal rearrangements (De Braekeleer et al. 2010). FISH has a relatively fast turnaround time, can be performed on formalin-fixed, paraffin-embedded (FFPE) samples, and does not require living cells (De Luca et al. 2020). Despite its good sensitivity and specificity to detect *FGFR2* fusions (Maruki et al. 2021), complex rearrangements can be missed due to the low resolution.

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<sup>5</sup> What is Next-Generation Sequencing (NGS)? URL: [https://www.thermofisher.com/au/en/home/life-science/sequencing/sequencing-learning-center/next-generation-sequencing-information/ngs-basics/what-is-next-generation-sequencing.html#:~:text=Next%2Dgeneration%20sequencing%20\(NGS\),diseases%20or%20other%20biological%20phenomena](https://www.thermofisher.com/au/en/home/life-science/sequencing/sequencing-learning-center/next-generation-sequencing-information/ngs-basics/what-is-next-generation-sequencing.html#:~:text=Next%2Dgeneration%20sequencing%20(NGS),diseases%20or%20other%20biological%20phenomena)



Intrachromosomal rearrangements can also lead to false-negative results of FISH analysis (De Luca et al. 2020). FISH is restricted to the detection on DNA.

*PASC noted that the applicant had originally requested NGS on DNA and RNA, and for FISH to be used where NGS testing was not available. However, the applicant's pre-PASC response proposed NGS on RNA only as the test intervention (i.e. remove FISH testing) based on advice from local experts that laboratories in Australia do not currently provide FISH testing of tumour tissue to detect FGFR2 status.*

*PASC discussed that FISH testing is useful when samples are too small or fragmented to be tested using NGS on RNA, and that it wouldn't be difficult to implement FISH testing for FGFR2, as a commercial FISH probe is available for FGFR2 testing<sup>6</sup>. However, given the rarity of the disease, it may not be economical for laboratories to perform FISH testing for FGFR2 unless there could be economies of scale (such as if one laboratory became the referral laboratory for FISH testing for FGFR2).*

*PASC noted that the applicant's clinical advice suggested that both RNA testing and DNA testing was not required, and that a small RNA fusion panel was appropriate for testing for FGFR2 fusions and rearrangements. The applicant's clinical expert advice also noted that full biopsy specimens for testing are often difficult to obtain for this patient group, and as a result samples obtained may be smaller and/or fragmented.*

*PASC considered the applicant's proposal for NGS on RNA reasonable. However, a method agnostic item may be reasonable noting that other testing methodologies such as NGS on DNA, and FISH testing of tumour tissue, could be used in Australia, and should therefore be evaluated to show the comparative test performances.*

*PASC agreed with the applicant's suggestion to not include testing on ctDNA, and applicant's clinical expert advice which suggested that cytology smears and archival tissue blocks should be included.*

### *Treatment*

For patients with locally advanced or metastatic CCA whose disease has progressed following at least one line of systemic therapy, the applicant is proposing the use of futibatinib as a targeted therapy for those with *FGFR2* fusions or rearrangements. Futibatinib was granted orphan drug designation (ODD) by the Therapeutic Goods Administration (TGA) in December 2023 for the treatment of CCA<sup>7</sup> and has been submitted for assessment by TGA.

Futibatinib is an oral kinase inhibitor that selectively and irreversibly inhibits FGFR 1-4 (Sootome et al. 2020). Its action results in the inhibition of the aberrant intracellular FGF-FGFR signalling pathways that play a critical role in tumourigenesis and cancer progression. In the key study of futibatinib (FOENIX-CCA2) presented in the application, treated patients were diagnosed with locally advanced or metastatic iCCA whose disease progressed on one or more prior lines of systemic therapy (patients previously treated with an FGFR inhibitor were excluded) and their tumour tissues harboured *FGFR2* fusions or rearrangements. All treated patients in the study were with good performance status (Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1) and without a history of or current clinically significant retinal disorder or a disorder of calcium-phosphorus metabolism that was not associated with their cancer (Goyal et al. 2023).

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<sup>6</sup> <https://www.molecular.abbott/int/en/products/oncology/all-solid-tumor>

<sup>7</sup> Therapeutic Goods Administration. Notice for Futibatinib (Adjutor Healthcare Pty Ltd). URL: <https://www.tga.gov.au/resources/designations-determinations/notice-futibatinib-adjutor-healthcare-pty-ltd-0>

In those without *FGFR2* fusions or rearrangements, the non-targeted treatment options are the same as for the comparator.

*PASC noted that although the 'Intervention' had been defined so that the total population included was the same as included for the 'Comparator' (i.e. those both with and without the biomarker), it was confusing defining the treatment for biomarker negative patients. The treatment intervention has therefore been defined as the targeted treatment, although for those without the biomarker, current treatment options as per the comparator are relevant.*

## **Comparators**

### *Test*

For patients with CCA, there is no testing for *FGFR2* fusions or rearrangements in the current clinical management pathway. Therefore, the comparator for the proposed testing is 'no testing for *FGFR2* fusions or rearrangement'.

### *Treatment*

The proposed comparator is standard of care (SOC) chemotherapy or palliative care with active symptom control. Following progression on first-line treatment, second-line 5-Fluorouracil (FU) and oxaliplatin (FOLFOX) is the preferred chemotherapy regimen for patients with disease progression and good performance status (ECOG PS < 2) (eviQ 2021; Lamarca, A. et al. 2021; NCCN Guidelines Version 2. 2023). Palliative care with active symptom control is generally the management in the second- and beyond line settings for patients who are more fragile (ECOG PS ≥ 2), those who cannot tolerate the toxicities from chemotherapy or those who elect no further treatment.

In the application, futibatinib is indicated to fully replace SOC chemotherapy in the second- and later line treatment settings in patients tested positive for the biomarker. For patients who have tested positive for the biomarker and whose disease progress following SOC chemotherapy, futibatinib is expected to replace palliative care in patients who are eligible for the drug. As such, palliative care may be a comparator in the subsequent line settings.

There is no PBS-listed targeted therapy for CCA in the Australian setting. Pemigatinib, an inhibitor of FGFR1, 2 and 3, has TGA's provisional approval for the treatment of adult patients with locally advanced or metastatic CCA with a *FGFR2* fusion or rearrangement that has progressed after at least one prior line of systemic therapy<sup>8</sup>. However, no submission has been made for PBS-listing of pemigatinib, so it is unlikely that application 1779 need consider pemigatinib as a near-market comparator. A request for PBS-listing for ivosidenib, a drug targeting the *IDH1* R132X variants in CCA, was considered at the July 2024 Pharmaceutical Benefits Advisory Committee (PBAC) meeting (outcome not yet published). Ivosidenib, together with the *IDH1* variant testing for the determination of patients' eligibility to the drug, may appear in the future. A scenario including the testing for *IDH1* variants in CCA disease workup and ivosidenib in the treatment algorithms is presented in the Appendix. It should be noted that ivosidenib would not be a comparator to futibatinib, as *IDH1* and *FGFR2* variants are reported to be mutually exclusive in CCAs.

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<sup>8</sup> Australian Product Information - Pemazyre®(pemigatinib). Available from URL: <https://www.tga.gov.au/sites/default/files/2023-07/auspar-pemazyre-230703-pi.pdf> [Accessed 18 July 2024]

*PASC noted that the treatment comparators proposed were non-targeted chemotherapy or palliative care, and that confirming the appropriate treatment comparator was a matter for PBAC consideration. PASC agreed with the applicant comments that the choice of chemotherapy or palliation is made on more factors than ECOG performance status, and patient choice is important.*

*PASC recommended that the 'comparator' should not reference or mention biomarker status, as it does not make sense (in the absence of testing).*

### **Clinical utility standard**

The clinical utility standard is defined as DNA-based NGS to identify *FGFR2* fusions or rearrangements.

The test method used in the FOENIX-CCA2 study to identify patients with an *FGFR2* fusion or rearrangement was NGS (using a 324-gene-panel assay (FoundationOne CDx assay, Foundation Medicine)) or FISH to test DNA from patients' tumour tissue, or ctDNA in patients' plasma (Goyal et al. 2023).

*The applicant requested that the clinical utility standard be defined as 'DNA-based NGS to identify *FGFR2* fusion or rearrangements' rather than specifying a commercial brand of test, given the majority of patients were identified via the clinical trial assay and not the commercial test. PASC supported this, and agreed to the removal of FISH and ctDNA samples from the description.*

*PASC explained that the trial would have been performed prior to RNA panels being widely available, and that an RNA panel may be more appropriate than a DNA panel for detecting *FGFR2* fusions and rearrangements. The submission should provide evidence comparing the population identified from the proposed testing strategy (NGS on RNA) with those identified from the clinical utility standard (NGS on DNA), and if they differ, then the effectiveness of treatment in those identified due to testing on RNA, who would not be identified due to having been tested on DNA, should be reported.*

### **Outcomes**

#### *Test-related outcomes*

- Treatment effect modification for futibatinib based on presence/absence of *FGFR2* fusions or rearrangements (predictive validity)
- Prognostic implications of *FGFR2* fusions or rearrangements
- Concordance between the proposed tests NGS on RNA and FISH on DNA and the clinical utility standard of NGS on DNA (overall, positive percent agreement and negative percent agreement) and implications of cases of discordance
- Comparative test performance of NGS RNA testing, NGS DNA testing and FISH testing on DNA
- Comparative reliability of the test methods (proportion of failed and equivocal test results, inter-rater reliability, inter-laboratory variability/agreement)
- Stability of the biomarker in tissue samples

#### *Other test-related considerations:*

- Number estimated to be tested & diagnostic yield of each method
- Number needed to test (to identify one case eligible for futibatinib), taking into account the proportion of patients whose CCA does not progress to being locally advanced or metastatic
- Test turn-around times
- Rate of re-biopsy (including due to test failure for *FGFR2* testing, and inadequate sample rate)

- *FGFR2* test failure rate
- Safety of re-biopsy

#### Treatment-related outcomes

##### Critical outcomes (GRADE)

- Progression-free survival (PFS)
- Overall survival (OS)
- Objective response rate (ORR)

##### Important outcomes (GRADE)

- Time from randomisation to study treatment discontinuation or death (TDT)
- Health-related quality of life (HRQoL)

#### Safety and tolerability

- Treatment-emergent adverse events (TEAEs)
- Physical examination and laboratory findings

#### Healthcare system

- Cost of testing and associated re-biopsies per patient
- Cost-effectiveness of testing and treatment
- Financial implications

*PASC noted that there were a large amount of outcomes requested, due to differences between the clinical utility standard and the proposed testing methods, and due to the key trial not sufficiently establishing the codependency between *FGFR2* status and futibatinib.*

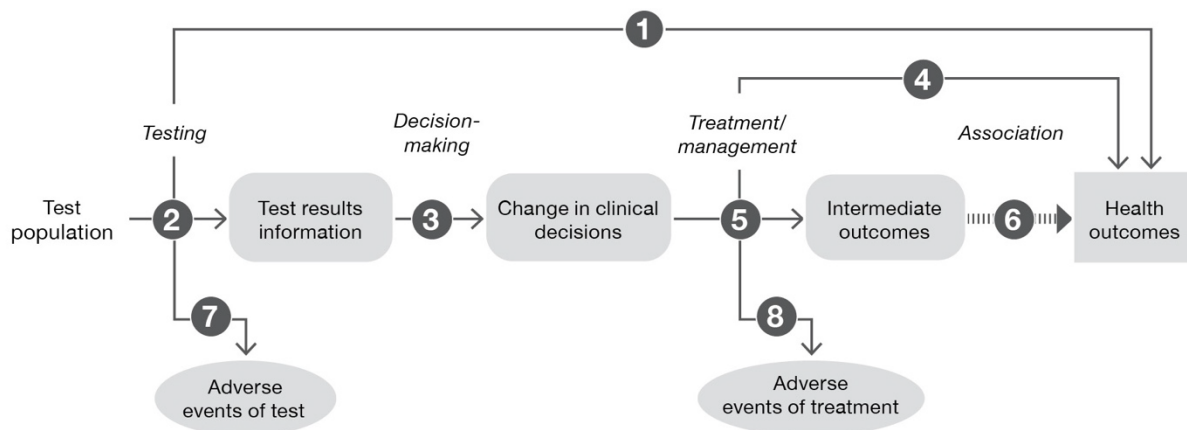
*PASC noted that the key trial for futibatinib was a case series restricted to patients with *FGFR2* fusions/rearrangements. PASC noted that it will be important for the submission to distinguish between the treatment effect (futibatinib vs chemotherapy or palliative care) and any prognostic difference (differences between those with *FGFR2* fusions/rearrangements and those without *FGFR2* fusions/rearrangements).*

*PASC discussed whether a comparison was still required between FISH and NGS (as FISH could be a possible method used if MSAC was to support a method-agnostic item descriptor). PASC confirmed that the applicant developed assessment report should include information on the accuracy of FISH for detection *FGFR2* fusions/rearrangements (if available) so MSAC may consider whether a method-agnostic item would be appropriate.*

## Assessment framework (for investigative technologies)

The aim of the codependent submission will be to demonstrate that testing for *FGFR2* fusions or rearrangements and targeted treatment with futibatinib results in superior health outcomes compared to no testing for *FGFR2* fusions or rearrangement, and SOC chemotherapy or palliative care in patients with locally advanced or metastatic CCA. The key study, FOENIX-CCA2, is an open-label, single-arm, Phase 2 study in patients with locally advanced or metastatic *FGFR2* fusion- or rearrangement-positive iCCA whose disease progressed following at least one prior line of systemic therapy. This provides indirect evidence (i.e. health outcomes only for those who test positive for *FGFR2* fusion or rearrangement) and does not make the

relationship between the biomarker and medicine explicit. The key study also does not provide evidence on the superiority of the biomarker testing and the subsequent use of futibatinib in those tested positive, in terms of treatment efficacy and safety, over no testing and no targeted treatment. Further evidence will be required to supplement the key study, in order to demonstrate that the medicine interacts with the biomarker (either directly through clinical evidence, or from *in vitro* studies, or by inference (e.g., if there is a biologically plausible basis to differentiate between those with and without an *FGFR2* fusion or rearrangement and response to the medicine)), as per Product type 4 of the PBAC guidelines. Further evidence will also be required to supplement the key study to demonstrate the improved health outcomes provided by the biomarker testing and its subsequent use of futibatinib in the target population, compared to no testing and no targeted therapy.



**Figure 1 Generic assessment framework showing the links from the test population to health outcomes**

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

*PASC noted that there was no evidence directly establishing the codependency between *FGFR2* fusion or rearrangement testing and use of futibatinib. Additional evidence will therefore be required in the submission to demonstrate the codependency.*

*As noted in the intervention, PASC advised that the evaluation of comparative test performance for the potential test methodologies (NGS on RNA or DNA, and FISH on DNA) is required.*

Research questions mapped to the assessment framework:

1. What is the safety and effectiveness of testing for *FGFR2* fusions or rearrangements and targeted treatment with futibatinib versus no testing for *FGFR2* fusions or rearrangement and SOC chemotherapy or palliative care in patients with locally advanced or metastatic CCA whose disease progress on one or more line of systemic treatment? (Direct evidence)
2.
  - a) What is the diagnostic yield of *FGFR2* fusions or rearrangements testing, using NGS or FISH in patients with CCA? (and the number needed to test to find one patient eligible for futibatinib)
  - b) Do *FGFR2* fusions or rearrangements influence the prognosis of patients with locally advanced or metastatic CCA receiving second- or later-line SOC chemotherapy or palliative care?
  - c) Do results from *FGFR2* fusions or rearrangements testing, using NGS or FISH predict a treatment effect modification with futibatinib, distinct from any prognostic effect?
  - d) Are the proposed tests reliable?

- e) How concordant are the results of the proposed testing strategy to the clinical utility standard? (are any additional patients identified as eligible for futibatinib from the proposed testing strategy, that would not be identified from the clinical utility standard?)
  - f) How accurate is testing for *FGFR2* fusions or rearrangements using NGS on RNA or DNA, or FISH on DNA?
3. a) What proportion of patients eligible for futibatinib based on the biomarker test result, meet all other eligibility criteria, and receive the treatment? (*note, evidence that patients are treated consistent with test results may be assumed for a codependent biomarker and medicine*).
  4. a) What is the effectiveness of futibatinib versus SOC chemotherapy or palliative care for overall survival in those with locally advanced or metastatic CCA whose disease progress on one or more line of systemic treatment and have an *FGFR2* fusion or rearrangement?  
b) If there are additional patients eligible for futibatinib based on proposed tests (but not the clinical utility standard), do they respond to futibatinib any differently than those detected by the clinical utility standard?
  5. In patients with locally advanced or metastatic CCA whose disease progress on one or more line of systemic treatment, and who have an *FGFR2* fusion or rearrangement, what is the effectiveness of futibatinib versus SOC chemotherapy or palliative care on the outcomes of progression-free survival and objective response rate (intermediate outcomes)?
  6. In patients with CCA, how valid is the link between progression-free survival or objective response rate and overall survival? (*if claim is based on these outcomes rather than overall survival*)
  7. What is the rate of re-biopsy required due to insufficient tissue available for testing, and any adverse events associated with re-biopsy?
  8. In patients with locally advanced or metastatic CCA whose disease progresses despite one or more line of systemic treatment, and have an *FGFR2* fusion or rearrangement, what is the safety of futibatinib versus SOC chemotherapy or palliative care?

## Clinical management algorithms

### ***Current clinical management algorithm for the identified population***

In the absence of Australian specific guidelines for the treatment of advanced or metastatic CCA, the clinical management algorithm (Figure 2) was developed according to current eviQ treatment protocols<sup>9</sup>, which takes into account the Australian specific PBS restrictions and Product Information criteria, and the 2023 National Comprehensive Cancer Network (NCCN) guidelines<sup>10</sup>.

For patients diagnosed with locally advanced (unresectable) or metastatic CCA (either a newly diagnosed disease or a recurrent disease after surgery) and with good performance status (ECOG PS 0 or 1), the preferred regimen for the first-line systemic treatment is chemotherapy with cisplatin and gemcitabine plus immunotherapy with durvalumab. This is based on the survival benefits demonstrated by the ABC-02 and TOPAZ-1 trials (Oh et al. 2022; Valle et al. 2010), and is recommended by NCCN and ESMO (NCCN Guidelines

<sup>9</sup> Cancer Institute of NSW, eviQ Pancreas and biliary medical oncology. Available from URL:

<https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/pancreas-and-biliary> [Accessed 1 July 2024]

<sup>10</sup> National Comprehensive Cancer Network. Available from URL:

[https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician\\_gls/pdf/btc.pdf](https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf) [Accessed 1 July 2024]

Version 2. 2023 ; Vogel et al. 2023), as well as endorsed by eviQ<sup>7</sup>. In patients with inadequate performance status (ECOG PS  $\geq 2$ ) or significant comorbidities, gemcitabine monotherapy is an option (Lamarca, A., Edeline & Goyal 2022). Combination of carboplatin and gemcitabine is an option for patients with contraindication to cisplatin (Williams et al. 2010).

For patients with good performance status whose disease has progressed following the first-line treatment, chemotherapy with 5-FU and oxaliplatin (FOLFOX) is considered the current SOC in the second-line setting and is the preferred regimen recommended by NCCN and ESMO (NCCN Guidelines Version 2. 2023 ; Vogel et al. 2023), and endorsed by eviQ<sup>7</sup>, based on the results from the ABC-06 trial (Lamarca, A. et al. 2021). In the ABC-06 trial, FOLFOX treated patients demonstrated modest improvement in overall survival (OS) compared to patients receiving palliative care/active symptom control (median OS 6.2 months vs. 5.3 months; adjusted hazard ratio 0.69;  $p = 0.031$ ). The usage of FOLFOX in Australia in treating advanced stage CCA patients beyond the first-line setting is unclear. The 5-FU and irinotecan (FORFIRI) regimen is considered a treatment option in the subsequent-line setting for patients with contraindication to oxaliplatin or whose disease progress on FOLFOX (Choi et al. 2021; Lamarca, A., Edeline & Goyal 2022). For patients whose disease does not respond to chemotherapy in the second- and beyond line settings or for those who are too fragile and cannot tolerate the toxicities from chemotherapy, palliative care with active symptom control is the option to preserve quality of life.

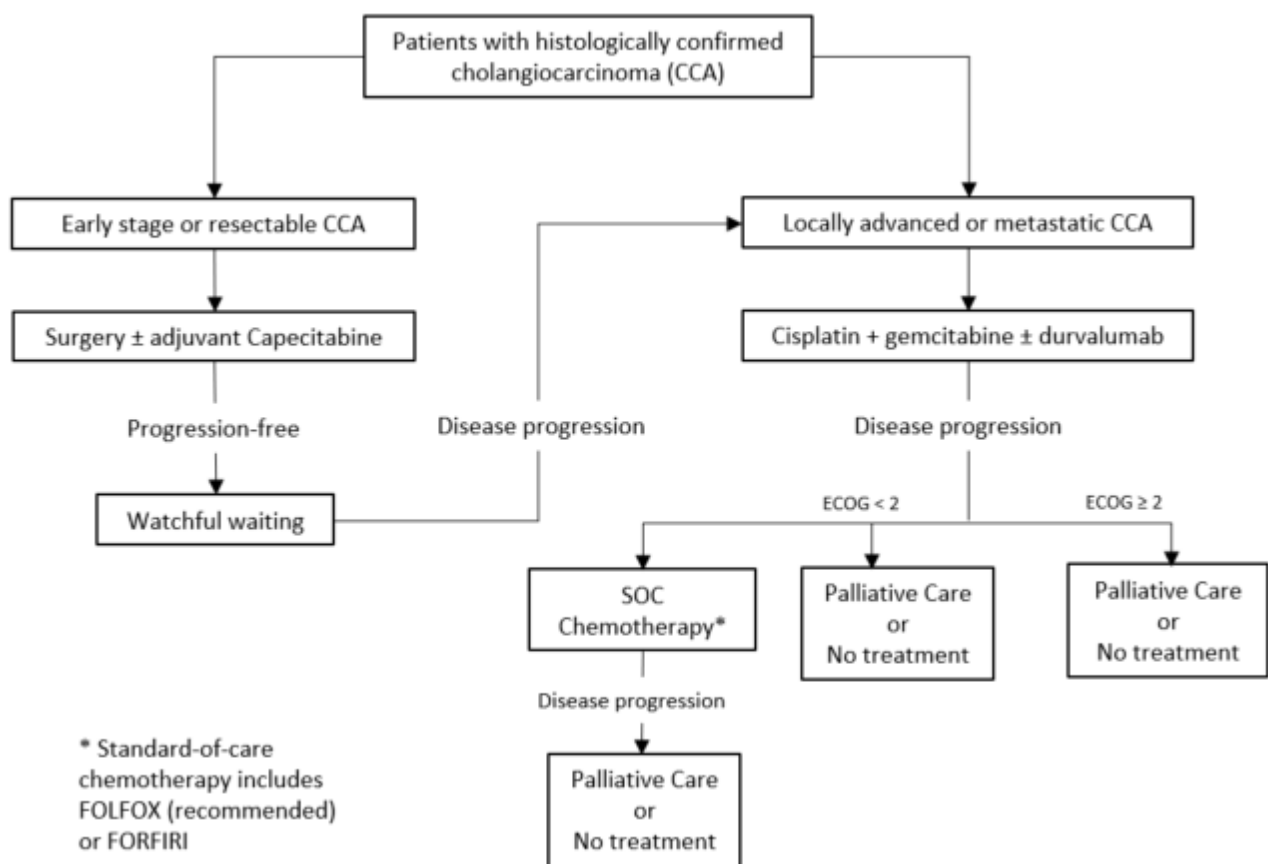


Figure 2 Current clinical management algorithm of locally advanced or metastatic CCA

### Proposed clinical management algorithm for the identified population

For patients diagnosed with locally advanced or metastatic CCA first-line SOC systemic treatment is chemotherapy with cisplatin and gemcitabine plus immunotherapy with durvalumab for those with adequate ECOG performance status. Patients with disease progression following the first-line treatment who continue to have adequate performance status would be eligible for targeted therapy with futibatinib in the second- or subsequent line treatment setting. SOC chemotherapy (FOLFOX or FORFIRI) is another option for these patients. For patients with progressive disease and inadequate performance status, palliative care with best symptom control would be an option.

For patients whose tumour tissue tested negative for *FGFR2* fusion or rearrangement, and whose disease progressed following the first-line treatment, SOC chemotherapy (FOLFOX or FORFIRI) would be given to those with adequate performance status. For patients who are more fragile and cannot tolerate the toxicities from chemotherapy, palliative care with best symptom control would be an option.

Note, although the algorithms only show up to the third-line of treatment, futibatinib and the comparators may be used in subsequent lines as well.

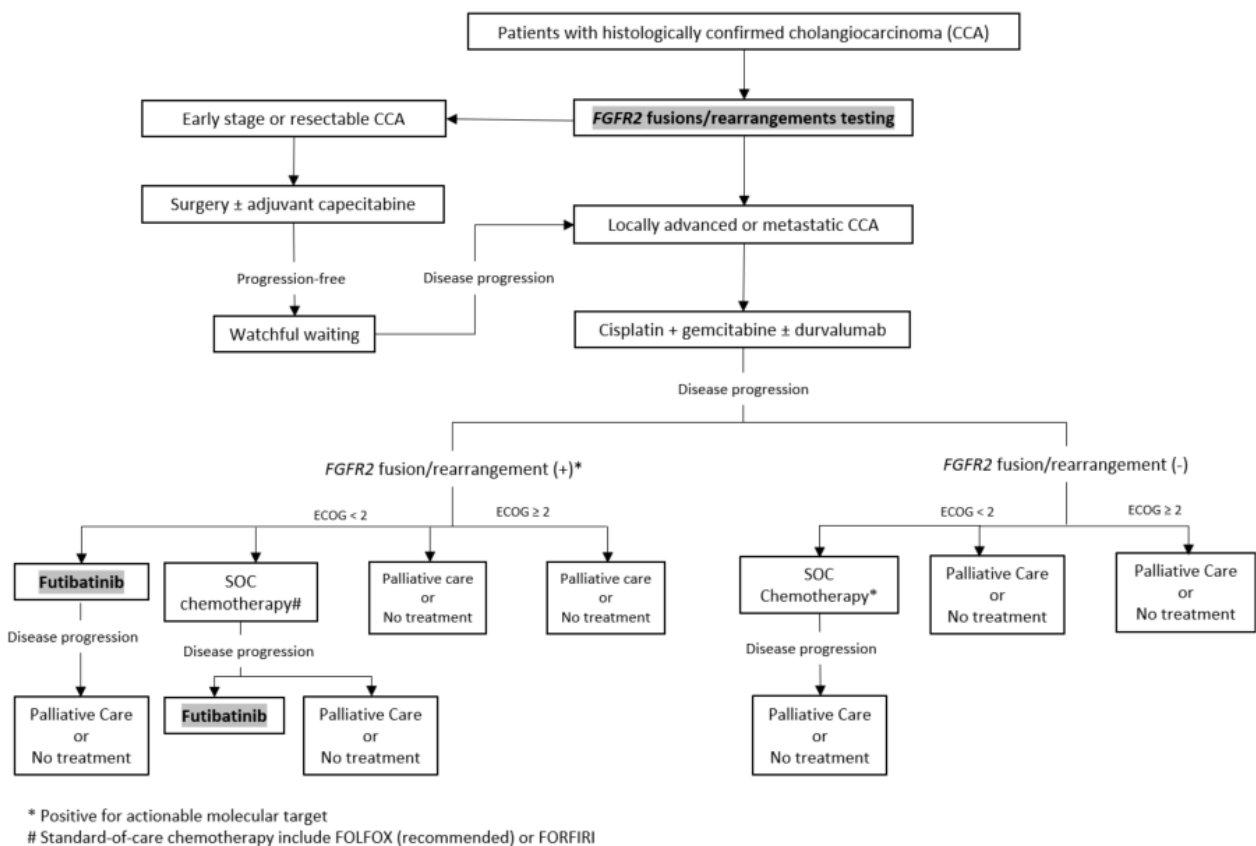


Figure 3 Proposed clinical management algorithm of locally advanced or metastatic CCA

PASC noted that the applicant suggested that the first-line treatment for locally advanced or metastatic CCA could be ‘cisplatin + gemcitabine with or without durvalumab’.

PASC supported amending of the clinical management algorithms to make it clear that the decision regarding active therapy versus palliation/no treatment is not determined solely on ECOG performance status, as some patients may choose not to undergo chemotherapy given the poor outcomes associated



with chemotherapy in this population. Some of these patients may choose to use futibatinib if available (i.e. futibatinib may replace the use of palliative care in some instances, and palliative care should therefore be a secondary comparator).

As previously noted in the population, PASC agreed that FGFR2 testing should be performed at the point of diagnosis of CCA, rather than after progression to having locally advanced or metastatic disease.

PASC discussed the possibility of a combined panel test for IDH1 and FGFR2 status, at initial diagnosis, if MSAC application 1750 is supported by MSAC. However, as the outcome of application 1750 is currently unknown, PASC considered that it would not be reasonable to consider a panel with IDH1 in the assessment report if the outcome of application 1750 was still unknown.

## Proposed economic evaluation

The overall clinical claim is that the proposed codependent technologies (FGFR2 fusions or rearrangement testing and futibatinib as targeted therapy) are superior in health outcomes compared with no testing for FGFR2 fusions or rearrangement, and untargeted treatment (this includes FOLFOX or FORFIRI in the second- or subsequent line setting and may include palliative care with active symptom control in the subsequent line setting) in patients with locally advanced or metastatic CCA whose disease does not respond to first or later-line chemotherapy and whose tumours have tested positive for an FGFR2 fusion or rearrangement. The appropriate type of economic evaluation to be included in the assessment report would be either a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA).

PASC noted that the appropriate form of economic analysis for a superiority claim is either a cost-effectiveness analysis or cost-utility analysis.

**Table 2 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation**

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain <sup>a</sup>	Noninferior <sup>b</sup>	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior <sup>b</sup>	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	<b>CEA/CUA</b>

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

<sup>a</sup> 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

<sup>b</sup> An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

## Proposal for public funding

Currently, testing for *FGFR2* fusions or rearrangements in tumour tissues is not publicly funded. The proposed MBS item descriptor for *FGFR2* fusions or rearrangements testing in patients with CCA is shown in Table 3.

**Table 3 Proposed MBS item descriptor for *FGFR2* testing**

Category 6 – Pathology Services	
Proposed item descriptor XXXXX	Group P7 - Genetics
Detection of <i>FGFR2</i> fusions or rearrangements in tumour tissue from a patient with cholangiocarcinoma, requested by a specialist or consultant physician to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme.	
Applicable only once per lifetime	
Fee: \$600.00 Benefit: 75% = \$450.00 85% = \$510.00	

The applicant proposed the testing for *FGFR2* fusions or rearrangements to be requested by a specialist or consultant physician if access to the targeted therapy is considered beneficial to the patient. Molecular testing is likely to be streamlined in the process of the initial diagnosis of CCA and be performed following the histological diagnosis of the disease by a pathologist, without requiring a specialist or consultant physician to put another request for the testing. PASC indicated that the item should be pathologist-determinable to allow for this scenario.

*FGFR2* fusions or rearrangements testing is likely to be conducted in specialist laboratories who must hold the appropriate accreditation and registration for this testing procedure to receive MBS funding for the proposed test. Laboratories will need to participate in a relevant external quality assurance program. Testing must be conducted, and the results interpreted and reported by suitably qualified and trained molecular pathologists.

Currently, NGS gene panels and single gene tests, looking for mutations in the *FGFR2* gene, are being offered privately within Australia. The Peter MacCallum Cancer Centre offers DNA and RNA gene testing, which includes *FGFR2* testing, starting from \$350 for a single gene test, \$600 for either a small RNA or DNA NGS panel, or \$885 for a panel gene test that includes testing DNA and RNA<sup>11</sup>. It should be noted that testing for *IDH1* can also be included as a part of the panel. There is no single gene test for *FGFR2* listed on the Australian Register of Therapeutic Goods (ARTG) and the only panel registered that includes *FGFR2* is for use in NSCLC. In the absence of an appropriate ARTG listed commercial test, laboratories will need to establish an in-house IVD, accredited by the National Association of Testing Authorities (both the laboratory and test need to be accredited), should the test be listed on the MBS.

It is expected that a patient will only be tested for *FGFR2* fusions or rearrangements once in their lifetime.

*PASC advised that a single MBS item, that is method-agnostic, with a fee suitable for a small RNA panel using NGS (\$600), would be appropriate. *FGFR2* testing is currently available on an NGS RNA panel*

<sup>11</sup> <https://www.petermac.org/health-professionals/services-for-health-professionals/pathology-health-professionals/molecular-pathology/somatic-testing>

(covering 16 variants) for a fee of \$600<sup>12</sup>. It was explained that although a small panel would be used, only the results for FGFR2 would be reported.

The rationale for methodology has already been discussed under the 'Intervention'.

PASC considered it appropriate for the item to be worded generically as 'to determine eligibility for a relevant treatment under the PBS' rather than specify 'for access to futibatinib', and for the item to be pathologist-determinable.

PASC discussed whether there was a problem with distinguishing between CCA and cancers originating in the pancreas. Although PASC acknowledged this was a problem, PASC considered that it was reasonable for the clinician or pathologist to determine which tumour it is likely to be, and test accordingly.

PASC could not foresee any reason why a patient would need to be tested multiple times, therefore supported the restriction of the item to once per lifetime.

PASC queried whether the test would be accessible for patients in rural and remote areas. The clinical expert for the applicant explained that samples can be sent to a laboratory, and the results returned to the treating oncologist, posing no access issues for rural or remote patients.

As previously mentioned, PASC considered that a combined panel for IDH1 and FGFR2 would not be considered in the assessment report if the status of application 1750 was still unknown.

## Summary of public consultation input

PASC noted and welcomed consultation input from 5 organisations and 2 individuals, 1 of whom was a consumer and 1 health professional. The 5 organisations that submitted input were:

- Centre of Molecular Oncology and Omico
- Liver Foundation
- Pancare Foundation (Pancare)
- Rare Cancer Australia (RCA)
- St. Vincent Hospital Sydney

The consultation feedback received was all supportive of public funding for testing of tumour tissue to detect *FGFR2* fusions or rearrangements in people with cholangiocarcinoma (CCA), to determine eligibility for treatment with PBS subsidised futibatinib. No disadvantages to public funding for *FGFR2* testing for cholangiocarcinoma were raised.

### Consumer Feedback

Consultation feedback from consumers and consumer organisations stated that given the poor prognosis of CCA, the diagnosis comes with substantial social and emotional effects – for both people diagnosed and their families (often with young children). People experience a wide range of serious physical side effects due to CCA and its treatment that impacts their energy and wellbeing and limits participation in employment, family life and other everyday activities.

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<sup>12</sup> <https://www.petermac.org/health-professionals/services-for-health-professionals/pathology-health-professionals/molecular-pathology/somatic-testing>

One consumer said they were using a medicine targeting *FGFR2* (not specified) through a clinical trial and have had a tumour response with treatment. The improved quality of life has allowed them to travel overseas, as side effects from previous treatments resolved and that they are no longer short of breath and coughing.

### **Clinical need and public health significance**

The main benefits of public funding received in the consultation feedback were improved outcomes from futibatinib treatment. This included improved quality of life, reduced side effects, access to effective personalised targeted therapies and improved survival. The feedback considered access to targeted therapy and improved quality of life, provided great hope to patients and their families, opportunities for patients to travel, stay active and spend time with family. Several respondents stated that there was an unmet clinical need for treatment options due to poor survival (five-year survival rate is just 20.2%) and rapid disease progression.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention was multidisciplinary care, including nurse and specialist medical professional coordination, occupational and physical therapy, social support, dietetics, and palliative care for symptom management.

### **Indication(s) for the proposed medical service and clinical claim**

The consultation feedback agreed with the proposed population. The Centre of Molecular Oncology and Omico input stated that all patients should have early access to molecular testing due to the natural history of the disease and likely disease recurrence.

The consultation feedback agreed with the proposed comparator.

The consultation feedback agreed with the clinical claim. The Centre of Molecular Oncology and Omico input stated that the value of knowing molecular test results for multiple CCA markers, as well as the sense of control from taking all available steps to increase the number of treatment options potentially available in the future, is important for patients.

### **Cost information for the proposed medical service**

The consultation feedback agreed with the proposed service descriptor and fee. Input stated that the MBS item should consider integrated panel testing using next generation sequencing (NGS) as there are multiple alternations in CCA that will have targeted therapies in the near future and the costs for sequencing comprehensively to identify all actionable targets rather than sequential individual targets is warranted.

Rare Cancers Australia (RCA) and Pancare both stated that people with CCA face a significant financial burden due to the physical effects of CCA and treatment side-effects. In addition, several respondents stated that patients were self-funding cost for medical testing and treatment, with some people trying to access superannuation early to pay for medication.

Consultation feedback also noted that some patients have limited tissue available from biopsies after histological confirmation of CCA and that liquid biopsy as an alternative should be considered.

*PASC noted that the public consultation responses were supportive of having a targeted treatment available for patients with CCA, as it is a severe condition without any appropriate targeted treatment options currently available. PASC noted that public consultation responses supported testing at the point of*

*diagnosis, as availability of tumour tissue can be problematic, and supported integrated panel testing rather than sequential testing.*

## **Next steps**

*PASC noted that the applicant has elected to progress its application as an Applicant Developed Assessment Report.*

## **Applicant Comments on Ratified PICO**

The applicant had no comment.

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