Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 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.**

Date of MSAC consideration: **3-4 April 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of the application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect fibroblast growth factor receptor 2 (*FGFR2*) fusions or rearrangements; and
- Pharmaceutical Benefits Scheme (PBS) Authority required (streamlined) listing of futibatinib for the treatment of locally advanced or metastatic cholangiocarcinoma (CCA) in patients with *FGFR2* fusion or rearrangement.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice 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. MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend futibatinib for the treatment of patients with locally advanced or metastatic CCA who have previously progressed on systemic therapy and have a *FGFR2* fusion or rearrangement, however considered the outstanding issues could be addressed in an early re-entry submission.

MSAC acknowledged that patients with CCA typically have a poor prognosis, and that there is a high clinical need for new treatment options for this patient population. MSAC considered the claim of codependency of *FGFR2* testing and futibatinib was reasonable based on the available (albeit limited) information. MSAC considered that *FGFR2* testing should occur in the whole CCA population at diagnosis to prevent any delays in treatment decisions as it is a rapidly progressing cancer and the tumour samples for testing are small. MSAC considered a combined next generation sequencing (NGS) test on DNA and RNA as the most appropriate method to ensure that *FGFR2* fusions and rearrangements are accurately detected, with NGS on RNA or DNA as the next preferred method should a combination test be unavailable. MSAC considered that Fluorescence In Situ Hybridisation (FISH) was not an appropriate testing option as it is less robust (compared to, and superseded by, NGS testing) in detecting tumours with *FGFR2* fusions and rearrangements. MSAC considered that a single MBS item for a DNA and RNA NGS panel test for *FGFR2* fusions and rearrangements and *IDH1* sequencing (Application 1750 supported by MSAC in November 2024 for the whole CCA population) would be appropriate if both tests are funded. MSAC considered an appropriate fee for the panel needed to be determined. MSAC considered there is a risk that test may be used outside of the intended CCA population for other cancers as

it can be difficult to differentiate CCA and other cancer in nearby organs (e.g. pancreatic cancers and cancers of unknown primary). MSAC requested further information on the cost effectiveness of a panel test and potential financial impact of testing if testing were to occur in these (unintended) populations in practice. MSAC considered that updated economic and financial analyses should be presented to MSAC via the direct MSAC assessment pathway.

Consumer summary

This was an application from Taiho Pharma Oceania Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of a tumour tissue test to detect *fibroblast growth factor receptor 2* (*FGFR2*) gene alterations in patients with cholangiocarcinoma. People whose tumours are identified as having *FGFR2* alterations through testing will then be eligible to access a medicine called futibatinib. The applicant has also requested listing of futibatinib on the Pharmaceutical Benefits Scheme (PBS) and this was considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

Cholangiocarcinoma is also known as bile duct cancer. The bile ducts are a group of thin tubes starting inside the liver that carry bile from the liver and gallbladder into the small intestine. Cholangiocarcinoma is a rare and aggressive form of cancer, with not many treatment options available. Because of this, survival after diagnosis is usually relatively short, with only half of the patients alive a year after diagnosis. Therefore, there is a need to have access to more effective treatments.

The target gene of the test is the *FGFR2* gene. *FGFR2* is associated with cell growth and differentiation, and is implicated in cancer growth. *FGFR2* alterations are mainly found in cholangiocarcinoma and not in other cancers.

The application was originally for the test to be performed once the spread of the cancer (from the bile duct) was confirmed. However, MSAC proposed that the test should be performed when a patient is first diagnosed with cholangiocarcinoma. This means a tumour sample will be taken during the initial biopsy of a suspected bile duct tumour and tested by a pathology laboratory. If the treating practitioner confirms that the patient has cholangiocarcinoma, then *FGFR2* testing should be performed. Because a biopsy is currently a standard procedure for tumour diagnosis, *FGFR2* testing can done on the same biopsy sample. Because a new biopsy is not needed, MSAC considered that adding this testing when diagnosing a patient does not change the safety of the diagnostic process for the patient. MSAC considered it appropriate to test all newly diagnosed patients because most (70%) cholangiocarcinoma patients are diagnosed with late-stage cancer, and the cancer tends to progress very quickly. MSAC also considered it beneficial to test patients at diagnosis, so they can receive test results and access appropriate treatment as soon as possible.

At its March 2025 meeting, the PBAC did not recommend listing futibatinib on the PBS because of uncertainties in the economic analysis including the effect of the medicine, the size of the patient population with cholangiocarcinoma, and the number of patients who have *FGFR2* alterations. PBAC has requested that these issues be addressed in a resubmission of the application.

MSAC highlighted that there are different gene targets that are relevant to cholangiocarcinoma patients (including testing for *IDH1* [Application 1750], which MSAC supported in November 2024). MSAC considered it appropriate that a gene panel be used to test for several genes at the same time, rather than having several different MBS items for each different gene. MSAC was concerned that, if the genes are tested separately, patients may miss out on being tested for other important gene targets, resulting in suboptimal care. MSAC was also concerned that individual gene testing may lead to large out-of-pocket costs for the patient if the pathology laboratory chose to perform a gene panel but are not adequately reimbursed for it.

MSAC acknowledged that *FGFR2* testing is safe and effective. However, MSAC considered that the test fee proposed was too low and advised that the economic and financial analysis be

Consumer summary
revised with a more appropriate fee. In addition, MSAC considered that cholangiocarcinoma can be a difficult cancer to diagnose, because it can look similar to several other cancers when examined under the microscope. MSAC considered that there is possibility that other cancers which are located close to the bile ducts may be thought to be cholangiocarcinoma when in fact they are not. Therefore, MSAC considered that this may increase the number of *FGFR2* testing than expected, and advised that this also be taken into account in the revised economic and financial analyses. MSAC deferred its advice and requested that these issues be addressed and submitted for re-consideration by MSAC. **MSAC's advice to the Commonwealth Minister for Health and Aged Care** MSAC deferred its advice on funding *FGFR2* genetic testing for patients with cholangiocarcinoma. MSAC considered that the test is safe and effective, however has uncertain economic and financial implications. MSAC requested that the economic and financial analyses be revised by including a more appropriate test fee and by incorporating more accurate estimates of the number of patients who would be tested in practice. MSAC also advised that it was supportive of a single MBS item for a gene panel test, for efficient testing of several relevant cholangiocarcinoma gene targets.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this codependent application from Taiho Pharma Oceania Pty Ltd was for the Medicare Benefits Schedule (MBS) listing of the testing of tumour tissue to detect *fibroblast growth factor receptor 2* (*FGFR2*) fusions or rearrangements in people with cholangiocarcinoma (CCA), to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS) subsidised futibatinib.

MSAC noted that, at its March 2025 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend the listing of futibatinib on the PBS for the treatment of patients with locally advanced or metastatic cholangiocarcinoma who have previously progressed on systemic therapy and have a *FGFR2* fusion or rearrangement. The PBAC considered that it can be difficult to differentiate between intrahepatic CCA (iCCA) and extrahepatic CCA and that it was likely futibatinib would provide benefit in the small number of patients with non-iCCA who have an *FGFR2* fusion or rearrangement. PBAC advised that a resubmission, through an early re-entry pathway, include a more realistic estimate of the clinical benefit in the economic model and revise utilisation estimates to more accurately reflect the prevalence of CCA and the number of patients with *FGFR2* fusions or rearrangements.

MSAC noted that CCA is a rare (1,300 cases in Australia each year) and aggressive cancer. CCA has a median survival of 12 months with most cases (70%) being diagnosed when already at the advanced or metastatic stage and only 2% of these patients surviving 5 years past diagnosis. As such, MSAC considered there was a significant unmet clinical need for more effective treatments for the management of CCA. MSAC noted the applicant-developed assessment report (ADAR) requested testing only for adults with locally advanced or metastatic CCA. However, MSAC considered it appropriate to expand the testing to all newly diagnosed patients with CCA, in agreement with the ESCs advice, as CCA is a rapidly progressive disease and therefore testing at diagnosis will prevent any delays and allow swift access to treatment on progression to advanced or metastatic disease. MSAC noted that this population also aligns with testing of CCA patients for *IDH1* variants, which MSAC supported at its November 2024 meeting (MSAC application 1750). MSAC considered that given there is no definitive histological marker for CCA, it can be difficult to distinguish CCA and other adenocarcinomas which occur at nearby sites, such as pancreatic cancer and cancers of unknown primary. Due to this diagnostic uncertainty, MSAC considered that there is a risk that the use of *FGFR2* testing may be higher than expected (due to

testing non-CCA tumours which are presumed to be CCA) and considered that the economic and financial assessment should take this into account and post implementation monitoring may be appropriate to review test and drug usage.

MSAC noted that the proposed test was next-generation sequencing (NGS) of the *FGFR2* gene to detect fusions and rearrangements. MSAC noted detecting *FGFR2* fusions is technically challenging because of the large number of possible fusion partners (>140 detected to date), some of which are within the same chromosome or are intragenic. Due to the large number of possible fusion partners, MSAC considered that current evidence[1,2] strongly supports a fusion partner agnostic testing approach and that an amplicon-based approach is suboptimal as it is limited to a predefined set of fusions determined by the primer design. MSAC also considered the use of fluorescent in-situ hybridisation (FISH) assays for this testing to be inappropriate because such assays have a poor performance in detecting rearrangements, particularly rearrangements which are spatially closer to each other.

MSAC noted from the clinical evidence presented in the ADAR that the concordance between NGS on DNA (clinical utility standard) and NGS on RNA is high (overall percentage agreement = 98.3% [95% CI 93.3-99.8%], adjusted positive predicted value = 96.2% [95% CI 80.4–99.9] and adjusted negative predictive value = 98.5% [95% CI 94.6–99.8]). MSAC also noted from the evidence that NGS on RNA is more likely to identify *FGFR2* fusions than NGS on DNA, and therefore, both methodologies may not necessarily detect the same variants. MSAC also noted that DNA is more robust than RNA in formalin-fixed, paraffin-embedded (FFPE) samples, but that DNA testing is computationally challenging, especially for intragenic rearrangements. Thus, MSAC agreed with the ESCs advice that combination testing of NGS on DNA and RNA would be the most accurate method of detecting *FGFR2* fusions and rearrangements. MSAC considered NGS on RNA or DNA the next preferred method if combination testing is not available. Regarding NGS on RNA, MSAC considered that RNA hybrid-capture fusion testing is preferred[1], but recognised that advances in sequencing technology may offer other options in the future.

MSAC noted that the ADAR did not present any information regarding the safety of the test. Given that MSAC advised for *FGFR2* testing to be done at diagnosis, there is unlikely to be any additional safety harms associated with obtaining a biopsy sample for testing, as the same sample already obtained for diagnosis will be used. However, if a re-biopsy is required for the purpose of obtaining a sample specifically for *FGFR2* testing, there will be associated safety risks which have not been considered in the ADAR. MSAC, however, considered that a re-biopsy would be a rare occurrence due to the rapid progression of CCA, which makes most patients too unwell for a re-biopsy. As such, MSAC considered that there would not be significant safety issues due to re-biopsy. MSAC noted that false negative results are more common than false positive results due to issues with RNA degradation or insufficient genetic material. However, MSAC considered that overall, NGS performs well with a low rate of false results.

MSAC agreed with the ESCs and the commentary that the available evidence suggests that patients with *FGFR2* alterations may have a positive prognostic impact, regardless of treatment. MSAC noted from the applicant's pre-ESC and pre-MSAC responses that a Phase 1 expansion study for futibatinib showed no anti-tumour activity in patients with wild type *FGFR*. Therefore, MSAC agreed with the ESCs that it is challenging and unethical to trial futibatinib on patients with wild-type *FGFR2* variants, who are unlikely to experience a treatment benefit and considered that the claim of codependency was reasonable based on the available (albeit limited) evidence.

---

[1] Neumann, Olaf et al. "Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing." *British journal of cancer* vol. 127,8 (2022): 1540-1549. doi:10.1038/s41416-022-01908-1

[2] Neumann, Olaf et al. "First proficiency testing for NGS-based and combined NGS- and FISH-based detection of FGFR2 fusions in intrahepatic cholangiocarcinoma." *The journal of pathology. Clinical research* vol. 9,2 (2023): 100-107. doi:10.1002/cjp2.308

MSAC agreed with the MBS items proposed by the ESCs. MSAC considered that the MBS descriptor specify 'nucleic-based test' in order to capture appropriate testing methodologies (NGS on DNA and NGS on RNA), while excluding FISH testing to ensure testing accuracy. MSAC considered that exclusion of FISH testing should also be specified in the explanatory note. MSAC also considered it appropriate that this test be pathologist-determinable, as this streamlines the referral process and time to result. MSAC considered that the proposed test fee of $350 was not appropriate. While a fee in this range would be appropriate for sequence variant testing in DNA (for example a fee of $340 was supported by MSAC for *IDH1* sequence variant testing), MSAC considered this fee to be too low for fusion and rearrangement testing as it is more technically challenging compared to sequence variant testing in DNA.

MSAC agreed with the Department that should *FGFR2* testing be supported for the whole CCA population, *IDH1* (supported by MSAC in Application 1750 for same population) and *FGFR2* testing should be combined as a gene panel test with a single MBS item, rather than as two separate tests. MSAC considered that laboratories are likely to preferentially perform a DNA and RNA panel test that includes *IDH1* and *FGFR2* testing, rather than testing individual genes on separate assays. MSAC noted that an appropriate MBS fee for this test needs to be determined to reflect the costs associated with a panel test, which ensures that patients do not encounter substantial out-of-pocket costs. MSAC also considered that having a panel test will help to futureproof the MBS item if supported, noting that the current National Comprehensive Cancer Network (NCCN) guidelines state that there are several relevant genes (beyond *IDH1* and *FGFR2*) that could be assessed for this patient group. Further, MSAC highlighted that if *IDH1* and *FGFR2* testing are listed as separate MBS items, it may inadvertently encourage substandard care as a decision may need to be made on which gene to test if limited tissue is available and not sufficient for multiple single gene tests.

MSAC noted that the economic evaluation was a cost-utility analysis using a partitioned survival analysis based on the results of a matched adjusted indirect comparison (MAIC). Given the possible positive prognostic impact of *FGFR2* alterations, MSAC agreed with the ESCs concern that the MAIC provided a highly uncertain and likely overestimated magnitude of effect due to not adjusting for *FGFR2* status. MSAC noted the base case incremental cost effectiveness ratio (ICER) was $95,000 to <$115,000 per quality-adjusted life year (QALY). MSAC noted the fee for testing used in the economic analysis ($350) was too low and advised that the economic model be revised with an appropriately justified fee. MSAC noted the submission had modelled 40% of testing at no cost, as this is currently provided by Omico in clinical practice. However, MSAC considered it was unlikely that Omico would continue testing for CCA at no cost if the item were MBS listed. As such, MSAC suggested that the modelling be revised to include all testing at full cost. MSAC noted that the economic model assumed a 20% prevalence of *FGFR2* alterations based on the evidence from the advanced CCA population. However, given the MSAC advice for testing to be done at diagnosis on all patients with CCA, MSAC considered that the prevalence would be much lower in this broader population. MSAC noted from the commentary that the prevalence in the whole CCA population was approximately 10%, and this may be further reduced if testing is also performed in pancreatic and cancers of unknown primary (as *FGFR2* alterations are predominantly found in iCCA).

Regarding the financial analysis, MSAC noted from the commentary that the net financial impact to the MBS from testing the CCA population is $0 to <$10 million in year 1 to $0 to <$10 million in year 6. MSAC considered that the financial impact would significantly increase if pancreatic cancer and cancer of unknown primary (that are presumed to be CCA) are also included in the testing population. MSAC noted from the post-ESC additional analysis that including the pancreatic cancer and cancer of unknown primary (assuming 100% uptake in these populations) increased the net cost to the MBS to $0 to <$10 million per year (with a fee of $682.35 per test which the ESCs considered to be appropriate for a single gene *FGFR2* test). MSAC considered that there is unlikely to be a significant increase to the net PBS cost despite the increased testing, as *FGFR2* alterations are predominantly found in intrahepatic CCA, and therefore the majority of the testing in the pancreatic cancer and cancer of unknown primary populations will be negative and therefore will not be eligible to receive the drug.

Overall, MSAC considered that there was a high unmet clinical need for effective treatments for patients with CCA and that NGS testing on DNA and RNA (preferred) or NGS on RNA or DNA alone was safe and effective in identifying patients with *FGFR2* fusions and rearrangements for eligibility to futibatinib. However, MASC deferred its advice and requested the applicant to present a revised economic and financial analysis using an appropriately justified test fee and also taking into account testing that may be performed in (unintended) non-CCA populations in practice (pancreatic cancers and cancers of unknown primary).

MSAC considered that the resubmission could proceed via the direct MSAC assessment pathway.

4. Background

The Applicant Developed Assessment Report (ADAR) 1779 was the first submission for *FGFR2* fusion/rearrangement testing for CCA to the MSAC, and the first submission for futibatinib for CCA to the PBAC.

MSAC application 1750 (Testing of tumour tissue to detect isocitrate dehydrogenase 1 [IDH1] mutations in patients with CCA to determine eligibility for ivosidenib on the PBS) was considered at the July 2024 PBAC/MSAC meetings. The PBAC did not recommend ivosidenib at the July 2024 meeting. MSAC deferred its decision at the July 2024 meeting due to PBAC not recommending ivosidenib at the time. This application was considered again by PBAC and MSAC at the November 2024 meetings and supported by both committees.

5. Prerequisites to implementation of any funding advice

At the time of consideration Futibatinib was not TGA registered. Futibatinib is proposed for the treatment of adult patients with locally advanced or metastatic CCA with a *FGFR2* fusion or rearrangement that have progressed after at least one prior line of systemic therapy. The submission considered that *FGFR2* fusions or rearrangements testing is expected 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 the relevant Royal College of Pathologist of Australasia (RCPA) Quality Assurance Program or a similar external quality assurance program. Testing must be conducted, and the results interpreted and reported by suitably qualified and trained molecular pathologists.

Through correspondence with the Department, the applicant confirmed that many laboratories in Australia currently offer National Association of Testing Authorities (NATA) accredited testing for *FGFR2* fusions, supported by established external quality assessment program. The submission also considered that these testing items would be regulated by the TGA as in-vitro diagnostic medical devices (IVDs), listed on the ARTG as Instrument/analyser IVDs. The commentary noted that the applicant did not provide information on any relevant IVD on the ARTG.

6. Proposal for public funding

The submission included two potential MBS descriptors. One was consistent with the 1779 Ratified PICO (Table 1) and the other is an alternate descriptor proposed in the submission (Table 2~~Table 2~~) based on additional considerations described below.

Table 1 Item descriptor (consistent with 1779 ratified PICO)

Category 6 – Pathology services	
Proposed item descriptor XXXXX	Group P7 – Genetics
Detection of FGFR2 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	

Source: Table 1.8, p51 of the submission.

Table 2 Item descriptor (Alternate proposed in submission)

Category 6 – Pathology services	
Proposed item descriptor XXXXX	Group P7 – Genetics
Next generation sequencing (NGS) test for FGFR2 fusion or rearrangement using RNA from tumour tissue from a patient with locally advanced or metastatic 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: $350.00 Benefit: 75% = $262.50 85% = $297.50	

Source: Table 1.9, p52 of the submission.

The key differences reflected between the two item descriptors were:

1. The submission's proposed alternate descriptor (Table 2) was a narrower population compared to the 1779 Ratified PICO's item descriptor (Table 1), as only patients with locally advanced or metastatic CCA (as opposed to all CCA) would be eligible for testing. The submission argued that in practice, the test population is understood to be adult patients with locally advanced or metastatic CCA. This was aligned with key clinical guideline recommendations (ESMO 2023[3]; NCCN 2024[4]) and current Australian clinical practice, as informed by local experts. The 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. "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." (p6, 1779 Ratified PICO – August 2024 PASC meeting);
2. The submission's proposed alternate descriptor specified that testing should be with next generation sequencing (NGS) on RNA whereas the item descriptor from the 1779 Ratified PICO was test agnostic. The submission stated that the most relevant test intervention is understood to be tumour tissue testing using NGS on RNA. Local expert advice suggests that aside from testing conducted by Omico (in which a large NGS panel is utilised), tumour tissue testing for *FGFR2* fusions is primarily undertaken using a small RNA fusion panel. Fluorescence in situ hybridisation (FISH) is not considered a viable option and the applicant has been unable to identify evidence of FISH being utilised for this purpose in clinical practice. At the PASC meeting, the applicant's clinical expert explained that it would not be cost effective for laboratories to set up FISH testing to detect *FGFR2* fusions and

[3] ESMO. (2023). Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, 34(2), 127-140.

[4] NCCN. (2024). Biliary Tract Cancers Version 3.2024.

rearrangements. According to the ratified PICO, PASC considered that a method agnostic item may be reasonable as other testing methodologies such as NGS on DNA and FISH could be used in Australia. The restriction of the item descriptor to NGS from RNA does not align with this view.; and

3. A reduced fee in the submission ($350) compared to the ratified PICO ($600). The submission identified a range of MBS fees listed for NGS. For example,

    - Item 73437 for a DNA and RNA-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer has a fee of $1,247.00;
    - Item 73439 for an RNA-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer has a fee of $682.55;
    - Item 73376 for the analysis of tumour tissue from a patient with sarcoma for the analysis of four or more genes has a fee of $800, or item 73374 for the analysis of tumour tissue from a patient with sarcoma for the analysis of one gene has a fee of $340; and
    - Item 73433 for an NGS test for neurotrophic receptor tyrosine kinase (NTRK) fusions by DNA or RNA in tumour tissue from a patient with a locally advanced or metastatic solid tumour has a fee of $1,000.00.

Currently, NGS gene panels and single gene tests, looking for variants in the *FGFR2* gene, are being offered privately within Australia. The sponsor considered that laboratories currently charge private fees ranging from approximately $350 (to report a single gene) to $700 using an RNA fusion panel test based on the sponsor's understanding of the price of NGS testing for *FGFR2* fusion or rearrangement using RNA from Peter Mac, LifeStrands and Monash Health. A fee of $350 per test is applied in the base case of the economic and financial analyses in this submission given testing is proposed using RNA only and reporting is limited to *FGFR2* fusions or rearrangements. The commentary noted that the economic model was not highly sensitive to cost of *FGFR2* testing.

Additionally, public consultation input for the 1779 ratified PICO stated that the MBS item should consider integrated panel testing using NGS as there are multiple alterations 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.

Moreover, the proposed MBS item descriptor in the 1750 application for IDH1 testing (for ivosidenib) as per MSAC advice in August 2024 was "(d)etection in tumour tissue of isocitrate dehydrogenase 1 (*IDH1*) variant status, in a patient with histologically confirmed cholangiocarcinoma, to determine access to a relevant treatment under the Pharmaceutical Benefits Scheme" (1750 public summary document), which was comparable with the item descriptor from the 1779 ratified PICO (Table 1). The proposed test in 1750 was associated with a proposed fee of $340, which MSAC considered appropriate (p4, Application 1750 PSD, MSAC meeting July 2024).

The commentary considered that overall, the item descriptor as presented in the 1779 Ratified PICO (Table 1) may better reflect Australian clinical advice received by the PASC and be more comparable with MSAC application 1750.

Table 3 presents the submission's PICO table.

Table 3 Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: adult patients with locally advanced or metastatic CCA Drug: adult patients with locally advanced or metastatic CCA with a *FGFR2* gene fusion or rearrangement that have progressed after at least one prior line of systemic therapy
Intervention	Test: tumour tissue testing for *FGFR2* gene fusions or rearrangements using RNA NGS Alternate test: tumour tissue testing for *FGFR2* gene fusions or rearrangements using FISH testing on DNA Drug: futibatinib 20 mg (5*4 mg tablets) taken orally once daily until disease progression or unacceptable toxicity
Comparator	Test: no testing for *FGFR2* gene fusions or rearrangements Drug: primary comparator: SoC chemotherapy, represented by guideline-preferred FOLFOX (modified FOLFOX 6 chemotherapy (oxaliplatin 85 mg/m2, calcium folinate 50 mg, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 continuous infusion over 46 hours; every 14 days for up to 12 cycles) Secondary comparator: palliative care (with active symptom control)
Outcomes[a]	Test: diagnostic yield, prognostic impact, treatment effect modification, reliability of testing, concordance between proposed testing method and clinical utility standard Drug: PFS, OS, ORR, HRQoL, safety
Clinical claim	Main claim: in patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement, identified by tumour tissue testing, that have progressed after at least one prior line of systemic therapy, futibatinib is superior in terms of efficacy (OS, PFS and ORR) and safety, compared to FOLFOX. Secondary claim: In adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement, identified by tumour tissue testing, that have progressed after at least one prior line of systemic therapy, futibatinib is superior in terms of efficacy (OS, PFS and ORR), compared to palliative care (with ASC), with a different safety profile that is manageable.

Source: Table 1.1, p21 of the submission.
DNA = deoxyribonucleic acid; CCA = cholangiocarcinoma; FGFR2 = fibroblast growth factor receptor 2; FISH = fluorescence in situ hybridisation; HRQoL= health related quality of life; NGS = with next-generation sequencing; ORR = objective response rate: OS = overall survival; PFS = progression free survival; RNA = ribonucleic acid; SoC = standard of care
a The list of outcomes related to the test in the submission's PICO was more limited than the Ratified PICO Criteria.

A key difference between the submission's PICO and the 1779 Ratified PICO was that the test population in submission's PICO was restricted to adult patients with locally advanced or metastatic CCA, whereas the test population in the 1779 Ratified PICO was adult patients with CCA. This reflects a difference in the requested test population with implications on the proposed treatment algorithm, diagnostic yield and utilisation.

7. Population

CCA refers to the group of rare and aggressive malignancies that arise from epithelial cells that line the biliary tree (Banales 2020; Howlader 2020). CCA is categorised depending on the location of the tumour and includes intrahepatic CCA (iCCA), which originates from peripheral bile ducts, proximal to the second-order ducts, and represents approximately 20% of cases, or extrahepatic CCA (eCCA), which represents the remaining 80% of cases (Banales, 2020; Valle 2021). Treatment guidelines generally recommend similar treatment pathways for both iCCA and eCCA.

CCA accounts for approximately 3% of all gastrointestinal malignancies and 26% of all liver and intrahepatic bile duct cancers (Banales 2020; Howlader 2020). CCA is most often diagnosed at a late stage, resulting in poor prognosis and limiting treatment options (Mukkamalla 2018).

The symptoms of CCA depend on location, presence of metastases, and underlying disease (such as liver failure) (Banales 2020; Valle 2021). Symptoms arise because of direct compression (such as biliary obstruction) or can be constitutional or due to underlying pathology (such as chronic liver disease). In eCCA, patients may present with biliary obstruction and jaundice, whereas in iCCA, patients are often asymptomatic prior to the appearance of late, nonspecific symptoms such as weight loss, nausea, fatigue, and abdominal pain (Banales 2020).

Up to 88% of all biliary tract cancers harbour pathological molecular aberrations/alterations (Lamarca 2020). The most frequent variants in CCA include *IDH1/2, FGFR2, BRAF, BAP1, ARID1A, KRAS, TP53, SMAD4, ERBB2/HER2, PRKACA-PRKACB* fusions, and *ELF3* (Banales 2020; Valle 2021). Genomic alterations in *FGFR2, IDH1/IDH2, BRAF, BAP1* and *ARID1A* occur more frequently in iCCA, while alterations in *ERBB2/HER2, PRKACA-PRKACB,* and *ELF3* are more frequent in eCCA (Banales 2020; Valle 2021)

The requested testing population is adult patients with locally advanced or metastatic CCA.

The commentary considered that the population targeted for testing in the submission was well described and considered it reasonable as it was consistent with international guidelines (ESMO 2023; NCCN 2024). However, as discussed above in the 1779 PICO confirmation, PASC supported testing for *FGFR2* gene fusion at the point of diagnosis, regardless of stage, as CCA is a rapidly progressive disease, whereas the submission has presented a narrower alternate population of patients with advanced or metastatic CCA for testing.

The commentary considered that given 80% of patients who are diagnosed with CCA are diagnosed at the locally advanced or metastatic stage (as assumed in the financial estimates and previously considered appropriate by the PBAC DUSC (Table 16, durvalumab PSD, March 2023 PBAC meeting)), the majority of CCA patients would not experience any difference in terms of the time of testing irrespective of whether the item descriptor from the 1779 Ratified PICO (Table 1) or the alternate proposed item descriptor in the submission (Table 2) was recommended. However, for patients who are diagnosed at an early stage, the experience may differ as follows: With the MBS item descriptor from the 1779 Ratified PICO, patients who are diagnosed at an early stage of CCA would be eligible for testing at the point of diagnosis. The advantage of this would be that the tissue sample would be fresh and less likely to be degraded, it would also streamline the diagnostic process and allow more efficient use of diagnostic tissue. However, potential disadvantages could be potential resource wastage as patients may not progress to requiring treatment with FGFR2 inhibitors, and patients who subsequently develop *FGFR2* variants may not be captured given that there is evidence that *FGFR2* variants may develop with treatment. There is also evidence that the diagnostic yield in the whole CCA population was lower than in advanced CCA. This is discussed further below in the diagnostic yield section of the executive summary.

The commentary noted that with the alternative item descriptor proposed in the submission, patients who are diagnosed at an early stage of CCA would not be eligible for testing at diagnosis, and only those who experience recurrence or metastasis would be eligible for testing. The advantage would be that there would be less potential resource wastage as patients are more likely to be eligible for FGFR2 inhibitors (which are restricted to advanced or recurrent disease) and it is likely more eligible patients may be identified based on observational diagnostic yield evidence. However, testing may be reliant on archival tissue which may have degraded and testing may be more difficult and/or less reliable. In some cases there may be additional safety risks for patients who may require a re-biopsy for testing.

Fibroblast growth factor receptors (FGFRs) are a type of receptor tyrosine kinase with high functional importance in a number of biological processes, including development, differentiation, survival, migration, and proliferation. The fibroblast growth factor (FGF) pathway consists of 22 human FGFs and 4 transmembrane receptors with intracellular tyrosine kinase domains (*FGFR1, FGFR2, FGFR3,* and *FGFR4*) (Goyal 2021). The binding of FGF ligands to FGFR leads to the dimerization of receptors and activates the intracellular tyrosine kinase of the FGFR transmembrane receptor via phosphorylation. This induces activation of intracellular pathways leading to gene transcription.

The presence of various types of *FGFR* aberrations/alterations can promote carcinogenesis through gene amplification, activating variants, point variants, fusions/ translocations and fusions/translocations (Goyal 2021; Goyal 2020; Helsten 2016; Dabney 2019; ESMO 2021).

Among CCA patients with *FGFR* alterations, *FGFR2* fusions have been found to be the most common alteration (approximately 70%). The most common *FGFR2* fusion partner in iCCA is *BICC1* (approximately 30% of fusions). Usually, *FGFR2* fusions are mutually exclusive with *IDH1* variants.

As noted in the 1779 Ratified PICO, 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 2020). The commentary noted that *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 2017).

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

The submission did not discuss the stability of the biomarker. The commentary noted that this was listed as an outcome in the 1779 Ratified PICO Confirmation. A literature search conducted during the evaluation identified limited information regarding the stability of *FGFR* biomarkers in general. In advanced non-small cell lung cancer, over 23% of *FGFR2/3* fusions may be associated with acquired resistance following treatment with epidermal growth factor receptor tyrosine kinase inhibitors (Raphael 2022)[5] which may point to alterations acquired by prior treatment.

Neuman 2023, which reported the results of a study assessing the early real-world performance of NGS on RNA and FISH on DNA for the identification of *FGFR2* alterations in patients with CCA in Germany, noted that "(t)he detection of full-length transcripts by RNA sequencing in [Formalin-fixed, paraffin-embedded] FFPE material is technically challenging due to the prominent degradation of RNA in FFPE samples." The prevalence data presented in the submission (see Table 6) also suggest that there may be higher prevalence of *FGFR2* variants in advanced CCA compared to CCA in general, though this may reflect underlying differences in the included studies than actual prevalence.

Therefore, given the uncertainty regarding stability of the biomarker, the commentary considered that it was unclear at what point would be the optimal time for FGFR2 testing, and whether testing should be performed once per lifetime in all patients (as proposed in the requested MBS item) and/or whether re-biopsy and retesting may be necessary in some patients.

8. Comparator

The nominated test comparator in the submission was no testing, consistent with 1779 Ratified PICO criteria. The commentary considered that this was reasonable.

The submission nominated standard of care (SoC) as the main comparator for futibatinib. Specifically, FOLFOX; as modified FOLFOX6 chemotherapy (oxaliplatin 85 mg/m^2, calcium folinate 50 mg, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 continuous infusion over 46 hours; given

[5] Raphael A, Dudnik E, Hershkovitz D, Jain S, Olsen S, Soussan-Gutman L, Ben-Shitrit T, Dvir A, Nechushtan H, Peled N, et al. FGFR Fusions as an Acquired Resistance Mechanism Following Treatment with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) and a Suggested Novel Target in Advanced Non-Small Cell Lung Cancer (aNSCLC). Journal of Clinical Medicine. 2022; 11(9):2475. https://doi.org/10.3390/jcm11092475

every 14 days for up to 12 cycles, as per eviQ protocol) was proposed as the SoC in Australian practice.

The submission noted that advice received from local experts suggests that futibatinib may replace a proportion of palliative care with active symptom control (ASC) in some patients where clinically appropriate, however advisers to the applicant confirmed that FOLFOX is the appropriate main comparator for this submission, as it is the regimen most likely to be replaced by futibatinib in practice (90-95%).

In the consideration of ivosidenib at the July 2024 PBAC meeting, it was considered that the nomination of palliative care/best supportive care (BSC) as the primary comparator and FOLFOX as the secondary comparator appeared reasonable (paragraph 5.3, ivosidenib PSD, July 2024 PBAC meeting). The ESC also noted that in TOPAZ-1, 51-54% of patients received subsequent chemotherapy and FOLFOX (based on ABC-06) has proven efficacy (paragraph 5.2, ivosidenib PSD, July 2024 PBAC meeting), suggesting that FOLFOX was a reasonable comparator and may in fact be used by the majority of patients in the second line setting. The PBAC also considered that FOLFOX was an important relevant comparator for a substantial proportion of patients. (paragraph 7.5, ivosidenib PSD, July 2024).

The commentary considered it unlikely that ivosidenib would be a comparator for the majority of patients as *IDH1* and *FGFR2* variants are generally considered mutually exclusive (Murugesan 2022) though 7/618 patients (1.1%) with *FGFR2* variants also had *IDH1* variant in Murugesan 2022.

The commentary considered that the nominated treatment comparator was consistent with the Ratified PICO confirmation, which considered the comparator to be second- or subsequent line treatment with standard of care chemotherapy or palliative care with active symptom control.

9. Summary of public consultation input

Consultation input was received from two medical, health, or other (non-consumer) organisations and three consumer groups or organisations. Two inputs were received from individuals – one health professional/ academic and one consumer.

The organisations that submitted input were:

- Centre for Molecular Oncology
- Liver Foundation
- Pancare Foundation
- Rare Cancers Australia (RCA)
- St Vincent's Hospital Sydney

Level of support for public funding

Both individuals and all organisations expressed support at the public funding of tumour tissue testing for *FGFR2* fusions/arrangements in people with cholangiocarcinoma (CCA).

Comments on PICO

Input from a health professional respondent agreed with details outlined in the PICO, but suggested limitations with the proposed approach, noting that tissue-only-testing relies on patients having sufficient tissue to detect *FGFR2* fusion/rearrangement, which is often not the case with individuals with this tumour-type. Liver Foundation agreed the population is appropriate, and the proposed approach to the delivery of the service was practical and likely to be successfully achieved. St Vincent's Hospital Sydney noted the proposed eligibility criteria was

appropriate, and agreed with the proposed approach, comparator, and outcomes as set out in the PICO.

Perceived Advantages

Input from both individuals and organisations described the benefits of those with CCA undergoing *FGFR2*-targeted therapies, noting improvements in quality of life, decreased symptoms such as shortness of breath and coughing, and increased ability to exercise and travel.

Perceived Disadvantages

Input did not outline any disadvantages of *FGFR2*-targeted therapies for the treatment of CCA, with the health professional respondent noting the current prohibitive cost as being the only barrier to treatment.

Support for Implementation /issues

The health professional respondent suggested a preference for integrated-panel testing next-generation sequencing (NGS) for the multiple genetic alterations in CCA, noting both the cumulative costs of targeting them sequentially, and the lack of availability of tissue often associated with this tumour-type. The health professional respondent also agreed with the proposed item descriptor(s) and implementation, but noted the need for upskilling of health professionals in interpreting molecular test results.

Moreover, the consumer respondent described the importance of additional support services for those with CCA, including nurse-coordination, occupational therapy, physiotherapy/ exercise physiology, social work, clinical psychology, dietician services, and palliative care.

Liver Foundation noted the expected effect of the proposed application would offer hope to patients and their families, with likely significant improved survival and quality of life. St Vincent's Hospital Sydney expressed support at the proposed fee.

10. Characteristics of the evidence base

The submission undertook a broad literature search to identify relevant studies for all steps in the linked evidence approach. The commentary considered that none of the included studies were in Australian populations which may affect their applicability, though many were from likely comparable health care systems such as the US and Europe and therefore may not present substantial applicability issues.

Table 4 Summary of the linked evidence approach

Criterion	Type of evidence supplied	Extent of evidence supplied			Overall risk of bias in evidence base	Used in modelled evaluation
Accuracy and performance of the test (cross-sectional accuracy)	Concordance with clinical utility standard	☒	k=3	n=368	Moderate - High	No
Prognostic evidence (longitudinal accuracy)	Meta-analysis of prognostic impact of *FGFR2* alteration on overall or progression-free survival in patients with CCA	☒	k=1[b]	n=1314	Moderate	No
Change in patient management	None [c]	☐	k=	n=	-	-
Health outcomes (clinical utility)	None [d]	☐	k=	n=	-	-
Predictive effect (treatment effect variation)	A retrospective analysis of patients from four US centres with *FGFR* alterations compared to those who do not have *FGFR* alterations (Jain 2018)	☒	k=1	n=337	Moderate - High	No
Treatment effect (enriched)	None [a]	☐	k=	n=		-

Source: pp57-91 of the submission.
CCA = cholangiocarcinoma; FGFR = Fibroblast growth factor receptor; k=number of studies, n=number of patients; SoC = standard of Care
[a] clinical evidence based on biomarker selected patients treated with futibatinib compared to non-biomarker selected patients treated with SoC only.
[b] One meta-analysis based on 6 studies.
[c] The submission presented calculations in the financial estimates to estimate impact on use.
[d] The economic model did not account for changes in patient management, as the model only followed positive FGFR2 patients, with an adjustment for costs of all tested patients.

11. Comparative safety

Adverse events from testing

No information on test safety was presented in the submission. The 1779 Ratified PICO included safety of re-biopsy as another test related consideration but inappropriately this was not discussed in the submission. The commentary considered that the safety of the test, especially relating to re-biopsy, should be considered unknown. Given the proposed MBS item descriptor restricts benefit to once per lifetime, re-biopsies may be rare. However, the diagnostic yield of FGFR2 fusion/rearrangement may vary depending on the stage of disease (see Table 6 and discussion below), and given the discrepancy between the timing of testing suggested by the PASC (at diagnosis of CCA) and by the submission (only for locally advanced or metastatic), there may be clinical reasons for re-biopsy in some patients despite the once per lifetime restriction.

Adverse events from changes in management

The submission did not present the consequences of false positives (resulting in patients without FGFR2 alterations receiving futibatinib), or false negatives (resulting in patients with FGFR2 alterations not receiving futibatinib). Although it would be expected that false negatives would result in patient management and outcomes consistent with current care, with potentially foregone benefit, the commentary noted that no data has been presented to estimate the impact of patients with Wild Type FGFR2 receiving futibatinib.

The commentary noted that no comparative safety evidence between futibatinib and FOLFOX was presented in the submission.

12. Comparative effectiveness

Table 5 presents the available data to inform the testing comparison. The commentary noted that the evidence was presented to estimate the impact of testing versus no testing, but no evidence was presented to estimate the impact of futibatinib treatment in biomarker negative patients. Additionally, no clinical data was presented for change of management.

Moreover, most of the included evidence reflected a test population of advanced or metastatic CCA. This is inconsistent with the PASC advice that testing occur in patients with CCA at time of diagnosis. The commentary considered that this difference could impact the diagnostic yield of testing.

Table 5 Data availability to inform comparisons

Proposed test vs no test	No study	
Proposed test vs alternative test [a]	Silverman 2022 and F1CDx Technical Information, Zou 2023	
	Futibatinib	**SoC**
Biomarker test positive	FOENIX-CCA2	Jain 2018
Biomarker test negative	No evidence presented	Jain 2018; Niu 2024

Source: pp57-91 of the submission.
[a] Alternative test is next generation sequencing on DNA.
F1CDx = Foundation One CDx assay; SoC = standard of care

Comparative accuracy/test performance

Diagnostic yield

The submission defined diagnostic yield as the inverse of the "number of patients with advanced CCA who need to be tested using RNA NGS to identify one patient with an *FGFR2* alteration" (p57 of the submission). Given there may be some patients who are not tested, or in whom treatment may be futile, the biomarker prevalence among those tested is likely less than the biomarker prevalence among all cases. Nonetheless, for the purpose of the commentary, diagnostic yield and prevalence are used interchangeably to be consistent with the submission.

The submission (p65) claimed that the literature search described above identified five citations providing data from five studies on the diagnostic yield of *FGFR2* fusions or rearrangements (alterations) testing in patients with locally advanced or metastatic CCA. However, the commentary noted that a total of six studies were used to inform diagnostic yield as presented below. Studies were eligible for inclusion for this specific outcome (i.e. diagnostic yield) if at least 75% of the population had advanced (stage III/IV) CCA and testing was predominantly carried out using NGS. However, FISH was nominated as an alternative test in the submission and was included as part of the research questions mapped to the assessment framework in the 1779 Ratified PICO therefore the commentary considered its exclusion may not be appropriate.

The following studies were included to inform diagnostic yield:

- Jain 2018[6]: a multicentre, retrospective analysis of 95 patients who had pathologically confirmed biliary cancer between January 2000 and December 2015. Patients had at least 3 months of follow up, and had FGFR alterations (*FGF19, FGFR1, FGFR2, FGFR3 or FGFR4*) on molecular testing. The comparison group included 282 patients with the same cancers from the same institutions without any known *FGFR* genetic alterations on molecular profiling with NGS using a common platform (Foundation-One);

[6] Jain et al. (2018). Cholangiocarcinoma With FGFR Genetic Aberrations: A Unique Clinical Phenotype. *JCO Precis Oncol,* 2:1-12.

- Lamarca 2020[7] was a consecutive, retrospective single centre analysis that included patients diagnosed with advanced biliary tract cancer including iCCA, eCCA, gallbladder cancer, and ampullary carcinoma who underwent molecular profiling between April 2017 and June 2020 based on analysis of either tumour samples (F1CDx/Oncomine® platforms) or circulating tumour DNA (ctDNA) (FoundationOne Liquid® platform;
- Rimini 2022[8] included 284 patients with iCCA treated for resectable, locally advanced or metastatic disease tested with F1CDx, and included details on prevalence of *FGFR* alterations;
- Tomczak 2022[9] conducted molecular profiling and matched treatment on 101 patients with primary liver cancer referred to their centre using both NGS on DNA and NGS on RNA on the same samples; and
- Vancanneyt 2023[10] reported results of molecular testing by either F1CDx or Foundation 1 Liquid NGS or an in-house developed 96 cancer gene panel were retrospectively collected from patients with locally advanced or metastatic CCA diagnosed between 01/12/2018 and 01/08/2021 in a single centre.

The submission noted that determination of the diagnostic yield of NGS on RNA for identification for *FGFR2* fusions and rearrangements requires identifying the proportion of samples that initially fail testing and identifying the prevalence of *FGFR2* alteration in samples that are successfully tested.

Additionally, Rizzato 2022[11] was identified by the submission as reporting prevalence of CCA patients with *FGFR2* variants but not specifically advanced CCA and so was excluded by the submission. However, the commentary considered that this was inaccurate as Rizato 2022 was a retrospective single centre study of 286 patients affected by locally advanced or metastatic biliary tract cancer (183 iCCAs, 67 eCCAs, 36 gallbladder carcinomas) who were profiled by means of targeted DNA/RNA NGS, immunohistochemistry and FISH for *FGFR2/3*, *ERBB2*, *NTRK* alterations, *IDH1/2* and *BRAF* variants and DNA mismatch repair complex proteins alterations/microsatellite instability. The prevalence results in CCA patients (excluding the 36 gallbladder carcinomas) from Rizzato 2022 was added to the advanced CCA patients below.

Table 6 presents the estimated prevalence of *FGFR2* alterations in advanced CCA using NGS testing (on DNA or RNA) or FISH (in Jain 2018) identified by the submission.

[7] Lamarca et al. (2020). Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. Journal of hepatology, 73(1):170-185.

[8] Rimini et al. (2022a). "Molecular profile and its clinical impact of IDH1 mutated versus IDH1 wild type intrahepatic cholangiocarcinoma." Sci Rep 12(1): 18775.

[9] Tomczak et al. (2022). "Precision oncology for intrahepatic cholangiocarcinoma in clinical practice." Br J Cancer 127(9): 1701-1708.

[10] Vancanneyt et al. (2023). "Therapeutic yield of extensive molecular profiling in cholangiocarcinoma: a retrospective single-center study." J Cancer Res Clin Oncol 149(11): 9173-9181.

[11] Rizzato et al. (2022). "Prognostic impact of FGFR2/3 alterations in patients with biliary tract cancers receiving systemic chemotherapy: the BITCOIN study." Eur J Cancer 166: 165-175.

Table 6 *FGFR2* alterations in advanced CCA – summary of the prevalence

Citation	Region/ Country	Study type	Testing population	Testing method	Prevalence n/N (%)
Advanced CCA					
Jain 2018	USA	Multicentre 2000-2015	CCA (Advanced 77%)	DNA NGS or FISH	74/317 (23.3)
Tomczak 2022	Germany	Single-centre (Heidelberg) 2018-2021	Advanced CCA	DNA/RNA NGS	22/101 (22)
Lamarca 2020	UK	Single-centre (Manchester) 2017-2020	Advanced CCA	DNA NGS	14/82 (17.1)
Vancanneyt 2023	Belgium	Single centre (University Hospitals Leuven) 2018-2021	Advanced CCA	Mostly DNA NGS	9/116 (7.8)
Rizzato 2022	*Italy*	*Single centre (Istituto Oncologico Veneto of Padua) 2008-2019*	*Advanced CCA [a]*	*DNA/RNA NGS and FISH*	*14/250 (5.6)*
Advanced CCA weighted average prevalence (excluding Rizzato 2022)					*119/616 (19.3)*
Advanced CCA weighted average prevalence (including Rizzato 2022)					*133/866 (15.3)*
Advanced iCCA					
Jain 2018	USA	Multicentre 2000-2015	iCCA (Advanced NR)	DNA NGS or FISH	74/273 (27.1)
Lamarca 2020	UK	Single-centre (Manchester) 2017-2020	Advanced iCCA	DNA NGS	13/62 (21.0)
Vancanneyt 2023	Belgium	Single centre (University Hospitals Leuven) 2018-2021	Advanced iCCA	Mostly DNA NGS	8/65 (12.3)
Rimini 2022	Italy and Spain	Multicentre 2013-2021	Advanced iCCA	NGS	25/247 (10)
Rizzato 2022	*Italy*	*Single centre (Istituto Oncologico Veneto of Padua) 2008-2019*	*Advanced iCCA [a]*	*DNA/RNA NGS and FISH*	*13/183 (7.1)*
Advanced iCCA weighted average prevalence (excluding Rizzato 2022)					*120/647(18.5)*
Advanced iCCA weighted average prevalence (including Rizzato 2022)					*133/830 (16.0)*

Source: table 2.5, p67 of the submission. BTC = biliary tract cancer; CCA = cholangiocarcinoma; FISH = fluorescence in situ hybridization; iCCA = intrahepatic cholangiocarcinoma; NGS = next generation sequencing; NR = not reported; UK = United Kingdom; USA = United States of America

[a] The submission erroneously did not include these patients as advanced CCA, though the publication specified that only advanced CCA patients were included

Text in italics indicate information extracted during evaluation

The submission proposed that 20% be used as the estimate of the diagnostic yield of testing for the presence of an *FGFR2* alteration with RNA NGS in a locally advanced or metastatic CCA population. The submission did not describe how this was calculated but was consistent with the weighted average prevalence from the included studies (119/616=19.3%, though this decreased to 15.3% when Rizzato 2022 was included). However it was noted that the publications presented in the submission (as summarised in Table 6) indicate a wide range of estimates (from 7.8% in Vancanneyt 2023 in all CCA to 27.1% in Jain 2018 in iCCA), and consequently, the commentary considered the diagnostic yield may be uncertain.

The submission also presented results from the broader CCA population (i.e. not limited to advanced CCA). The reported prevalence in a broad CCA population was in the range of 6.1% to 16.9%, while prevalence in a broad iCCA population is in the range of 4.6% to 20.7%.

As previously noted, the PASC recommended testing at diagnosis of CCA and not at the advanced or metastatic stage. When studies of *FGFR* in all CCA patients were considered, a lower average prevalence rate in a population not limited to advanced or metastatic stage (1,016/10,041=10.1%) was estimated. As such, the commentary considered the diagnostic yield of *FGFR2* variants may be dependent on what stage of cancer the testing occurs.

Reference standard and clinical utility standard

The PASC and the submission did not nominate a reference standard.

The clinical utility standard in the submission was NGS on DNA for detection of *FGFR2* fusions or rearrangements. The commentary considered that this was in alignment with PASC advice.

The submission noted that the pivotal futibatinib study, FOENIX-CCA2, was divided into three separate sub studies: a dose escalation study, an expansion study and a Phase 2 study. To be eligible for entry into Phase 2 of the study, patients had to have histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harbouring *FGFR2* gene fusions or other *FGFR2* rearrangements based on the results of either:

- Central testing: testing by Foundation Medicine as part of study pre-screening; or previously tested by Foundation Medicine (in this case, tumour tissue was to be provided to Foundation Medicine if available); or
- Local testing: local laboratory testing using NGS, FISH, or other assays able to determine *FGFR2* gene fusions or other *FGFR2* rearrangements on tumour tissues or from ctDNA. Patients enrolled on this basis were requested to provide tumour tissues to Foundation Medicine, if available from either archival samples or fresh tumour biopsy.

The treated population comprised 103 patients with *FGFR2* alterations, and patients without *FGFR2* alterations were excluded. Of these, 99 had their FGFR2 alterations identified in either tissue samples taken from the primary (55; 53.4%) or metastatic (44; 44.4%) tumour sites via the following testing methods:

The commentary noted that there were discrepancies in the specific NGS on DNA performed in FOENIX-CCA2. Goyal 2023 (the publication for FOENIX-CCA2) noted that the test performed in FOENIX-CCA2 was the F1CDx assay. However, the FOENIX-CCA2 CSR stated that patients were tested with:

- The Foundation Medicine Inc. (FMI) DNA NGS clinical trial assay (F1CTA) – 68 patients.
- The FMI commercially-available Food and Drug Administration (FDA)-approved DNA NGS test (F1CDx) – 25 patients.
- Local NGS testing other than F1CDx – 5 patients; and
- Local FISH testing - 1 patient

Consequently, both F1CDx and F1CTA could represent the proposed clinical utility standard of NGS on DNA based on testing in FOENIX-CCA2. As the test used to identify the most patients in the pivotal study, F1CTA was likely the more reasonable clinical utility standard. Appropriately, the submission provided results of a concordance analysis between F1CTA, and the commercially available F1CDx tests.

The MSAC Guidelines, (p102) state that the clinical utility standard is the test (and methods of testing) that was used to generate direct clinical outcomes in patients with and without a biomarker. However, the submission did not present any clinical data on biomarker negative patients treated with futibatinib. The commentary considered that this potentially presents a barrier to establishing the codependency proposed in the submission.

Concordance

The following studies were included in the assessment of concordance between different tests:

- Silverman 2022[12] and F1CDx Technical Information provide a description of the testing used in the FIGHT-202 study (a single arm study which evaluated pemigatinib, an FGFR1-3 inhibitor, in previously treated patients with advanced CCA with *FGFR2* fusion or other rearrangement) and analyses of the concordance between i) the F1CTA (NGS on DNA) and the commercially available Companion Diagnostic (F1CDx; NGS on DNA) and ii) the F1CDx (NGS on DNA) and an externally validated RNA NGS assay (evNGS); and

- Zou 2023[13] assessed the concordance of FISH on DNA with NGS on DNA with samples from 167 iCCA patients.

Table 7 presents a summary of the key features of the included concordance evidence.

Table 7 Key features of the included test accuracy evidence comparing different FGFR2 tests

Citation	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcomes	Result used in economic model
Silverman 2022 and F1CDx Technical Information	181	Concordance study Moderate	Samples from patients with CCA	F1CDx DNA NGS (FGFR2) Reference standard	F1 CTA DNA NGS (FGFR2) Clinical utility standard	PPA, NPA, OPA, Adj PPV, Adj NPV	No
	159	Concordance study Moderate	Samples from patients with CCA	F1CDx DNA NGS (FGFR2) Reference standard	EV RNA NGS (FGFR2) Index test	Adj PPA, Adj NPA, Adj OPA, PPV, NPV	No
Zou 2023	28	Concordance study High	Samples from patients with iCCA	SU-Panel and Illumina Platform DNA NGS (FGFR2) Reference standard	Break-apart FISH (FGFR2) Index test	Consistency test (Post hoc calculation of PPA, NPA, OPA, PPV and NPV)	No

Source: Table 2.15, p82 of the submission.
CCA = cholangiocarcinoma; CTA = clinical trial assay; EV = externally validated; F1CDx = FoundationOne Companion Diagnostic; NGS = next generation sequencing; NPA = negative percent agreement; NPV = negative predictive value; OPA = overall percent agreement; PPA = positive percent agreement; PPV = positive percent value
Note: As Goyal 2023 and Tas-120-101b-report-body did not include concordance data, but were rather used to describe and define the clinical utility standard, the submission did not include risk of bias assessments for these.

The commentary considered that the submission's characterisation of the test accuracy evidence was unclear, particularly in its identification of what the reference test and index test were for each study. For example, the submission identified evNGS on RNA as the index test in Silverman 2022, when evNGS on RNA had been externally validated in the Silverman 2022 study and thus would actually have been the reference standard. Since each test arm was evaluated for risk of bias the inconsistent labelling of reference standard and index test does not impact the actual assessment of overall risk of bias.

[12] Silverman et al. (2022). "Validation and Characterization of FGFR2 Rearrangements in Cholangiocarcinoma with Comprehensive Genomic Profiling." J Mol Diagn 24(4): 351-364.
[13] Zou et al. (2023). Molecular Detection of FGFR2 Rearrangements in Resected Intrahepatic Cholangiocarcinomas: FISH Could Be An Ideal Method in Patients with Histological Small Duct Subtype. J Clin Transl Hepatol, 11(6):1355-1367.

The submission considered that all the included studies had a moderate risk of bias except for Zou (2023), which had a high risk of bias.

The commentary considered that due to high risk of patient selection bias and flow and timing bias, the submission's assessment of high risk of bias for Zou 2023 was reasonable.

For Silverman 2022, it was unclear on what basis the risk of bias was considered moderate as opposed to high or uncertain, given that there were domains with 'not reported' or 'high risk of bias'. The commentary considered that it may be more reasonable to have assumed that Silverman 2022 had a high risk of bias due to the risk of bias being unclear in some domains.

The submission noted that data reported by Silverman 2022 as well as in the F1CDx Technical Information provide confirmation of the concordance between the F1CDx and F1CTA assays. The clinical utility standard proposed in the current submission was NGS on DNA, and both F1CDx and F1CTA assays were NGS on DNA. However, given the lack of clarity regarding the differences between these tests, the commentary considered that the submission's presentation of concordance information between the F1CTA assay predominantly used in FOENIX-CCA2 and the commercially available F1DX assays was appropriate as it provides comparative data between the two potential clinical utility standards.

Following testing by the F1CTA in the FIGHT-202 study, residual DNA for patients was banked to support clinical bridging study testing with the F1CDx assay. Silverman 2022 was conducted to assess the clinical efficacy of F1CDx in identifying *FGFR2* rearrangement positive patients for treatment with pemigatinib and the concordance between *FGFR2* rearrangement status (mutant and non-mutant) tested with the F1CTA and F1CDx. Residual DNA was available for 108 patients screened with the F1CTA, in addition to 73 *FGFR2* rearrangement-negative specimens for a total of 181 positive and negative F1CDx evaluable samples included in the analysis.

Table 8 shows the assessment of the concordance between the F1CTA (NGS on DNA) assay used to identify patients for inclusion in the FIGHT-202 study and the F1CDx (NGS on DNA) assay. In Silverman 2022, F1CDx results were 100% concordant with those of F1CTA.

Table 8 Concordance between F1CDx NGS on DNA and F1CTA NGS on DNA in Silverman 2022

		F1CTA DNA			
		FGFR2 +	**FGFR2 –**	**Total**	
F1CDx DNA	FGFR2 +	84*	0	84	Adj PPV = 100% [73.1-100]
	FGFR2 –	0	97	97	Adj NPV = 100% [99.5-100]
	Total	84	97	181	
		Adj PPA = 100% [95.7-100]	Adj NPA = 100% [96.3-100]		Adj OPA = 100% [98.0-100]

Source: Table 2.17, p86 of the submission.
DNA = deoxyribonucleic acid; F1CDx = FoundationOne Companion Diagnostic; F1CTA = FoundationOne Clinical Trial Assay; FGFR = fibroblast growth factor receptor; NPA = negative percent agreement; NPV = negative predictive value; OPA = overall percent agreement; PPA = positive percent agreement; PPV = positive predictive value; RNA = ribonucleic acid
Notes: Numbers within square brackets represent 95% 2-sided confidence intervals and prevalence adjusted; * One sample was enrolled by the F1 Heme assay and was analysed as an F1 result for the concordance analysis.

In Silverman 2022, an analytical concordance study was also performed to evaluate the agreement between F1CDx (NGS on DNA) and an evNGS assay using the ArcherDX FusionPlex platform (Table 9). FFPE samples from 26 *FGFR2* rearrangement-positive CCA samples and 133 *FGFR2* rearrangement-negative CCA samples were run on both platforms. Of these samples, 142 were iCCA, with the remaining 17 not classified as to intrahepatic or extrahepatic.

There was disagreement between tests for three of the 159 included samples: two samples testing positive on the RNA-based evNGS were negative on the DNA NGS F1CDx test, while one sample testing negative on the RNA-based evNGS tested positive on the F1CDx test. The overall percent agreement was 98.3%, while the adjusted PPV was 96.2% (80.4-99.9) and the adjusted NPV was 98.5% (94.6-99.8).

Table 9 Concordance between NGS on DNA (F1CDx) and NGS on RNA (evNGS) in Silverman 2022

		evNGS RNA				
		FGFR2 +	FGFR2 –	Invalid	Total	
F1CDx DNA	FGFR2 +	25	1	0	26	Adj PPV = 96.2% (80.4-99.9)
	FGFR2 –	2	130	1	133	Adj NPV = 98.5% (94.6-99.8)
	Invalid	0	0	0	0	
	Total	27	131	1	159	
		Adj PPA = 87.1% (61.4-98.3)	Adj NPA = 99.6% (92.9-100)	-		Adj OPA = 98.3% (93.3-99.8)

Source: Table 2.19, p88 of the submission.

Adj = adjusted; DNA = deoxyribonucleic acid; EV = externally validated; F1CDx = FoundationOne Companion Diagnostic; FGFR = fibroblast growth factor receptor; NPA = negative percent agreement; NPV = negative predictive value; OPA = overall percent agreement; PPA = positive percent agreement; PPV = positive predictive value; RNA = ribonucleic acid

Notes: Numbers within square brackets represent 95% 2-sided confidence intervals and prevalence adjusted (9.6%) to account for sampling differential; * One sample was enrolled by the F1 Heme assay and was analysed as an F1 result for the concordance analysis.

The submission (p87) noted that the main difference between NGS on DNA versus RNA is that NGS on RNA is more likely to identify *FGFR2* fusions than NGS on DNA, and two (out of 27) patients identified as having *FGFR2* variant using NGS on RNA were considered to be Wild Type *FGFR2* using NGS on DNA. The submission considered that, given the results presented in the context of the treatment effect modification showing that the use of FGFR-directed therapy in patients with an *FGFR2* alteration provides a substantial survival benefit over standard chemotherapy, this suggests that there is no negative impact of identifying additional patients with *FGFR2* fusions using NGS on RNA rather than NGS on DNA. The commentary considered that it was unclear how any evidence presented in this submission supported the claim that there is no negative impact to (incorrectly) identifying additional patients with *FGFR2* fusions using NGS on RNA. FOENIX-CCA2 only enrolled patients who were found to be *FGFR2* positive on NGS DNA. Therefore, this study does not provide any information regarding the efficacy of futibatinib in patients who would have been classified as FGFR2 positive on NGS on RNA if tested but not NGS on DNA. Data to inform a discussion of the risks of treating patients without *FGFR* variant (due to false positives) has not been included in this submission as no data on futibatinib in Wild Type *FGFR2* patients was provided.

One of the 26 patients identified as having an *FGFR2* alteration via NGS on DNA was not identified on NGS using RNA. The submission considered that, given the F1CDx assay was being validated against evNGS in this study, it is assumed this result is a true negative and, using NGS on RNA as testing, this patient would have avoided receiving an FGFR2 inhibitor unnecessarily. The commentary considered the submission's assumption that the discordant result is a true negative was not reasonable and is inconsistent with the submission's nomination of NGS on DNA as the clinical utility standard.

The submission considered that the results of the two main concordance analyses presented in Silverman 2022 suggested that the NGS test on DNA and RNA are highly concordant and that the patient population identified by the methodology proposed for MBS listing (NGS on RNA) would find virtually identical patients to those identified in the futibatinib trial, resulting in no appreciable difference in drug effect between the trial population and the likely Australian population. The commentary considered that while the concordance between NGS on RNA (an evNGS) and NGS on DNA was generally high, the tests would not identify 'virtually identical patients' as claimed by the submission given the PPA for *FGFR2* variant positive patients was less than 100%. In Silverman 2022 NGS on RNA was more likely to identify patients as being *FGFR2* fusion/rearrangement positive (n=27) compared to NGS on DNA (n=25) and there may be a number of false positives (i.e. positive as per NGS on RNA, but negative as per NGS on DNA) for whom the efficacy of futibatinib was unknown.

Zou 2023 reported on a concordance analysis evaluating the agreement between NGS on DNA (using the SU-450 panel and Illumina platform) and FISH on DNA (10q26 gene break-apart probe set) (Table 10). A total of 167 FFPE samples from patients who underwent surgical resection of

iCCA in Zhongshan Hospital, Fudan University (China) were collected, and a total of 28 were tested with both NGS and FISH.

The authors considered that FISH on DNA was shown to be consistent with NGS on DNA, with the results showing a Kappa value of 0.696 (p<0.001), with four cases being discordant.

Post hoc calculations of concordance/diagnostic accuracy conducted for this submission are presented in Table 10. The submission considered that these results show that FISH on DNA has a lower negative percent agreement than NGS on RNA when both are compared with NGS on DNA and highlighted why NGS is the preferred molecular testing method for identification on *FGFR2* alterations in clinical practice guidelines.

Table 10 Concordance between NGS on DNA and FISH on DNA in Zou 2023

		NGS on DNA			
		FGFR2 +	**FGFR2 –**	**Total**	
FISH on DNA	FGFR2 +	16	4	20	PPV = 80% (64.3, 89.9)
	FGFR2 –	0	8	8	NPV = 100% (63.1, 100)
	Total	16	12	28	
		PPA = 100% (79.4, 100)	NPA = 66.7% (34.9, 90.1)		OPA = 85.7% (67.3, 96.0)

Source: Table 2.20, p89 of the submission.
DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptor; FISH = fluorescence in situ hybridisation; NGS = next-generation sequencing; NPA = negative percent agreement; NPV = negative predictive value; OPA = overall percent agreement; PPA = positive percent agreement; PPV = positive predictive value
Note: All calculations conducted post hoc using https://www.medcalc.org/calc/diagnostic_test.php

The submission noted that concordance between FISH on DNA and NGS on DNA (and by extension NGS on RNA) is less robust, which was consistent with recommendations in clinical practice guidelines that it only be used where NGS cannot. The commentary considered that this was reasonable.

Reliability:

The submission identified one study that provides data on the reliability of NGS on RNA and FISH on DNA for detection on *FGFR2* fusions in patients with iCCA (Neumann 2023).

Neumann 2023 reported the results of a study assessing the early real-world performance of NGS on RNA and FISH on DNA for the identification of *FGFR2* alterations in patients with CCA in Germany. The study involved two steps: (Step 1) an internal validation of the results by different academic centres (panel institutes) and (Step 2) an external round robin test. In Step 1, a cohort of 10 CCAs with known *FGFR2* status (four fusion positive and six fusion negative) was tested by the Institute of Pathology, University Hospital Heidelberg, Germany; data were validated by four academic pathology departments in Germany. In a second step, a round robin test involving 21 academic and non-academic centres testing with RNA-based NGS approaches was carried out. Five participant centres also performed FISH testing (Group A) and the remaining 16 performed NGS only (Group B).

For the internal validation in the Neumann 2023 study (Step 1), each of the 10 cases selected and analysed by the lead panel institute was cross tested by four different academic centres (panel institutes) using a targeted RNA-based NGS assay. Additionally, two centres employed a FISH assay. All panel institutes successfully identified and annotated the fusion-positive and fusion-negative cases.

The five centres in Group A submitted their results and were able to correctly detect the fusion-positive cases by FISH with the exception of Case 10.

The success rate of the centres in the NGS part of the NGS and FISH arm (Group A) was 60% (3/5). 40% (2/5) of the institutes failed to correctly identify fusions in Cases 4 and 7 when using amplicon-based panels because no primers for the partner gene were included. 60% (3/5) of the participating centres were not able to correctly analyse Case 10. Two out of the five centres participating in the combined NGS and FISH arm failed the NGS part due to using assays

(Thermo Fisher OFA assay, AmoyDx HANDLE Classic Panel) that did not contain the primers to detect the *FGFR2*::*DBP* and *FGFR2*::*ATE1* fusions.

The success rate of the centres in the NGS-only arm (Group B) was 81% (13/16). 62.5% (10/16) of the participating centres were not able to correctly analyse Case 10. The authors of Neumann 2023 stated that a comprehensive re-analysis showed that the material was not the issue, but rather the NGS panels and technologies used. For example, 6.25% (1/16) and 12.5% (2/16) of the institutes, respectively, failed to correctly identify fusions in Cases 4 and 7 when using amplicon-based panels because no primers for the partner gene were included. One of the assays used lacked a *FGFR2* imbalance test (or the partner primers) so it did not detect some variants, and another assay had an imbalance test which did not identify the gene fusion event.

Specifically, Neuman 2023 noted that Case 10 contains a *FGFR2*::*ATE1* fusion, causing an out-of-frame fusion transcript containing only the 3'-untranslated region (UTR) of the *ATE1* gene. This fusion is defined by the loss of the inhibitory domains/motifs in exon 18 of *FGFR2*. The gene locus of *ATE1* is directly downstream of the *FGFR2* gene locus. This rearrangement leads to a fusion of *FGFR2* and *ATE1* where the fluorochrome-labelled probes are located further upstream of both *FGFR2* and *ATE1*. The authors considered this case is challenging because it can hardly be detected using a break-apart FISH and NGS-based detection requires specific settings of the bioinformatics pipeline.

The submission did not comment on the reliability of testing described in Neuman 2023 but considered that in terms of applying these results to the Australian setting, as noted in the MSAC Guidelines (p113), while inter-laboratory variability/agreement should be considered, "any variability between laboratories should be mitigated (or controlled) by an appropriate National Association of Testing Authority–approved quality assurance program."

Overall, the commentary considered that it was unclear if the NGS testing reliability described in Neuman 2023, which was low, would be reflective of Australian practice. In particular, NGS testing appears to be able to correctly identify the negative results, but much less reliable when it comes to identifying positive results.

Prognostic evidence

The submission identified seven citations providing data on the prognostic impact of *FGFR2* alteration testing in patients with CCA. These included a meta-analysis by Niu et al (2024), and the six individual studies included in that meta-analysis (Abou Alfa 2022, Boerner 2021, Buckarma 2022, Javel 2016, Pu 2021, Rizzato 2022).

The meta-analysis was based on a comprehensive search to July 2023 conducted across the PubMed, Embase, Web of Science, and the Cochrane Library databases, with the objective being to identify relevant publications comparing the prognosis of *FGFR2* alterations and no *FGFR2* alterations groups among patients with CCA undergoing surgical resection or other systemic therapies. The primary outcome indicators were overall survival (OS) and disease-free survival (DFS). Quality of the individual included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (reported as the NOS score).

A summary of the main characteristics of the studies as reported in the Niu 2024 meta-analysis is provided in Table 11.

Table 11 Characteristics of studies included in the Niu 2024 meta-analysis

Citation	Study type (location)	Study interval	Tumour type: N	Group: N	Mean age (y)	Sex (n)	Therapy	FU (months)	NOS score[d]
Abou-Alfa 2022	Retrospective (USA)	2013-2019	iCCA: 124	FGFR+: 15 FGFR–: 109	58.0 64.0	M=6; F=9 M=53; F=62	Systemic	160	8
Boerner 2021	Retrospective (USA)	1993-2019	iCCA: 412	FGFR+: 92 FGFR–: 320	NR	NR	Resection	60	7
Buckarma 2022	Retrospective (USA)	2008-2014	iCCA: 95	FGFR+: 12 FGFR–: 83	62.3 53.1	M=42; F=41 M=2; F=10	Systemic; resection	120	8
Javle 2016	Retrospective (USA)	NR	iCCA: 224	FGFR+: 30 FGFR–: 194	NR	NR	Systemic; resection	60	7
Pu 2021	Retrospective (China)	2005-2017	iCCA: 173	FGFR+: 9 FGFR–: 164	57.0 61.3	M=6; F=3 M=79; F=85	Resection	120	8
Rizzato 2022	Retrospective/ prospective (Italy)	2008-2019/ prospective until 2020	iCCA: 183 eCCA+GBC: 103	FGFR+: 15 FGFR–: 271	60 65	M=7; F=8 M=142; F=129	Systemic	120	8

Source: Table 2.6, p69 of the submission.
eCCA = extrahepatic cholangiocarcinoma; F = female; FU = follow-up; GBC = gallbladder cancer; iCCA = intrahepatic cholangiocarcinoma; M = male; NOS = Newcastle-Ottawa Scale; NR = not reported
[d] As reported in the Niu 2024 meta-analysis. The maximum score on the Newcastle-Ottawa Scale is 9, and a score 7 or higher indicates a high-quality study

The commentary considered that the submission's inclusion of studies to determine prognostic impact was incomplete, as among the evidence used by the submission in other parts of the submission, two studies were also relevant and should have been included:

Firstly, Jain 2018 was identified by the submission and used to support treatment effect modification (discussed below). Jain 2018 reported OS outcomes in 377 CCA patients, 95 with *FGFR* (77 with *FGFR2*) variant and 282 without *FGFR* alterations. Therefore, results from Jain 2018 may be potentially used to inform the prognostic effect.

The submission also identified a conference abstract of Shroff 2022 (referred to as the Flatiron study in the submission, this will be referred to as Shroff 2022 in the commentary) as part of the evidence of natural history of CCA patients. Shroff 2022 used the Flatiron Health-Foundation Medicine CCA database and identified 571 CCA patients, and reported the OS in 75 patients with *FGFR2* fusions/rearrangements and 496 patients with Wild Type *FGFR2*. A key secondary objective was to evaluate the influence of *FGFR* status on OS after adjusting for potential prognostic variables. Shroff 2022 was considered to be directly relevant to informing the prognostic impact of *FGFR2* fusions/rearrangements. However, as it was only available as a conference abstract and details regarding any peer review processes was not apparent.

Table 12 Impact of *FGFR2* status on overall survival

Study author	Testing population	Method of detection	Timing of outcome measurement	*FGFR2* positive Median OS (95% CI)	*FGFR2* WT Median OS (95% CI)	Difference	Publication-reported HR (95% CI) P value	Meta-analysis - reported HR (95% CI)
Abou-Alfa 2022	iCCA (Stage IV – 60%)	NGS	From diagnosis	N=9 31.3 months (5.8−NA)	N=109 21.7 months (16.1−26.6)	9.8 months	NR NR	1.95 (0.98, 3.89)[a]
			From first-line therapy	N=9 24.8 months (3.4, NE)	N=90 14.5 months (12.2, 20.2)	10.3 months	NR NR	
			From second-line therapy	N=4 23.2 months (10.8, NE)	N=70 8.2 months (6.5, 14.6)	15.0 months	NR NR	
Buckarma 2022	Resected iCCA (Stage NR)	FISH	From diagnosis	N=12 5-year OS: 83% 10-year OS: 46%	N=83 5-year OS: 32% 10-year OS: 22%	5-year OS: 51% 10-year OS: 24%	2.33 (1.01, 5.56[b]) P=0.01 P=0.04	1.91 (0.50, 7.23)[a]
Rizzato 2022	Surgically resected, advanced iCCA	NGS	From diagnosis	N=15 29.2 months (NR)	N=271 14.8 months (NR)	14.4 months	2.50 (1.19, 5.26)[c] P=0.01	1.31 (0.53, 3.22)
			From first-line therapy	N=11 29.2 months (16.0, NA)	N=151 15.0 months (12.2, 17.8)	14.2 months	2.94 (1.09, 7.69)[d] P=0.03	
			From second-line therapy	N=7 24.7 months (9.2, NA)	N=83 10.0 months (8.1, 14.1)	14.7 months	2.70 (0.84, 8.33)[e] P=0.08	
			From first-line therapy	N=17 24.9 months (17.7, NA)	N=145 14.8 months (12.2−17.8)	10.1 months	3.13 (1.18, 8.33)[f] P=0.02	
Boerner 2021	iCCA (Stage IV – 43%)	NGS (fusions)	From resection	N=46 46.8 months (24.7, 74.8)	N=264[g] 29.6 months (24.5, 33.8)	17.2 months	1.12 (0.76, 1.67)[h] P=0.20	1.17 (0.80, 1.70)
Pu 2021	Resected iCCA (Stage IV – 24.2%)	FISH	From resection	N=9 28.3 months (4, 53)	N=164 45.1 months (3, 82)	-16.7 months	NR P=0.98	1.48 (0.70, 3.15)
Javle 2016	iCCA (Stage IV – 18%)	NGS	From diagnosis	N=30 NA	N=194 187 weeks (172, 226)	NA	NR P=0.001[i]	0.84 (0.31, 2.24)[j]

Source: Table 2.7, p71 of the submission.

CI = confidence interval; iCCA = intrahepatic cholangiocarcinoma; *FGFR2* = fibroblast growth factor 2; FISH = fluorescence in situ hybridization; HR = hazard ratio; OS = overall survival; NGS = next generation sequencing; NA = not applicable; NE = not evaluable; NR = not reported; WT = Wild Type

[a] Unclear timing of outcome measurement.

[b] Based on univariate analysis. Recalculated from the reported death HR 0.43 (0.18, 0.99); Note that for the multivariable analysis the death HR was 0.23 (0.09, 0.62).

[c] Based on univariate analysis – relates to FGFR2 aberrations only. Recalculated from the reported death HR 0.40 (0.19, 0.84). Includes patients who received FGFR2 inhibitors.

[d] Based on univariate analysis – relates to FGFR2 aberrations only. Recalculated from the reported death HR 0.34 (0.13, 0.92). Includes patients who received FGFR2 inhibitors.

[e] Based on univariate analysis – relates to FGFR2 aberrations only. Recalculated from the reported death HR 0.37 (0.12, 1.19). Includes patients who received FGFR2 inhibitors.

[f] Based on univariate analysis – relates to FGFR2/3 aberrations. Recalculated from the reported death HR 0.32 (0.12, 0.85). Excludes 8 patients who received FGFR2 inhibitors.

[g] Excludes patients with IDH1 alterations.

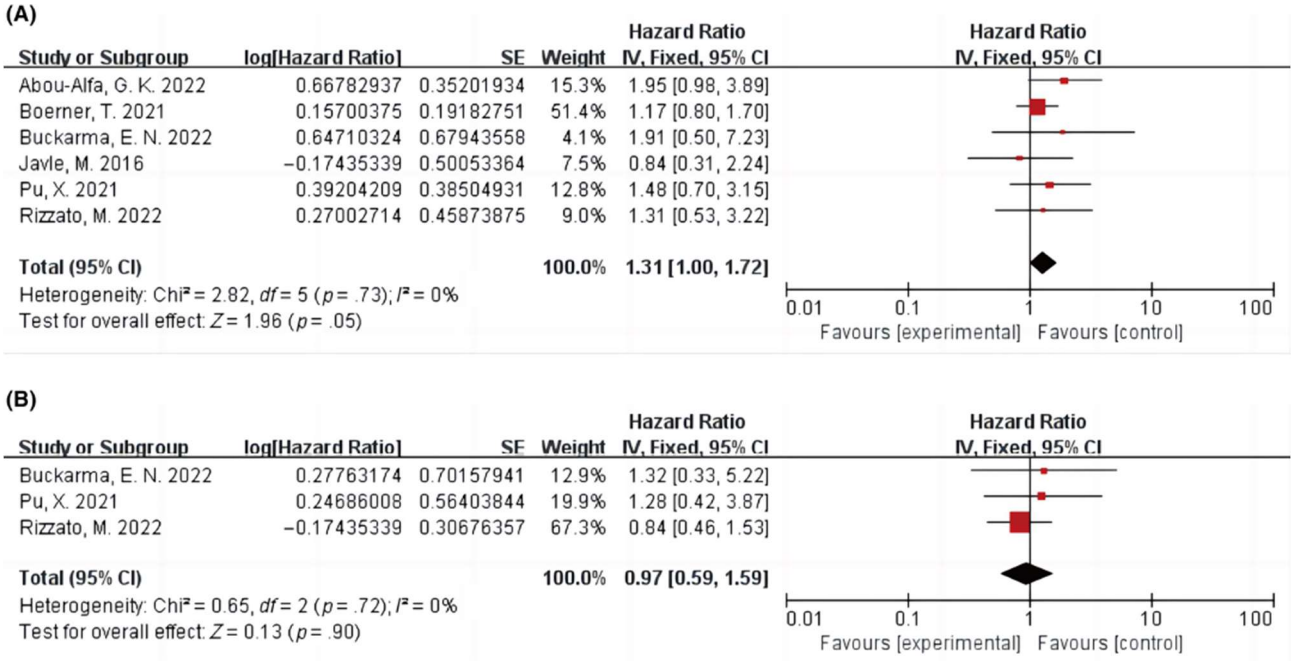
[h] Based on univariate analysis. Recalculated from the reported OS HR 0.89 (0.60, 1.31) – given OS is higher in the FGFR2+, and the HR should be >1, the result was inverted.

[i] On multivariate analysis, FGFR alteration was significantly associated with increased OS (P=0.03).

[j] Based on the survival curve (Figure 4 of the publication), the HR should be >1

Figure 1 presents forest plots of the association between *FGFR2* alterations and OS and DFS in CCA patients as reported in the meta-analysis by Niu 2024.

Figure 1 Forest plot for the association for OS (A) and DFS (B) between FGFR2 alterations and iCCA patients – Niu 2024



Source: Figure 2.2, p73 of the submission.
Abbreviations: CI = confidence interval; SE = standard error
Notes: A: Forest plot for the association between FGFR2 alterations and OS in iCCA patients; B: Forest plot for the association between FGFR2 alterations and DFS in iCCA patients.

The results suggest a better prognosis in terms of OS for patients with CCA with an *FGFR2* alteration compared with those without (HR 1.31; 95% CI 1.00, 1.72; p=0.049), and no difference in prognosis in terms of DFS HR 0.97; 0.59, 1.59; p=0.90). The submission, however noted that there are a number of limitations with the meta-analysis and individual included studies:

- There were discrepancies between the HRs used in the meta-analysis and those extracted from the individual study publications for this submission. The submission identified three studies (Buckarma 2022, Rizzato 2022 and Boemer 2021) in which the OS HR used in the Niu 2024 meta-analysis differed to the respective publications. However, the commentary noted that it appears that the point estimates of the meta-analysis reported OS HR were more conservative (i.e. lower in magnitude of difference between *FGFR2* positive and *FGFR2* Wild Type) than the publication reported HR in both Buckarma 2022 (1.91 vs 2.33) and Rizzato 2022 (1.31 vs 2.50-3.13) and only slightly higher in Boemer 2021 (1.17 vs 1.21). As such, in as much as there was any bias in the use of HR derived from digitising of graphs, it may actually have underestimated the difference in OS between patients with *FGFR2* variants and Wild Type *FGFR2*.
- The lack of clarity from most studies on whether the *FGFR2*-altered populations included patients already treated with *FGFR2*-directed therapies; and
- The magnitude of the result for OS appears to be largely driven by the result from the Abou-Alfa 2022 study. When this study was removed from the analysis, the OS HR was reduced and the 95% CI was no longer statistically significant (HR 1.22; 0.91, 1.63; p=0.18). The commentary noted that the submission did not present any justification for why exclusion of Abou Alfa 2022 would be reasonable. Abou Alfa 2022 had the highest score on the Newcastle-Ottawa Quality Assessment Scale (score of 8), suggesting that it

was the highest quality study of all included studies, and no other study had longer follow-up. Importantly, Abou Alfa 2022 explicitly excluded patients who had received FGFR inhibitors from the OS and PFS analyses.

The submission concluded that while the results from the meta-analysis by Niu 2024 suggest that the presence of an *FGFR2* alteration may result in a positive prognostic impact in terms of overall survival, limitations in the conduct of the meta-analysis, as well as the individual studies themselves, suggest that this remains uncertain. The commentary noted that it was unclear if this was a reasonable conclusion. The evidence in Niu 2024 does appear to suggest that CCA patients with FGFR2 fusion/rearrangement have a better prognosis than patients with Wild Type FGFR2.

Moreover, the commentary noted that there were other relevant studies which could be used to inform prognostic impact that were not considered by the submission:

- Jain 2018 reported a median OS of 20 months (95% 17 to 26) among 282 CCA patients without *FGFR* variants, compared to a median OS of 30 months (95% CI 20 to 97) among 59 patients with *FGFR* variants who did not receive FGFR-directed therapy. The difference was associated with a p value of 0.02666 which the authors considered to be significant; and
- Shroff 2022 reported that median OS was numerically higher in 75 patients with *FGFR2* fusion/rearrangements (median age 63 years, 64% female, 95% iCCA, 68% stage IV at initial diagnosis) with a median OS of 12.1 months (95% CI 8.5, 17.1) compared to 7.1 months (95% CI 5.7, 8.8) among 496 patient with Wild Type *FGFR2* (median age 65 years, 48% female, 74% iCCA, 55% stage IV at initial diagnosis) though the difference was not considered statistically significant (log rank p = 0.184). Similar outcomes were observed when considering only iCCA (12.1 months [95% CI 8.4, 17.1] for patients with *FGFR2* variants and 7.8 months [95% CI 6.1, 10] for Wild Type *FGFR2*, log rank p = 0.375). Shroff 2022 also stated that *FGFR2* status was not a significant factor contributing to OS in any model adjusting for potential prognostic covariates.

Overall, the commentary considered that while the methodological limitations of retrospective studies, small sample sizes of several studies and uncertainty regarding treatment received in some of the included studies introduced substantial uncertainty regarding the prognostic impact of *FGFR2* fusions/rearrangement, the evidence on the whole suggested better prognosis associated with *FGFR2* alteration. The magnitude of this difference however is uncertain. Importantly, this suggests that the benefit observed in a biomarker selected group (as is the case for FOENIX-CCA2) may be overestimated as the biomarker selection itself may have conferred some OS benefit compared to the Wild Type.

Predictive evidence

The literature search described above identified one citation providing data on the treatment effect modification of *FGFR2* alteration testing in patients with CCA (Jain 2018). The submission noted that this study examined *FGFR* alterations but was not limited to *FGFR2* alterations.

In Jain 2018, a total of 377 patients with CCA were identified from four centres in the USA. Of these, 95 harboured *FGFR* alterations that were identified via NGS and FISH. While not limited to *FGFR2* alterations, 78% were *FGFR2*-related (including 63 fusions, 1 amplification and 7 mutations), with the remaining cases being alterations in *FGFR19* (11.6%; all amplifications), *FGFR3* (7.4%; 1 fusion, 6 amplifications and 1 mutation), *FGFR1* (2.1%; 2 mutations) and *FGFR4* (2.1%; 2 mutations).

The presence of an *FGFR* alteration (predominantly *FGFR2* fusions) resulted in a statistically significantly improved OS in all patients with CCA regardless of treatment received (17 months; P<0.001), with this improvement in OS remaining when patients who had received FGFR-directed therapy were excluded from the analysis (10 months; P=0.03). There was no difference in

median OS between CCA with *FGFR2* fusions (n = 63; 37 months) versus other *FGFR* alterations (n = 29; 33 months; P = 0.66).

Table 13 presents the impact of FGFR alterations reported in Jain 2018. On univariable analysis, FGFR-directed treatment (P=0.01) was significantly associated with improved OS in patients with an *FGFR* alteration.

Table 13 Impact of FGFR mutation on overall survival and effect of FGFR-directed therapy – Jain 2018

	FGFR alteration	No FGFR alteration	Difference P-value
All patients	N=95 37 months (24, 65)	N=282 20 months (17, 26)	17 months P<0.001
Patients receiving no FGFR-directed therapy	N=59 30 months (20, 97)	N=282 20 months (17, 26)	10 months P=0.03
Univariate sensitivity analysis (treatment received)			
Patients receiving FGFR-directed therapy [a]	N=36 44.8 months (24.5, NE)	-	20.5 months HR 0.19 P=0.01
Patients receiving standard chemotherapy	N=50 24.3 months (18.2, 49.8)	-	

Source: Table 2.9, p76 of the submission.
FGFR = fibroblast growth factor receptor; HR = hazard ratio; NE = not evaluable
a Infigratinib (n=23), ponatinib (n=8), futibatinib (n=3), dovitinib (n=1) and PRN1371 (n=1).

In addition, on multivariable analysis (adjusting for other variables significant on univariate analysis: radiation, surgery and TP53 presence), FGFR-directed therapy remained correlated with improved OS, with an estimated risk of 0.19 (P=0.003). However, the commentary considered it was possible that the patients in Jain 2018 who received FGFR-directed therapy did so in clinical trials; of the 36 patients who received FGFR-directed therapy, 23 received BGJ398 (infigratinib), eight received ponatinib, three received TAS-120 (futibatinib), one patient received dovitinib and one patient received PRN1371. Given that experimental names were used for the treatment received by 27 of the 36 patients, it may be reasonable to assume that all of these patients were selected for clinical trials. Selection into clinical trials usually infer a healthier patient with a better prognosis. For example, FOENIX-CCA2 included only patients with ECOG performance status 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) and excluded patients with severe comorbidities (e.g. systemic infection and severe heart disease) or reduced life expectancy (e.g. brain metastases). As such, the OS comparison between patients treated with FGFR-directed therapy and patients not treated with FGFR-directed therapies was likely to be biased in favour of FGFR-directed therapy given these other factors were not adjusted for.

The submission concluded that treatment with an FGFR-directed therapy appears to have an independent, positive impact on OS in patients with an FGFR (and specifically FGFR2) alteration, above any potential prognostic impact of the alteration itself. The commentary noted that the results of Jain 2018 suggest that there is both a prognostic impact of *FGFR* alteration itself, (a 10 month survival difference by *FGFR* alteration status in patients not treated with an FGFR-inhibitor), and a potential treatment impact of treatment with an FGFR-inhibitor (17 month survival difference versus patients with no *FGFR* alteration, though only 36/95 [38%] of patients received an FGFR-inhibitor). However, the incremental benefit conferred by the use of an FGFR inhibitor compared to SoC in a patient with *FGFR2* alteration in Jain 2018 was uncertain as there were likely confounders which were unadjusted for (e.g. patients who received FGFR inhibitors may have been healthier).

Importantly, the commentary considered that the key study used to inform the efficacy of futibatinib, FOENIX-CCA2, cannot be used to address this research question as it was a single arm study in which only patients with *FGFR2* fusion/rearrangements were identified. As such, there is no direct evidence to inform the incremental benefit (if any) associated with futibatinib compared to the nominated comparator of FOLFOX in patients with *FGFR2*

fusion/rearrangement, nor is there any evidence to demonstrate that futibatinib is more efficacious in patients with *FGFR2* fusion/rearrangements compared to patients with Wild Type *FGFR2*. There may be reason to believe that futibatinib may provide benefits for patients with Wild Type *FGFR2*. Futibatinib is an FGFR2 inhibitor that acts on the receptor, not the gene, and there is evidence that activation of FGFR2 signalling can be observed in patients with Wild Type *FGFR2*[14], and FGFR mRNA expression in CCA also occurs frequently in the absence of genetic alterations in *FGFR*[15]. Both FGFR2 signalling and FGFR mRNA expression are potentially relevant to the activity of futibatinib and potential targets for FGFR inhibitors. The lack of direct evidence on the efficacy and incremental benefit of futibatinib in different subgroups based on *FGFR2* fusion/rearrangement is a significant barrier to establishing the codependence as proposed in the submission.

The submission's evidence for the efficacy of futibatinib was primarily based on an unanchored matched adjusted indirect comparison (MAIC) of futibatinib from FOENIX-CCA2 (n=103) compared to FOLFOX arm of ABC-06 (n=81). Results of the MAIC suggested that futibatinib was more effective for progression free survival (PFS; adjusted HR = 0.30, 95%CI 0.22-0.41), OS (adjusted HR = 0.24, 95% CI 0.18, 0.32) and objective response rate (ORR; adjusted OR = 18.74, 95% CI = 7.2, 61.3)[16]. However, there were substantial known differences in these study arms such as tumour site (FOENIX-CCA2 was 100% iCCA whereas ABC-06 included iCCA, eCCA, gallbladder cancers and ampullar cancers) and *FGFR2* status (100% *FGFR2* alterations in FOENIX-CCA2, with unknown status in ABC-06) which affected transitivity. Published indirect comparisons by Paine 2022 and Borad 2022 which included only patients with *FGFR2* alterations for both futibatinib and chemotherapy reported lower magnitudes of benefit for PFS, OS and ORR (see Table 14 below), suggesting that the submission's estimates may be overestimated. Additionally, the unanchored nature of the comparison confers a high risk of bias to unknown treatment effect modifiers. Consequently, the commentary considered that the magnitude of effect is highly uncertain and likely overestimated.

[14] Brandi G, Relli V, Deserti M, Palloni A, Indio V, Astolfi A, Serravalle S, Mattiaccio A, Vasuri F, Malvi D, Deiana C, Pantaleo MA, Cescon M, Rizzo A, Katoh M, Tavolari S. Activated FGFR2 signalling as a biomarker for selection of intrahepatic cholangiocarcinoma patients candidate to FGFR targeted therapies. Sci Rep. 2024 Feb 7;14(1):3136. doi: 10.1038/s41598-024-52991-8. PMID: 38326380; PMCID: PMC10850506. https://pubmed.ncbi.nlm.nih.gov/38326380/

[15] Sridharan V, Neyaz A, Chogule A, Baiev I, Reyes S, Barr Fritcher EG, Lennerz JK, Sukov W, Kipp B, Ting DT, Deshpande V, Goyal L. FGFR mRNA Expression in Cholangiocarcinoma and Its Correlation with FGFR2 Fusion Status and Immune Signatures. Clin Cancer Res. 2022 Dec 15;28(24):5431-5439. doi: 10.1158/1078-0432.CCR-22-1244. PMID: 36190545; PMCID: PMC9751751. https://pubmed.ncbi.nlm.nih.gov/36190545/

[16] Note that these results are derived from analyses conducted by the applicant specifically for the purposes of informing the PBAC and MSAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC and MSAC outcome and should not be used for any other purpose.

Table 14 Indirect comparison results between futibatinib and chemotherapy in *FGFR2* altered patients in Paine 2022 and Borad 2022

	Futibatinib, Median months (95% CI)	Chemotherapy, Median months (95% CI)	Unadjusted HR (95% CI, p value)	Adjusted HR (95% CI, p value)
Paine 2022				
PFS	*9.0 (6.9, 13.1)*	*4.4 (3.0- 5.7)* [a]	***0.40 (0.27-0.59, <0.0001)***	***0.48 (0.30-0.76, 0.002)*** [b]
OS	*21.7 (14.5-NE)*	*12.1 (8.4-17.1)* [c]	***0.54 (0.35-0.81, 0.003)***	***0.48 (0.31-0.74, 0.001)***
Borad 2022				
PFS	*NR*	*NR*	***0.40 (0.27-0.59, ≤0.01)***	***0.53 (0.33-0.86, ≤0.01)***
OS	*NR*	*NR*	***0.53 (0.35-0.81, ≤0.01)***	***0.49 (0.31-0.79, ≤0.01)***
ORR	*NR*	*NR*	*1.32 (0.76-2.31, NR)*	*1.43 (0.78-2.65, NR)*
DOR	*NR*	*NR*	*0.73 (0.40-1.33, NR)*	*0.75 (0.37-1.51, NR)*
Submission				
PFS	8.9 (6.7-11.0) [d]	4.0 (3.2-5.0) [e]	**0.43 (0.31-0.59, <0.0001)** [g]	**0.30 (0.22-0.41, <0.0001)** [g]
OS	20.0 (16.4-24.6)	6.2 (5.4-7.6) [e]	**0.26 (0.18-0.37, <0.0001)** [g]	**0.24 (0.18-0.32, <0.0001)** [g]
ORR	NA	NA	**13.8 (5.49-44.12, <0.001)** [f,g]	**18.74 (7.20-61.31, <0.001)** [f,g]

Source: Paine 2022, Borad 2022, Table 2.61, p 159, Table 2.62, p161, Table 2.63, p162, Table 2.64, p163 and Table 2.66, p164 of the submission.

[a] based on Pre-FIGHT-202; Unadjusted median PFS is an estimation across reported values for second-line (4.4 months, 95% CI 3.0–5.3) and third-line (6.6 months, 95% CI 2.7–9.7) therapy.

[b] adjusted for age, sex, ECOG PS, proportion of patients with ≥2 lines of prior chemotherapy, albumin ≤ 35 g/L and prior surgery

[c] based on Shroff 2022

[d] reported for PFS by independent review committee

[e] based on FOLFOX arm of ABC-06

[f] reported as odds ratio and not hazard ratios

[g] Note that these results are derived from analyses conducted by the applicant specifically for the purposes of informing the PBAC and MSAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC and MSAC outcome and should not be used for any other purpose.

CI = confidence interval; DOR = duration of response; HR = hazard ratio; NA = not applicable; NE = not estimable; NR = not reported; OS = overall survival; ORR = objective response rate; PFS = progression free survival

Text in italics indicate values extracted during evaluation

Text in bold indicate HR or OR for which the 95% confidence interval excludes the value of 1.

Change in management in practice

The submission did not present any change in management evidence identified during the literature search. The submission noted that proportion of patients eligible for futibatinib treatment based on the biomarker test result is calculated with the financial estimates of this submission. This was largely determined by the proportion of patients eligible for treatment based on the proposed PBS restriction criteria and the assumed uptake rate.

The submission did not present the consequences of false positives (resulting in patients without *FGFR2* alterations receiving futibatinib), or false negatives (resulting in patients with *FGFR2* alterations not receiving futibatinib). As discussed in Section 8, it would be expected that false negatives would result in patient management and outcomes consistent with current care, with potentially foregone benefit. No data has been presented to estimate the impact of patients receiving futibatinib in the absence of an *FGFR2* alteration.

Claim of codependence

No data was presented to show the efficacy (or lack thereof) of futibatinib in patients with Wild Type *FGFR2* as the FOENIX-CCA2 study enrolled only *FGFR2* positive patients, limiting the empirical evidence around the biomarker and presenting an impediment to establishing codependence. There is some evidence that activation of FGFR2 signalling can be observed in patients with Wild Type *FGFR2*, and FGFR mRNA expression in CCA also occurs frequently in the absence of genetic alterations in *FGFR*.

The commentary considered that overall, while a claim of codependence may be plausible, codependence could not be unequivocally established based on available evidence.

The ESCs agreed with the commentary that the available evidence suggests that the presence of FGFR2 *alterations improve prognosis, regardless of treatment.*

The ESCs noted that the key trial (FOENIX-CCA2) was restricted to iCCA patients with FGFR2 *fusions or rearrangements (i.e. the trial did not include any patients with wild-type* FGFR2*). As such, the ESCs agreed with PASC advice that the claim of codependency between* FGFR2 *status and futibatinib was not able to be established based on this key trial. However, the ESCs noted from the applicant's pre-ESC response that an earlier Phase 1 expansion study for futibatinib had included a patient population with* FGFR *wild-type (these patients had some FGF alteration) showed no anti-tumour activity. The ESCs agreed with the applicant that with this available evidence, it is challenging and unethical to trial FGFR inhibitors on a patient population without FGFR2 fusions and rearrangements, for whom treatment is unlikely to be effective. The ESCs considered the claim of codependency reasonable based on the available (albeit limited) information.*

13. Economic evaluation

The submission presented an economic evaluation, based on the results of the MAIC comparing futibatinib and FOLFOX. The commentary considered that given concerns regarding the results of the MAIC which did not adjust for tumour site or *FGFR2* status in the FOLFOX arm, resulting in clinical benefits which may be overestimated, the underlying clinical benefit used to inform the economic evaluation was uncertain. The ability to simply run sensitivity analyses using alternative MAIC results from Paine 2022 or Borad 2022 was not included in the model operability.

The type of economic evaluation presented was a cost utility analysis. The key components of the economic evaluation is presented in Table 15.

Table 15 Key components of the economic evaluation

Component	Description	Justification/comments
Comparison modelled	Futibatinib 20mg versus FOLFOX chemotherapy every 14 days for up to 12 cycles)	*Considering that ASC was also an appropriate comparator in the ivosidenib submission for CCA, it was unclear if assuming 100% FOLFOX comparator was reasonable.*
Outcomes	LYG, QALY	*Reasonable.*
Time horizon	10 years versus median follow-up of 25.0 months at final data cut off in FOENIX-CCA2	*May be too optimistic, in its consideration of ivosidenib for CCA, the PBAC had requested a re-specification to a 5-year time horizon.*
Methods used to generate results	Partitioned survival analysis	*Reasonable*
Health states	PFS, PD, death	*Reasonable*
Cycle length	21 days (half cycle correction applied)	*There was an error in the application of the half cycle correction, which led to the overestimation of patient flow probabilities which was relied upon to inform the number of patients in each health state.*
Test parameters		
Implications of false positive and false negative results	Not accounted for in model.	*Given concerns regarding the reliability of FGFR2 testing using NGS on RNA it is unclear if this was appropriate, though it was acknowledged that the ivosidenib July 2024 submission also assumed 100% sensitivity and specificity.*
Allocation to health states	Based on extrapolated OS and PFS from MAIC described in clinical section	*Given concerns regarding the results of the MAIC, the underlying clinical benefit used to inform the economic evaluation was uncertain and likely overestimated. The ability to run sensitivity analyses using alternative MAIC results was not included in the model operability.*
Extrapolation method	Parametric model fitted to each treatment arm with gamma extrapolation selected in base case for PFS in both arms (and loglogistic for OS in both arms) based on statistical fit, visual fit and clinical plausibility. The submission fitted the distributions separately for each treatment arm. Switch from KM to extrapolation was estimated based on Gebski 2006. The switch occurred at 22 months for OS and 14 months for PFS for futibatinib and 11 months for OS and 7 months for PFS for FOLFOX.	*The model was moderately sensitive to extrapolation. However, given the uncertainty in the underlying data, sensitivity analyses around extrapolation method alone may not adequately address the issues surrounding the submission's estimates of comparative effect.*
Health related quality of life	Futibatinib PFS: 0.796 based on EQ-5D-3L of FOENIX CCA-2 FOLFOX PFS: 0.70 based on ABC-06 supplement Futibatinib PD: 0.68 (based on NICE 474) FOLFOX PD: 0.584 (based on applying same decrement from PFS to PD as futibatinib)	*The submission did not present a clinical comparison of QoL outcomes to justify treatment-based utilities.* *The utilities for FOLFOX may have been underestimated as it was informed by a single value at month 4 in ABC-06. Given the treatment duration (2 weekly cycles, up to 12 cycles) the QoL at month 4 may be lower than at earlier timepoints due to repeated chemotherapy cycles.*

Source: Table 3.2, p186 of the submission.

ASC = active symptom control; KM = Kaplan-Meier LYG = life-year gained; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = Progressed disease; PFS = progression free survival; QALY – Quality adjusted life-year; QoL = quality of Life;

[a] oxaliplatin 85 mg/m2, calcium folinate 50 mg, 5-fluorouracil 400 mg/m2 bolus and 2400 mg/m2 continuous infusion over 46 hours

The submission assumed 100% specificity and sensitivity of *FGFR2* testing. Consequently, the commentary noted that the impacts of false positives and false negatives of the test were not factored into the model. Given concerns regarding the reliability of *FGFR2* testing using NGS on RNA discussed above in Section 9 of the executive summary under concordance it is unclear if this was appropriate. However, no efficacy data for futibatinib in patients with Wild Type *FGFR2* were available to accurately inform false positive results. As the submission assumed 100% sensitivity and sensitivity of the test, the model did not account for costs of false negative or false positive tests.

The submission estimated a cost of NGS testing for *FGFR2* fusion or rearrangement testing from tumour tissue of $1,050 per identified patient (see Table 16 and Table 15). This was based on assumed MBS fee for an RNA test of $350, unless testing is done by Omico, where there will be no additional cost to the health system as a consequence of the PBS listing of futibatinib.

The submission noted that Omico provides Comprehensive Genomic Profiling to patients with advanced and incurable cancer, including CCA, to help identify potential treatments or clinical trials at no cost to the patient via their Cancer Screening Program. The submission claimed that expert opinion indicates that a large proportion of patients in the target PBS population are currently screened via this program. The submission assumed that 40% of testing would be conducted by Omico. The commentary considered that this was inappropriate as once available from the MBS, it is unlikely that current testing by Omico would continue at this rate. Moreover, patients would be able to claim the MBS rebate even if the service is provided through Omico providers (as long as they provide an MBS eligible service and are an eligible provider). To estimate the long-term cost-effectiveness of listing *FGFR2* testing on the MBS, the assumption of all testing costs being borne by the MBS would be more reasonable. Adjusting testing costs to reflect this had only a small impact (Redacted% increase) on the ICER.

The cost per patient identified was also based on assumption of 20% prevalence of *FGFR2* alteration in advanced disease. The commentary considered that this was consistent with the prevalence presented by the submission. However, as previously discussed, there was substantial variation in estimates of prevalence, with a weighted average prevalence of 10% in all CCA settings (reflective of testing at diagnosis). Assuming a weighted average prevalence of 10% would increase the cost per futibatinib patient identified to $2,100 and increased the ICER by Redacted%.

Consistent with the MBS item descriptor, the submission assumed only one test per lifetime. The commentary considered that this was reasonable. However, given concerns regarding the stability of the biomarker and RNA in FFPE, it is possible that some patients may benefit from later testing especially if they were first tested in an earlier setting. Nonetheless, doubling *FGFR2* test cost and assuming 100% of tests were conducted on the MBS had only a small impact (Redacted%) on the ICER.

Table 16 presents the estimation of *FGFR2* testing costs in the economic evaluation.

Table 16 FGFR2 Genetic testing costs

Description	Amount	Proportion	Totals
Genetic testing costs (RNA) MBS	$350.00	60%	$210.00
Genetic testing costs (RNA) Omico	$0.00	40%	$0.00
Weighted test cost			$210.00
Proportion of people tested eligible for treatment with futibatinib (diagnostic yield)			20.00%
Cost per futibatinib patient identified in submission base case			$1,050.00
Cost per futibatinib patient identified assuming 100% MBS			*$1,750.00*

Source: Table 3.17, p218 of the submission.
Text in italics indicate values calculated during the evaluation.
RNA = ribonucleic acid

Table 17 presents the results of the stepped economic evaluation. During the development of the commentary, an error was identified in the application of the half-cycle correction, which has been corrected in the final estimates. Additionally, during the development of the commentary, the half cycle correction was removed for futibatinib costs.

Table 17 Results of the stepped economic evaluation

Step and component	Futibatinib	FOLFOX	Increment
Step 1: Based on the PFS and OS data represented with parametric functions. Time horizon of 2 years (OS follow-up time in FOENIX-CCA2). Costs: Drug acquisition, drug administration and AE management			
Costs	**$Redacted**	$8,298	**$Redacted**
LYG	1.50	0.74	0.76
Incremental cost/extra LYG gained			**$Redacted**[1]
Step 2: PFS and OS data extrapolated with parametric functions until 10 years. 5% discounting of costs and outcomes. Costs: as in Step 2 + disease management and monitoring, subsequent therapy and terminal care. Outcomes: LYs gained over the modelled time horizon			
Costs	**$Redacted**	$60,226	**$Redacted**
LYG	2.32	0.84	1.48
Incremental cost/extra LYG gained			**$Redacted**[2]
Step 3: KM data used for PFS and OS until unreliable, then data extrapolated with parametric functions until 10 years Costs: As in Step 3 Outcomes: LYs over the modelled time horizon			
Costs	**$Redacted**	$59,994	**$Redacted**
LYG	2.33	0.84	1.49
Incremental cost/extra LYG gained			**$Redacted**[2]
Step 4: Transformation of LYs to QALYs. Costs: As in Step 3 Outcomes: QALYs over the modelled time horizon			
Costs	**$Redacted**	$59,994	**$Redacted**
QALYS	1.72	0.55	1.17
Incremental cost/extra LYG gained			**$Redacted**[3]
Step 5: Evaluation- correct half cycle correction and remove half cycle correction from drug acquisition costs.			
Costs	***$Redacted***	*$59,481*	***$Redacted***
QALYS	*1.67*	*0.51*	*1.16*
Incremental cost/extra LYG gained			***$Redacted***[3]

Source: Table 3.19, p221 of the submission.
AE = adverse events. KM = Kaplan Meier; LYG = life years gained; OS = overall survival; PFS = progression free survival; QALYs = quality adjusted life years
The redacted values correspond to the following ranges:
[1] $155,000 to <$255,000
[2] $75,000 to <$95,000
[3] $95,000 to <$115,000

Table 18 presents test related sensitivity analyses. The model was not highly sensitive to test costs (the submission tested test cost up and down by 20%, and the evaluation tested doubled test cost). As stated above, the economic model did not include operability for test accuracy and assumed 100% sensitivity and specificity.

Table 18 Results of test-related sensitivity analyses (corrected for half cycle correction).

Analyses	Incremental cost	Incremental QALY	ICER	% Change
Base case	***$Redacted***	***1.16***	***$Redacted[1]***	-
Testing cost down by 20% (per identified pt)	***$Redacted***	*1.16*	***$Redacted[1]***	***Redacted%***
Testing cost up by 20% (per identified pt)	***$Redacted***	*1.16*	***$Redacted[1]***	***Redacted %***
Testing assumed 100% MBS/ 0% Omico (BC: 60% MBS/ 40% Omico)	***$Redacted***	*1.16*	***$Redacted[1]***	***Redacted %***
Testing assumed 100% MBS and test cost doubled ($700)	***$Redacted***	*1.16*	***$Redacted[1]***	***Redacted %***
Assume 10% prevalence for testing costs (BC: 20%)	***$Redacted***	1.16	***$Redacted[1]***	***Redacted %***

Source. Attached Economic model, adjusted to remove half cycle correction for futibatinib acquisition costs and corrected error for half cycle correction in costs and outcomes.
AE = adverse events; BC = base case; EOL = end of life; FUTI = futibatinib; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; MBS = Medicare Benefits Scheme; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = progressive disease; PF = progression free disease; QALY = quality adjusted life year; RDI = relative dose intensity;
[a] Time horizon of 5 years and using utilities to durvalumab PBAC submission (PF 0.857; PD 0.766)
Text in italics indicate analyses or values calculated during the evaluation.
[1]The redacted values correspond to the following range: $95,000 to <$115,000

The commentary considered that overall, it was extremely likely that the submission's ICER was underestimated due to overestimated incremental futibatinib benefit in the MAIC, the lack of convergence of OS assumed, and the cost of futibatinib (which may be underestimated due to misalignment between the model's cycle length (every three weeks) with the dispensing frequency (every four weeks)), the assumption of a 83.26% dose intensity from the start of the model, and the lack of adjustment for post progression use as observed in FOENIX-CCA2. See the PBAC public summary document for a more detailed description of the economic evaluation.

14. Financial/budgetary impacts

The submission took an epidemiological approach to provide the financial estimates. The submission assumed that testing will only occur once patients progress after first line durvalumab, and only in patients who will consider futibatinib (Redacted% uptake rate). The commentary considered that this was not consistent with the proposed test population of 'adult patients with locally advanced or metastatic CCA', and as such, the number of tests may be underestimated. However, the number of tests was based on number of patient-years of treatment with futibatinib in incident patients rather than the number of patients treated. As the treatment duration per patient (12.5 months) exceeded one year, the number of patient-years was higher than the number of patients treated. This resulted in an estimated 5.2 tests per patient treated, which was inconsistent with the assumption of 20% prevalence (with no retesting) and may be a slight overestimate.

Table 19 presents the estimated use and financial implications of *FGFR2* testing to the MBS. The submission estimated a test cost of $350, consistent with the economic evaluation and a diagnostic yield of 20%. Based on these estimates, the cost to detect one FGFR2 fusion/rearrangement was $1750. Sensitivity analyses around the testing population is also presented below. The commentary considered that a key uncertainty was the use of adult population (aged 18 to 100) instead of all Australian population (age 0-100) to derive number of CCA patients in the estimates despite the incidence rate being based on the full population. Given that paediatric CCA is extremely rare, the incidence rate in adults would be higher than the incidence rate in the full population. Therefore, the application of the incidence rate of the full population to the adult only population will result in an underestimate of the number of cases. During the development of the commentary, financial estimates using all Australian populations were calculated and included below.

As discussed in Section 10, Economic Evaluation of the MSAC executive summary, it was unlikely testing via Omico would continue at the same rate after MBS item recommended. Moreover, patients would be able to claim the MBS rebate even if service is provided through Omico providers as long as the provider is eligible and as such the distribution of Omico relative to non-Omico would not impact the financial estimates.

The submission (p216) notes that the futibatinib PI states: Ophthalmological examination should be performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. In the financial estimates, two optical coherence tomography (OCT; MBS item 11219) was included for each patient treated with futibatinib (assumed treatment duration of 56.05 weeks).

An 80% rebate was applied to all MBS item costs. The commentary noted that no justification was provided for this by the submission, although it was acknowledged that the MSAC guidelines (p214) indicate that if proportion of the different levels of MBS benefit (75% or 85%) was unknown, a pragmatic approach assuming the 80% level of MBS item may be used. The financial impact to the MBS assuming an 85% rebate was calculated as a sensitivity analysis during the evaluation.

Table 19 Estimated use of *FGFR2* testing and financial implications to MBS budget

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of FGFR2 testing						
Total CCA population	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Patients diagnosed with advanced CCA (locally advanced, metastatic) (80% of all CCA)	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]	Redacted[1]
Number of patients tested[a]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]
Number of patients likely to receive a positive test result (20% diagnostic yield)	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]	Redacted[2]
Estimated financial implications of FGFR2 testing and listing of futibatinib to the MBS						
Cost to MBS for *FGFR2* testing [b]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS for OCT [c]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost offset to MBS for reduction in FOLFOX [d]	$Redacted[4]	$Redacted[4]	$Redacted[4]	$Redacted[4]	$Redacted[4]	$Redacted[4]
Net cost to MBS	$Redacted[4]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Sensitivity analyses around cost of *FGFR2* testing						
Cost to MBS of FGFR2 testing assuming testing in entire CCA population [e]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS of FGFR2 testing assuming testing in locally advanced, metastatic CCA [f]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assume 85% rebate (base case 80%)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS for FGFR2 testing assuming 100% uptake (base case 92.5%)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Cost to MBS of FGFR2 testing using all Australian population estimate (0-100) instead of just adult (18-100)	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Net cost to MBS (inclusive of OCT and offset from reduction in FOLFOX administration)						
Base case (test when progress to 2L)	$Redacted[4]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assume testing in entire CCA population [g]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assume testing in locally advanced, metastatic CCA [h]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assume 85% rebate (base case 80%)	$Redacted[4]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assuming 100% test uptake (base case 92.5%)	$Redacted[4]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
***Post-ESC additional analysis:* Net cost to MBS (inclusive of OCT and offset from reduction in FOLFOX administration)**						
Assume testing in CCA population + pancreatic cancer population (100% test uptake) + cancer of unknown primary population (100% test uptake) [i]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]
Assume testing in CCA population + pancreatic cancer population (25% test uptake) + cancer of unknown primary population (25% test uptake) [i]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]	$Redacted[3]

Source: Table 4.16, p241 of the submission and attached financial spreadsheet

2L = second line; CCA = cholangiocarcinoma; FGFR2 = fibroblast growth factor receptor 2; OCT = optical coherence tomography

Text in italics indicate values calculated during evaluation

[a] The submission did not present an estimate of number of patients tested. During the evaluation the implied estimates were calculated based on the submission's estimate of number of units of testing presented in the financial workbook, which was estimated by multiplying the number of patient years of futibatinib treatment in the incident population (12.5 months; 1.04 patient years per patient treated) by 500% (based on an assumed 20% prevalence).

[b] Based on $350 per test, assuming 80% rebate

[c] Assumed to occur twice per patient; based on MBS Item 11219, with a fee of $45.50 and 80% rebate

[d] Includes Chemotherapy administration (MBS Item 13950: $123.05), insertion of a central venous access device (CVAD) (MBS item 34528, $310.35), removal of CVAD for 73.6% of patients (MBS item 34530, $232.60), anaesthesia (MBS item 20400+23010, $90.20),and cleaning the CVAD (MBS item 14221, $59.80). All assumed 80% rebate.
[e] estimated by multiplying total CCA population in each year by $280 (80% MBS benefit of $350, the proposed MBS benefit for *FGFR2* testing)
[f] estimated by multiplying advanced CCA population in each year by $280 (80% MBS benefit of $350, the proposed MBS benefit for *FGFR2* testing)
[g] estimated by taking Cost for *FGFR2* testing in entire CCA population (see e above), adding cost of optical coherence tomography and subtracting cost offsets from reduction in FOLFOX administration
[h] estimated by taking Cost for *FGFR2* testing in locally advanced, metastatic CCA (see f above), adding cost of optical coherence tomography and subtracting cost offsets from reduction in FOLFOX administration
[i] *FGFR2* test uptake in pancreatic cancer and cancer of unknown primary highly uncertain. Sensitivity analysis tested with assumption of 100% test uptake (upper limit) and 25% test uptake. Test cost was assumed to be $682.35.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] <500
[3] $0 to < $10 million
[4] net cost saving

The commentary noted that the 1750 ivosidenib codependent submission considered by the MSAC and PBAC at the July 2024 meetings used an alternative approach to estimating patient numbers, which included patients with biliary tract CCA. The financial estimates using patient numbers from the 1750 ivosidenib codependent submission is presented in the committee in confidence section of the commentary.

15. Other relevant information

Nil.

16. Committee-In-Confidence information

Redacted.

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- Silverman 2022 reported a positive percentage agreement (PPA) of 87.1% between next generation sequencing (NGS) on DNA and NGS on RNA, with NGS on RNA being more likely to classify patients as being FGFR2 fusion positive, which may suggest that although there is high concordance between the two methodologies, NGS on RNA may not necessarily select the same patients as NGS on DNA (the clinical utility standard). Combination testing of NGS on DNA and RNA would be the most accurate method to ensure that FGFR2 fusions and rearrangements are detected, with NGS on RNA the next preferred method if combination testing is not available. Concordance of fluorescence in situ hybridisation (FISH) testing is less robust and use of FISH testing for the purpose of detecting FGFR2 fusions and rearrangements is likely not appropriate.
- Although the MBS items proposed in the current submission only included FGFR2 testing, in contemporary clinical practice genetic testing of CCA is performed using a gene panel. For example it would be clinically appropriate to undertake FGFR2 fusion testing in the same population as IDH1 mutation testing (if it is supported by MSAC), and both tests would likely be undertaken in parallel.
- Testing is likely to be needed in patients presenting with CCA (regardless of the stage of disease, as opposed to only testing patients with locally advanced or metastatic disease as proposed in the submission), but this will capture a proportion of pancreatic cancer and cancer of unknown primary. The overall diagnostic yield of the test including testing these non-CCA cancer types is uncertain.

Financial issues

- FGFR2 testing costs were applied only to patients who progressed from first line durvalumab. This was a narrower population than both the proposed testing population of adult patients with locally advanced or metastatic CCA (i.e. inclusive of patients prior to first line treatment) and the testing population of adult patients with CCA as proposed by the PASC, and may underestimate the cost of FGFR2 testing.
- If FGFR2 testing occurs at cancer diagnosis, this may contribute to a higher than expected use of FGFR2 testing if difficult to diagnose adenocarcinomas which occur at the same site as CCA (such as some pancreatic cancers and cancers of unknown primary) are presumptively diagnosed as CCA. The increased testing would lead to an increased financial impact.

ESCs discussion

The ESCs noted that the integrated codependent submission sought Medicare Benefits Schedule (MBS) listing for the testing of tumour tissue to detect *fibroblast growth factor receptor 2* (*FGFR2*) fusions or rearrangements in people with cholangiocarcinoma (CCA), to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS) subsidised futibatinib. The ESCs considered that the current application had similarity to MSAC application 1750 - Testing of tumour tissue to detect *IDH1* mutations in patients with CCA to determine eligibility for ivosidenib on the PBS (considered by MSAC in November 2024, outcome not yet published), in that it also requested public funding for testing in patients with CCA to gain access to a PBS subsidised treatment.

The ESCs noted that CCA is typically a diagnosis of exclusion, whereby a reasonable amount of clinical work-up is performed on adenocarcinomas of the biliary tree to exclude the possibility that it may be metastasised from a different primary site. CCA can be categorised into two

differing types, intrahepatic (iCCA, ~20% of the CCA population) and extrahepatic (eCCA, ~80% of the CCA population). The ESCs noted that *FGFR2* fusions or rearrangements are most common in patients with iCCA (~20%) and are only present in a smaller percentage of patients with eCCA (~1%). The ESCs noted that the European Medicines Agency has granted conditional marketing authorisation to futibatinib for the whole CCA population, while the US Food and Drug Administration has granted conditional marketing approval only for the iCCA population. The ESCs noted that futibatinib is currently under evaluation by the Therapeutic Goods Administration.

The ESCs noted that no consultation input was received through the pre-MSAC consultation process for the testing component of the current application as of the date of the ESCs consideration.

The ESCs noted from the submission that access to futibatinib, is proposed only for patients at the locally advanced or metastatic stage, however, for the reasons outlined below, the ESCs agreed with PASC advice that testing should occur in the whole CCA patient population at diagnosis. The ESCs noted PASC advice that CCA was a rapidly progressive disease, and test results for a *FGFR2* fusion may take up to 2-8 weeks to become available, and therefore testing at diagnosis will prevent any delays in treatment decisions. Furthermore, the ESCs considered that even when the CCA is surgically resected, only a small proportion of surgeries will be curative, while the majority (more than 80%) of the cases will progress rapidly to cancer recurrence. The ESCs considered that retrieving archived material or later re-biopsy once reoccurrence is confirmed will result in delays and higher costs than testing at diagnosis. While the key FOENIX-CCA2 trial only included patients with iCCA, the ESCs considered that patients with *FGFR2* fusions or rearrangements in eCCA may plausibly benefit from treatment with futibatinib as it would likely inhibit the oncogenic FGFR signalling in eCCA via the same mechanism of action as in iCCA. Taking all these factors into consideration, the ESCs considered that testing should be performed in the whole CCA population at diagnosis.

The ESCs advised that it is difficult to diagnose adenocarcinomas which occur at the same site as CCA, such as some pancreatic cancers and cancers of unknown primary. The ESCs considered this diagnostic uncertainty could contribute to higher than expected use of *FGFR2* testing if these tumours are presumptively diagnosed as CCA. Given that the majority of *FGFR2* fusions and rearrangements are observed in patients with iCCA, the ESCs considered that testing in tumours other than iCCA may lead to a considerable number of futile tests and uncertain diagnostic yield. However, given that only patients with *FGFR2* variants can access the drug, and because the majority of *FGFR2* variants are found in iCCA, the ESCs considered that it was unlikely the projected utilisation of the drug would increase significantly despite the increased utilisation of the test, as negative tests would not result in increased PBS costs.

The ESCs considered that *FGFR2* testing can be undertaken using cytology samples which were used for CCA diagnosis, however, considered that there may be a preference to perform core or repeat biopsies solely to obtain material for molecular testing. Therefore, the ESCs considered that the availability of the *FGFR2* test may lead to increases in procedures such as repeated biopsy, but considered that such procedures will likely only be performed in a minority of patients.

The ESCs noted PASC advice that all methods of testing for *FGFR2* status, including next generation sequencing (NGS) on DNA and RNA, and fluorescence in situ hybridisation (FISH), should be evaluated to demonstrate comparative performance. The ESCs noted the submission proposed two item descriptors, one which was test agnostic and another which was for NGS using RNA only to detect *FGFR2* variants. The ESCs considered that there was high concordance between NGS on DNA and NGS on RNA, but noted concerns raised in the commentary that NGS on RNA may not necessarily select the same patients as NGS on DNA (the clinical utility standard). However, the ESCs considered that NGS on RNA to be more sensitive in detecting fusion/rearrangement events compared to NGS on DNA. The ESCs considered NGS on RNA would be more likely to identify a fusion or rearrangement with a new partner gene. It was also noted that concordance of FISH testing was less robust and the ESCs considered that use of

FISH testing for the purpose of detecting *FGFR2* fusions and rearrangements should be discouraged. The ESCs considered that the MBS item descriptor could include wording such as 'molecular testing' or 'amplification testing' so that it excludes FISH testing, but that the wording is broad enough to capture appropriate testing methodologies (NGS on DNA, NGS on RNA). The ESCs considered that combination testing of NGS on DNA and RNA would be the most accurate method to ensure that *FGFR2* fusions and rearrangements are detected, with NGS on RNA the next preferred method if combination testing is not available.

The ESCs considered that testing *FGFR2* using a gene panel with other appropriate biomarkers/key driver events (including *IDH1* if MSAC application 1750 is supported) is preferred over a single gene test. The ESCs considered it more efficient to test all the key driver events at the same time, as these are considered to be mutually exclusive (for example, knowing a patient has a *IDH1* variant will rule out the presence of *FGFR2* fusions and rearrangements).The ESCs noted that in practice testing will likely occur on the same panel platform used for lung cancer testing. These platforms are routinely used by laboratories and are already established in Australia for other panel tests, such as the MBS item for lung cancer testing (MBS 73437). The ESCs considered that a combined panel test may help ensure efficiency for laboratories conducting the test and add more prognostic value for the patient than a single test item. The ESCs considered that the MBS item fee should be aligned to other established MBS items for panel testing such as item 73437 for sequence and fusion testing in lung carcinoma (MBS fee $1,247.00). The ESCs considered that if an RNA testing panel alone is supported, a fee comparable to MBS item 73439 for fusion testing in lung cancer would be appropriate ($682.35).

The ESCs considered that a frequency restriction of once per lifetime to be appropriate as patients with *FGFR2* fusions or rearrangements would likely contain the variant from the first malignant cell and are unlikely to lose the variant with time, although may accumulate resistance mutations. The ESCs considered that the frequency restriction would only pose an issue in instances where there is a false negative result (which is not a common occurrence for NGS methods) or an inadequate test. The ESCs also considered that the item should be pathologist determinable as this would allow the effective use of the diagnostic tissue sample proceeding from histological confirmation.

Based on the above considerations, the ESCs proposed the following MBS item descriptor if a single gene test for *FGFR2* is supported.

Category 6 – Pathology Services	
Proposed item descriptor XXXXX	Group P7 - Genetics
A nucleic acid-based test of tumour tissue for FGFR2 fusions or rearrangements in a patient with cholangiocarcinoma requested by, or on behalf of, a specialist or consultant physician to determine access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS) Applicable only once per lifetime.	
Fee: $682.35 Benefit: 75% = $511.80 85% = $580.00	

The ESCs proposed the following MBS item descriptor if panel testing is supported.

Category 6 – Pathology Services	
Proposed item descriptor XXXXX	Group P7 - Genetics
A nucleic acid-based multi-gene panel test of tumour tissue from a patient with cholangiocarcinoma requested by, or on behalf of, a specialist or consultant physician, if the test is: (a) To detect at least IDH1 variant status[a], and (b) To detect the fusion or rearrangement status of at least FGFR2 (c) To determine access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS) Applicable only once per lifetime.	
Fee: $TBC Benefit: 75% = $TBC 85% = $TBC	

[a]Note that this would only be included if *IDH1* testing is MBS listed.

The ESCs considered that it was reasonable to accept the claim of superior efficacy of futibatinib over both FOLFOX and palliative care, however considered that the magnitude of benefit is likely overestimated in the submission. The ESCs noted that no comparative safety data was presented in the submission. However, given the known safety issues related to FOLFOX, the ESCs considered the claim of superior safety compared to FOLFOX likely reasonable and agreed with the submission that futibatinib had inferior safety compared to palliative care, but that this is manageable.

The ESCs noted that the submission presented a cost utility analysis using a partitioned survival analysis based on the results of a matched adjusted indirect comparison (MAIC) of futibatinib (based on the FOENIX-CCA2 trial) versus FOLFOX (based on the ABC-06 trial). The ESCs considered that there were transitivity issues as the ABC-06 trial included patients with biliary tract cancer (including CCA and gallbladder or ampullary carcinoma), and unknown *FGFR2* status. Given that *FGFR2* alterations may confer an improved prognosis, the ESCs considered that the MAIC provided a highly uncertain and likely overestimated magnitude of effect due to not adjusting for *FGFR2* status. The ESCs noted that the base case incremental cost effectiveness ratio (ICER) was $95,000 to <$115,000/QALY. The ESCs noted that the model did not account for false positives or negatives, assuming 100% specificity and sensitivity of *FGFR2* testing. The ESCs discussed the appropriateness of this assumption, given concerns of NGS on RNA's potential reliability issues. However, the ESCs considered that this may be appropriate given application 1750 for *IDH1* testing had also assumed 100% specificity and sensitivity testing, which MSAC accepted. The ESCs also noted that a weighted cost was used in the model for conducting tests based on the test provider (the submission assumed that 40% of the tests will be performed by Omico at $0 per test and the remaining 60% of the tests will be conducted by other providers at $350 per test). The ESCs considered that this weighting was not appropriate and considered that all *FGFR2* tests should be priced at the proposed MBS fee ($350). However, ESC noted from the sensitivity analysis conducted by the commentary that incorporating this change only had a minimal impact (Redacted% increase) on the ICER.

The ESCs discussed the financial impact of *FGFR2* testing. The ESCs noted that the submission only applied testing costs to patients who had locally advanced/metastatic disease and had progressed from first line durvalumab treatment. The ESCs agreed with the commentary that this was not consistent with the proposed test population of 'adult patients with locally advanced of metastatic CCA'. As discussed above, the ESCs considered that testing should be performed at CCA diagnosis and noted from the commentary that for testing the entire CCA population the net cost to the MBS was $0 to <$10 million in year 1, rising to $0 to <$10 million in year 6. The ESCs agreed with the commentary that there may be a potential underestimation of the current adult population of CCA patients in Australia estimated in the submission due to the incidence rate used to determine the population being based on the full population of CCA patients, rather than just the adult population. The ESCs requested that a sensitivity analysis on the financial estimates be presented to include the population of all CCA patients which include the potential increase in incidence of CCA (as discussed earlier) if the test is listed on the MBS.

18. Applicant comments on MSAC's Public Summary Document

The Applicant is committed to working collaboratively with MSAC to ensure that testing is available to determine eligibility for treatment with PBS subsidised futibatinib.

19. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website