

5.09 Futibatinib

Tablet 4 mg,

Lytgobi®

Taiho Pharma Oceania Pty Ltd

1 Purpose of submission

- 1.1 A Category 1 integrated codependent submission requesting MBS listing of fibroblast growth factor receptor 2 (*FGFR2*) RNA next generation sequencing (NGS) and a PBS General Schedule Authority Required (STREAMLINED) listing of futibatinib for the treatment of patients with locally advanced or metastatic cholangiocarcinoma (CCA) who have previously progressed on systemic therapy and have a *FGFR2* fusion or rearrangement.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus Standard of Care (SoC) FOLFOX chemotherapy.
- 1.3 Table 1 presents the key components of the clinical issue addressed by the submission.

Table 1: 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 <i>FGFR2</i> fusion or rearrangement that have progressed after at least one prior line of systemic therapy
Intervention	Test: tumour tissue testing for <i>FGFR2</i> fusions or rearrangements using RNA NGS Alternate test: tumour tissue testing for <i>FGFR2</i> 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 <i>FGFR2</i> fusions or rearrangements Drug: primary comparator: SoC chemotherapy, represented by FOLFOX (modified FOLFOX 6 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; every 14 days for up to 12 cycles) Secondary comparator: palliative care (with active symptom control)
Outcomes	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 <i>FGFR2</i> 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 <i>FGFR2</i> fusions or rearrangements, 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;

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Delegate's Overview and the minutes from the Advisory Committee on Medicines (ACM) were available.
- 2.2 Futibatinib is proposed for provisional registration for the following indication:
- for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.
- 2.3 The TGA Delegate was inclined to approve the provisional registration for futibatinib for the treatment of patients with intrahepatic CAA. The Delegate requested advice from the ACM regarding approval for all patients with CCA (i.e., including extrahepatic CCA). This was discussed at the ACM meeting of 6 February 2025, and the ACM recommended approval for the provisional registration for futibatinib for the treatment of patients with intrahepatic CAA that have progressed after at least one prior line of systemic therapy.

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

3 Requested listing

- 3.1 Secretariat suggested additions are in italics and deletions are in strikethrough.

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Table 2: Essential elements of the requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FUTIBATINIB 4 mg tablets, 35	4	140	5	Published: \$ [REDACTED] Effective: \$ [REDACTED]	LYGTABI Taiho Pharma Oceania
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [new/existing code]					
Indication: Locally advanced or metastatic cholangiocarcinoma					
Clinical criteria: Patient must have evidence of a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement					
AND					
Clinical criteria: Patient must have received at least one prior line of systemic therapy					
AND					
Clinical criteria: Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of no greater than 1 at prior to treatment initiation with this drug					
AND					
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition					
AND					
Clinical criteria: Patient must not have developed disease progression while being treated with this drug for this condition.					
Administrative Advice: No increase in the maximum amount or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					

Source: Table 1.113 of the submission.

- 3.2 The submission requested a special pricing arrangement (SPA).
- 3.3 The submission considered that the requested maximum amount and number of repeats were consistent with the dosage recommendation in the draft TGA Product Information (5 × 4 mg = 20 mg orally once daily), the treatment duration in the key trial (median duration of 9.1 months) and the proposed listing of futibatinib for the treatment of CCA.
- The maximum quantity is sufficient for 28 days of treatment at the recommended dose; and

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- The number of repeats is sufficient for 6 months of treatment at the recommended dose.
- 3.4 The submission anticipated that less than five patients will require grandfathering to the PBS from a patient access program. The submission claimed that the eligibility criteria for the access program are aligned with the proposed PBS restriction criteria and that a grandfathering restriction is not sought, as the proposed restriction will enable access to futibatinib on the PBS for these patients.
- 3.5 The requested restriction was broader than the TGA indication for futibatinib recommended by the Delegate and ACM, and the enrolment criteria for the pivotal FOENIX-CCA2 study, which only included patients with intrahepatic CCA (iCCA), whereas patients with extrahepatic CCA (eCCA) would also be eligible under the requested restriction. Additionally, the ESCs noted that, with a broad CCA listing, clinicians may test patients with pancreatic ductal adenocarcinoma (PDAC). Although the efficacy of futibatinib in eCCA (or PDAC) was not informed by the FOENIX-CCA2 study, the ESCs considered that a broader restriction for CCA may be reasonable, as:
- it can be difficult to differentiate between iCCA and eCCA without performing a resection, and therefore in practice, both groups are likely to be tested regardless of the restriction;
 - as noted in the Pre-Sub-Committee Response (PSCR), there is no biological reason that futibatinib would not provide benefit to people with non-iCCA with *FGFR2* fusions or rearrangements, and international guidelines and local clinical practice implicitly accept that CCA tumour location is not expected to alter the activity of futibatinib;
 - only a very small number (<1%) of non-iCCA patients (eCCA and PDAC) have *FGFR2* fusions or rearrangements;
 - therefore inclusion of all CCA adenocarcinoma patients with *FGFR2* fusions or rearrangements for futibatinib treatment is unlikely to have a large impact on treatment costs (while there will be additional testing costs associated with testing patients with eCCA and PDAC);
 - further, as noted in the PSCR the broader request may avoid an equity of access issue for the small group of patients with eCCA with *FGFR2* fusions or rearrangements who would benefit from access to futibatinib.
- 3.6 Patients in FOENIX-CCA2 were allowed to continue treatment with futibatinib post progression after discussion between the investigators and the sponsor, with 13/103 patients (13%) having received futibatinib after imaging-based disease progression because of continued clinical benefit. However the evaluation noted that under the requested restriction, futibatinib cannot be used if disease progression developed while being treated with futibatinib.

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

4 Population and disease

- 4.1 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 iCCA, which originates from the bile ducts proximal to the second-order ducts and represents approximately 20% of cases, or eCCA, which represents the remaining 80% of cases (Banales, 2020; Valle 2021). Treatment guidelines generally recommend similar treatment pathways for both iCCA and eCCA; the PSCR noted that NCCN and ESMO recommend molecular profiling for targetable mutations in advanced CCA regardless of tumour location.
- 4.2 Following the availability of reimbursed *FGFR2* fusion or rearrangement testing and futibatinib, the submission proposed that in patients whose tumour tissue tests positive for an *FGFR2* alteration, first-line standard of care systemic treatment (primarily with cisplatin + gemcitabine ± durvalumab) will remain unchanged. In patients with disease progression, futibatinib or standard of care chemotherapy will be treatment options in the second and subsequent-line settings.
- 4.3 Futibatinib is a highly selective FGFR1-4 inhibitor. Futibatinib binds covalently to a conserved cysteine residue in the P-loop of the kinase domain of FGFR1-4, and has demonstrated strong selectivity for FGFR1-4 against a panel of 296 human kinases (IC50 values of 1.4 to 3.7 nM/L). Futibatinib inhibits FGFR phosphorylation and downstream signalling pathways, and reduces cell proliferation in tumour cell lines harbouring FGFR genomic aberrations/alterations.

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

5 Comparator

- 5.1 The submission nominated SoC as the main comparator. Specifically, FOLFOX; as modified FOLFOX6 chemotherapy (oxaliplatin 85 mg/m², calcium folinate 50 mg, fluorouracil 400 mg/m² bolus and 2400 mg/m² continuous infusion over 46 hours; given every 14 days for up to 12 cycles, as per eviQ protocol) was proposed as the SoC in Australian practice.
- 5.2 The submission also considered palliative care with active symptom control (ASC) is generally the management in the second- and subsequent line settings for patients with poor performance status or those who elect no further treatment, likely to preserve quality of life given the limited efficacy and poor safety profile associated with chemotherapy. As such, some consideration was also given to palliative care with ASC in this submission.
- 5.3 The submission noted that advice received from local experts suggests that futibatinib may replace a proportion of palliative care with ASC in some patients where clinically appropriate, however advisers to the sponsor 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%). The evaluation noted that in the

consideration of ivosidenib for the treatment of locally advanced or metastatic CCA in patients who have evidence of an *IDH1* variant and whose disease has progressed on at least one prior line of systemic therapy, it was considered that the nomination of palliative care/BSC as the primary comparator and FOLFOX as the secondary comparator appeared reasonable (paragraph 5.3, ivosidenib (Public Summary Document (PSD), July 2024 PBAC meeting). The PBAC also previously considered that FOLFOX was an important relevant comparator for a substantial proportion of patients (paragraph 7.5, ivosidenib PSD, July 2024 PBAC meeting).

- 5.4 The evaluation 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* alterations also had *IDH1* variant in Murugesan 2022.
- 5.5 The evaluation noted that pemigatinib, an inhibitor of FGFR1, 2 and 3, has provisional TGA approval for the treatment of adult patients with locally advanced or metastatic CCA with *FGFR2* fusions or rearrangements that has progressed after at least one prior line of systemic therapy. However, pemigatinib is not currently listed on the PBS and thus may be considered a near market comparator.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, the available clinical evidence, and how the drug would be used in practice. The clinician acknowledged that the evidence to support futibatinib is limited, as it based on a single arm trial, and a 'poor' cross trial comparator (ABC-06). He also noted that the 21 month median OS reported in NEJM may be long. However, he asserted that it is the best evidence that will be available due to the very low patient numbers, and the promising cross-study results for futibatinib, meaning that it would be unfeasible and unethical to randomise patients to a chemotherapy comparator.
- 6.2 Further, the clinician noted the high infection risk (10-20%) and peripheral neuropathy associated with FOLFOX, which is not observed for futibatinib, making it the more attractive treatment option. The clinician suggested that patients may go on to have FOLFOX after relapsing post-futibatinib, but they are unlikely to opt for FOLFOX second-line, when futibatinib presents a more efficacious and less toxic option. The clinician also noted that the futibatinib oral form does not have to be administered at a hospital, and therefore promotes better quality of life, and lower hospital resource utilisation than chemotherapy.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from organisations (4) via the Consumer Comments facility on the PBS website. Comments described a range of benefits of treatment with futibatinib including improvement in daily functioning, prolonged progression free survival, and the tablet form meaning autonomy over administration and reduced hospital visits, which is particularly beneficial for patients in rural and remote areas.
- 6.4 The PBAC noted the advice received from Pancare Foundation, Liver Foundation and Rare Cancers Australia (RCA) in support of the futibatinib submission. These consumer organisations described the high morbidity associated with CCA and its impact of patients and their families, and the Pancare Foundation also provided an in-depth report regarding the impact of upper GI cancers and the challenges of treatment. Input from both Liver Foundation and Pancare noted that patients diagnosed with cholangiocarcinoma are often diagnosed late, when chances of survival are reduced and treatment results in serious physical side effects, major impact on quality of life, and high financial burden. Comments noted the PFS and OS gains for patients treated with futibatinib was considered meaningful to patients, given the limited survival rate for CCA and lack of alternative therapies. Comments from RCA and the Liver Foundation noted that futibatinib is expected to improve the daily functioning of people with cholangiocarcinoma, and all groups anticipated that PBS listing would to remove the financial burden (or ‘financial toxicity’) of self-funding treatment. RCA described known futibatinib side-effects of fatigue, decreased appetite, diarrhea, and irregular heartbeat as manageable. Comments from the three consumer groups also noted that the oral administration for futibatinib has substantial benefits for patients compared with chemotherapy, especially for rural and remote patients.
- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its support for the futibatinib submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for futibatinib, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) 1, based on a comparison with placebo.
- 6.6 The PBAC noted that input regarding unmet clinical need for this population was useful.

Overview of the evidence base

- 6.7 The approach taken in the submission was to present evidence showing that futibatinib is superior to FOLFOX in patients with *FGFR2* fusions or rearrangements

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

CCA. The evaluation noted that the submission did not present evidence for futibatinib in biomarker negative CCA.

Table 3: 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	<input checked="" type="checkbox"/> k=3 n=368	Moderate - High	No
Prognostic evidence (longitudinal accuracy)	Meta-analysis of prognostic impact of <i>FGFR2</i> alteration on overall or progression-free survival in patients with CCA	<input checked="" type="checkbox"/> k=1 ^b n=1314	Moderate	No
Change in patient management	None ^c	<input type="checkbox"/> k= n=	-	-
Health outcomes (clinical utility)	None ^d	<input type="checkbox"/> k= n=	-	-
Predictive effect (treatment effect variation)	A retrospective analysis of patients from four US centres of patients with <i>FGFR</i> alterations compared to those who do not have <i>FGFR</i> alterations (Jain 2018)	<input checked="" type="checkbox"/> k=1 n=337	Moderate - High	No
Treatment effect (enriched)	None ^a	<input type="checkbox"/> 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.

6.8 Table 4 presents the available data to inform the testing comparisons.

Table 4: 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

Clinical studies on the safety/effectiveness of futibatinib

6.9 The submission was based on FOENIX-CCA2, an open-label, single-arm, phase 2 trial of futibatinib in patients with unresectable or metastatic *FGFR2* fusion-positive or *FGFR2* rearrangement-positive iCCA, and disease progression after one or more previous lines of systemic therapy; and

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- ABC-06, an open-label randomised phase 3 trial of active symptom control (ASC) and FOLFOX in patients with locally advanced or metastatic biliary tract cancer (including CCA and gallbladder or ampullary carcinoma).

6.10 FOENIX-CCA2 and ABC-06 formed the basis of an unanchored matched adjusted indirect comparison (MAIC) of futibatinib versus FOLFOX on the outcomes of progression free survival (PFS), overall survival (OS) and objective response rate (ORR) in advanced CCA presented to support a claim of superior efficacy for futibatinib. Additionally, a MAIC of futibatinib compared to ASC for OS was also presented.

6.11 Details of the studies presented in the submission are provided in Table 5.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
FOENIX-CCA2 NCT02052778 TAS-120-101 EUCT2013-004810-16 JapicCTI-184178	Clinical Study Report TAS-120-101 Part 1, Phase 1/2, dose escalation and dose expansion	12 August 2021
	Clinical Study Report TAS-120-101b Part 2, Phase 2 (TAS-120-101 Clinical Study Report Addendum	4 August 2021 30th October 2021
	Goyal, L., Meric-Bernstam, F., Hollebecque, A., Valle, J. W., Morizane, C., & et al. Futibatinib for <i>FGFR2</i> -Rearranged Intrahepatic Cholangiocarcinoma.	NEJM 2023; 388:228-39.
	Merich-Bernstam, F., Hollebecque, A., Furuse, J., Oh, D., Bridgewater, J. A., Shimura M, Anderson B, Hangai N, Wacheck V and Goyal L. Safety Profile and Adverse Event Management for Futibatinib, An Irreversible <i>FGFR1-4</i> Inhibitor: Pooled Safety Analysis of 469 Patients.	Clin Cancer Res 2024; 30(8):1466-1477.
	Bahleda, R., et al. Phase I, first-in-human study of futibatinib, a highly selective, irreversible <i>FGFR1-4</i> inhibitor in patients with advanced solid tumors.	Ann Oncol 2020; 31(10): 1405-1412.
Möhler, et al. Foenix-CCA2 quality of life data for Futibatinib-treated intrahepatic cholangiocarcinoma (ICCA) patients with <i>FGFR2</i> fusions/rearrangements.	Oncology Research and Treatment 2021; 44(SUPPL 2), 223-224. [abstract]	
Valle, et al. 58P Quality of life (QoL) outcomes with futibatinib treatment in FOENIX-CCA2 - A phase II study in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring <i>FGFR2</i> gene fusions/rearrangements	Annals of Oncology 2021; Volume 31, S263 - S264. [abstract]	
ABC-06 NCT01926236 CFTSp048 A16281 EUCT2013-001812-30 ¹	Lamarca, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial	Lancet Oncol 2021; 22(5):690-701.
	Lamarca, et al. 54MO Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial	Annals of oncology 2022; 33, S564-S565 [abstract]
	Lamarca, et al. P-88 Clinical role of tumour markers in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+mFOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial	Annals of oncology 2022; 33, S280 [abstract]

Source: Table 2.30, pp106-108 of the submission.

¹ study previously considered by the PBAC as part of indirect comparison to ivosidenib at the July 2024 PBAC meeting

6.12 The key features of the included evidence are summarised in Table 6

Table 6: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Patient population	Outcomes	Use in modelled evaluation
Futibatinib					
FOENIX-CCA2	103	MC, OL SAS	Unresectable or metastatic iCCA; FGFR2 fusion or other rearrangement; Measurable disease per RECIST v1.1; ≥ 1 prior systemic gemcitabine + platinum-based chemotherapy Progression after ≥ 1 systemic therapy;	OS, PFS ORR	Yes
FOLFOX					
ABC-06	161	MC, OL, R	Locally advanced or metastatic biliary tract cancer (including CCA, gallbladder carcinoma, and ampullary carcinoma) Documented radiological disease progression to previous first-line GP doublet chemotherapy FGFR2 status unknown	OS, PFS, ORR	Yes

Source: Table 2.29, pp104-105 of the submission.

iCCA = intrahepatic cholangiocarcinoma; MC=multi-centre; OL=open label; ORR = objective response rate; OS=overall survival; PFS=progression-free survival; R=randomised, SAS = single arm study;

- 6.13 FOENIX-CCA2 did not include durvalumab as part of the prior therapy, which the PBAC ESC noted is currently PBS listed as a first line treatment in combination with gemcitabine/cisplatin. The submission noted advice from the Advisory Board that use of durvalumab would not have impacted clinical decision making in subsequent lines of therapy. The evaluation noted that no evidence for futibatinib in patients who progressed after durvalumab was presented, and considered whether the efficacy of futibatinib would be the same after first-line durvalumab, or if prior immunotherapy may be a treatment effect modifier. The ESCs noted that only 5% of patients in the FOENIX-CCA2 study had received prior immunotherapy. The evaluation noted that a similar issue was considered previously by the PBAC ESC for ivosidenib, where no clinical evidence was presented in the submission regarding the efficacy and safety of ivosidenib in patients who have previously received durvalumab, however the PBAC ESC previously considered that, given the different mechanism of action of ivosidenib, efficacy and safety outcomes are unlikely to be affected by prior durvalumab (paragraph 6.12, ivosidenib PSD, July 2024).
- 6.14 Only patients with *FGFR2* fusions or rearrangements were enrolled in FOENIX-CCA2, whereas patients enrolled in ABC-06 were not selected for *FGFR2* alterations and their *FGFR2* status was unknown.

6.15 The evaluation noted that the submission’s search failed to identify two relevant publications:

Paine 2022², which presented a MAIC of futibatinib versus chemotherapy and pemigatinib in CCA patients with *FGFR2* fusions or rearrangements. Paine 2022 was available as an abstract and conference poster; and

Borad 2022³, which presented a simulated treatment comparison (STC) of futibatinib versus chemotherapy and pemigatinib in CCA patients with *FGFR2* fusions or rearrangements and was available in abstract form. Borad 2022 and Paine 2022 appear to have used the same data for analysis, but the method of indirect comparison differed.

6.16 Importantly, the evaluation noted that unlike the submission’s MAIC, Paine 2022 and Borad 2022 included only patients with *FGFR2* fusions or rearrangements in the chemotherapy arm. Results of Paine 2022 and Borad 2022 are discussed further in paragraphs 6.46 to 6.50.

Comparative effectiveness

FOENIX-CCA2 and ABC-06 individual study/trial results

6.17 A summary of the FOENIX-CCA2 PFS by independent review is provided in Table 7.

² Paine A et al. (2022) CO78 Matching-Adjusted Indirect Comparison of Futibatinib Versus Chemotherapy and Pemigatinib in Cholangiocarcinoma Patients With *FGFR2* Fusions/Rearrangements. *Value in Health*, Volume 25, Issue 12 Page S33. <https://doi.org/10.1016/j.jval.2022.09.157>.

Poster available at https://www.ispor.org/docs/default-source/euro2022/isporeu22thomco78-pdf.pdf?sfvrsn=6ebb5668_0
Accessed 26/11/24

³ [Mitesh J. Borad et al.](#), Indirect treatment comparison of futibatinib with chemotherapy and pemigatinib in cholangiocarcinoma with *FGFR2* fusions/rearrangements.. *JCO* 40, 440-440(2022). DOI:[10.1200/JCO.2022.40.4_suppl.440](https://doi.org/10.1200/JCO.2022.40.4_suppl.440).
Accessed 26/11/24

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Table 7: Summary of Progression-free Survival by Independent Review – FOENIX-CCA2

	All Treated Patients (N=103) n (%)	
	October 2020 cut-off (Median follow-up 17.1 months)	May 2021 cut-off (Median follow-up 25 months)
Disease progression or deaths, n (%)	64 (62.1)	78 (75.7)
Censored patients, n (%)	39 (37.9)	25 (24.3)
No baseline assessment	0	0
No post-baseline assessment	1 (1.0)	1 (1.0)
New anticancer treatment	3 (2.9)	4 (3.9)
Treatment discontinued without PD/death	5 (4.9)	9 (8.7)
PD/Death greater than 21 days after the last dose	10 (9.7)	11 (10.7)
Patient still on treatment without PD	20 (19.4)	0
PFS (months)		
Median (95% CI)	9.0 (6.9, 13.1)	8.9 (6.7, 11.0)
1st quartile (95% CI)	4.8 (2.9, 6.0)	4.8 (2.9, 5.1)
3rd quartile (95% CI)	15.6 (13.3, 19.1)	15.0 (12.5, 16.7)
PFS Rate (%) (95% CI)		
At 3 months	82.9 (73.9, 89.0)	82.9 (73.9, 89.0)
At 6 months	66.1 (55.7, 74.6)	65.0 (54.6, 73.6)
At 9 months	50.0 (39.4, 59.8)	48.1 (37.6, 57.9)
At 12 months	40.0 (29.1, 50.7)	35.4 (25.5, 45.4)

Source: Table 2.45, p135 of the submission. CI = confidence interval; PD = progressive disease; PFS = progression-free survival

6.18 Table 8 presents a summary of OS results for FOENIX-CCA2.

Table 8: Summary of OS results – FOENIX-CCA2

	All Treated Subjects (N=103) n (%)	
	October 2020 cut-off (Median follow-up 17.1 months)	May 2021 cut-off (Median follow-up 25 months)
Deaths, n (%)	40 (38.8)	58 (56.3)
Censored subjects, n (%)	63 (61.2)	45 (43.7)
Patient discontinued treatment due to any reason before data cut-off	32 (31.1)	45 (43.7)
Patient still alive at data cut-off	31 (30.1)	NR
Overall survival (months)		
Median (95% CI)	21.7 (14.5, NE)	20.0 (16.4, 24.6)
Overall survival rate (%) (95% CI)		
At 3 months	97.1 (91.2, 99.0)	97.1 (91.2, 99.0)
At 6 months	88.1 (80.0, 93.1)	88.1 (80.0, 93.1)
At 9 months	81.1 (72.0, 87.5)	81.1 (72.0, 87.5)
At 12 months	72.2 (62.0, 80.1)	73.1 (63.2, 80.7)

Source: Table 2.46, p137 of the submission.

CI = confidence interval; NE = not estimable

Note: Point estimates of overall survival rate are based on Kaplan-Meier method and 95% confidence intervals are based on the Greenwood Formula

6.19 In the primary analysis by independent review, confirmed complete response (CR) or partial response (PR) was recorded for 43 of the 103 patients in the efficacy

population, resulting in a confirmed ORR of 41.7% (95% confidence interval [CI]: 32.1, 51.9). The ORR rate was unchanged at the May 2021 cut-off point.

- 6.20 As a sensitivity analysis, ORR was also assessed by the local investigator or radiologist. The confirmed ORR per local assessment was 36.9% (95% CI: 27.6, 47.0) including 37 patients with PR and one patient with CR. The submission considered that this ORR was overall consistent with the ORR by the Independent Review Committee (IRC), in particular when considering the largely overlapping 95% CIs of both independent assessments.
- 6.21 In FOENIX-CCA2, health related quality of life (HRQoL) outcomes included European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQoL 5-dimension survey (EQ-5D-3L). These outcomes were collected at screening, Cycles 2 and 4, every 3 cycles after Cycle 4, and at the end of treatment.
- 6.22 Baseline mean (SD) EORTC QLQ-C30 global health status score was 70.1 (19.4) and EurQoL Visual Analog Scale (EQ VAS) score was 71.7 (20.3). The submission stated that patient reported outcomes (PRO) data were evaluated through to cycle 13 because this was the last visit before data were missing for more than 50% of the patients in the patient-reported outcome population. The evaluation considered that this suggested that the methodology for assessment of the HRQoL outcomes was not pre-specified and that these outcomes likely had a high risk of attrition bias. The evaluation considered that it was possible that loss to follow-up could be correlated with generally worse health and given the natural history of advanced or metastatic CCA, HRQoL outcomes would be expected to be worse with time. Consequently, it was possible that HRQoL outcomes were overestimated in the trial.
- 6.23 In the October 2020 analysis, 92 (89%) enrolled patients had PRO data at baseline and at least one follow-up assessment; 48 patients had PRO data at Cycle 13.
- 6.24 Table 9 presents the ABC-06 PFS by investigator results in the eCCA, iCCA, and whole trial population.

Table 9: PFS outcomes for patients with primary cholangiocarcinoma – ABC-06 trial, subgroup analysis

	All patients	iCCA	eCCA
N (ASC alone)	81	38	19
N (ASC+FOLFOX)	81	34	26
Progression-free survival			
Median PFS (ASC+FOLFOX); months (95% CI)	4.0 (3.2-5.0)	3.3 (2.5-5.2)	4.0 (2.9-5.9)
3 month PFS rate (ASC+FOLFOX) (%)	66.7%	64.7%	65.4%
6 month PFS rate (ASC+FOLFOX) (%)	32.1%	29.4%	30.8%
12 month PFS rate (ASC+FOLFOX) (%)	8.6%	11.8%	3.9%

Source: Table 2.49, p143 of the submission.

PFS = progression free survival; iCCA = intrahepatic cholangiocarcinoma; eCCA = extrahepatic cholangiocarcinoma; OS = overall survival; CI = confidence interval; HR = hazard ratio; ASC = active symptom control; N = number of patients

* HRs adjusted for stratification factors are provided.

- 6.25 Table 10 presents a summary of the OS outcomes in ABC-06 in the whole study population, which included iCCA, eCCA and gall bladder cancer, and not selected for

FGFR2 alterations and *FGFR2* status was unknown. Median OS was 6.2 months (95% CI 5.4–7.6) in the ASC plus FOLFOX group versus 5.3 months (4.1–5.8) in the ASC alone group (adjusted OS HR 0.69 [95% CI 0.50–0.97]).

Table 10: OS outcomes for patients with primary cholangiocarcinoma – ABC-06 trial, subgroup analysis

	All patients	iCCA	eCCA
N (ASC alone)	81	38	19
N (ASC+FOLFOX)	81	34	26
Overall survival			
Adjusted* HR (95% CI) OS	0.69 (0.50 – 0.97)	0.64 (0.38, 1.06)	0.84 (0.45-1.57)
Median OS months (ASC-alone); months (95% CI)	5.3 (4.1, 5.8)	5.2 (3.7, 5.8)	5.4 (3.9-6.4)
Median OS months (ASC+FOLFOX); months (95% CI)	6.2 (5.4, 7.6)	5.7 (4.1, 7.4)	6.2 (4.0-7.9)
6m OS rate (ASC-alone) (%)	35.5%	30.8%	36.8%
6m OS rate (ASC+FOLFOX) (%)	50.6%	44.1%	53.9%
12m OS rate (ASC-alone) (%)	11.4%	11.2%	10.5%
12m OS rate (ASC+FOLFOX) (%)	25.9%	26.5%	15.4%

Source: Table 2.48, p142 of the submission.

PFS= progression free survival; iCCA = intrahepatic cholangiocarcinoma; eCCA = extrahepatic cholangiocarcinoma; OS = overall survival; CI = confidence interval; HR = hazard ratio; ASC = active symptom control; n = number of patients; ne = not estimable.

* HRs adjusted for stratification factors are provided.

6.26 The submission noted that no HRQoL outcomes were reported with the main published trial results of ABC-06 in Lamarca 2021. The submission identified a conference abstract from ESMO 2022, reporting descriptive analyses of the quality of life (QoL) measures from baseline and 4-month follow-up for ABC-06 (Lamarca 2022). The submission presented “available case analysis” of 138/162 patients with evaluable results. The evaluation noted that it was unclear what this population signified or what was the criteria for inclusion into this population.

6.27 The submission noted that the interpretation of the data is limited given the data are sourced from a conference abstract. Based on this analysis, the addition of FOLFOX to ASC did not appear to induce worsening of the QoL parameters assessed. In contrast, patients in the ASC-alone arm appeared to experience worsening of the EQ-5D utility values and most of the QLQ-30 scales (including global, physical, social and role scales). There also appeared to be worsening of nausea and pain, which remained stable in the ASC+FOLFOX arm.

MAIC of futibatinib versus FOLFOX and ASC

6.28 The submission identified the following differences in baseline characteristics between FOENIX-CCA2 and the ASC+FOLFOX arm of ABC-06: median age, and the proportion of patients with CCA (ABC-06 enrolled patients with CCA and bile duct cancer, with iCCA representing 47% of the sample compared to 100% of patients with

iCCA in FOENIX-CCA2). Table 11 presents the potential cofounders in baseline characteristics identified in the submission.⁴

Table 11: Across trial comparison of potential confounding variables in the ITC

Trial ID	FOENIX-CCA2	ABC-06;	
	Whole trial population	FOLFOX+ASC	ASC
Age, median (range)	58 (22–79) Mean 55.7 (SD 12.2)	65 (26–84)	65 (26–81)
Gender male, n (%)	45 (43.7)	43 (53)	37 (46)
iCCA, n (%)	103 (100)	34 (42)	38 (47)
Baseline ECOG PS, n (%)	0: 48 (46.6) ≥1: 55 (53.4)	0: 25 (31) ≥1: 55 (68) Missing: 1 (1)	0: 28 (35) ≥1: 52 (64) Missing: 1 (1)
Baseline albumin, n (%)	20 (19.4) ≥35 83 (80.6)	<35: 19 (23) ≥35: 62 (77)	<35: 21 (26) ≥35: 60 (74)
Prior systemic Tx lines for adv/meta disease, n (%)	1: 48 (46.6) >1: 55 (53.4)	1: 81 (100)	1: 81 (100)
Prior surgical resection of primary tumour, n (%)	Primary tumour resection: 21 (20.4) Any prior cancer surgery: 41 (39.8)	34 (42)	38 (47)
Race	Caucasian/White: 51 (49.5)	NR	NR
% TP53 alteration (unaltered or unknown)	12.6 (87.4)	NR	NR
FGFR2 fusion or rearrangement positive	100%	NR	NR

Source: Table 2.60, p158

ASC = active symptom control; CCA = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group Performance Score; FOLFOX = folinic acid, fluorouracil, and oxaliplatin; NR = not reported SD = standard deviation; Tx = treatment.

Text in italics indicate values added during evaluation

Note that the results presented in Table 11 are derived from analyses conducted by the applicant 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.

- 6.29 The submission’s MAIC controlled for age, gender, ECOG status, prior surgery, and baseline hypoalbuminemia status in the ITC of futibatinib and FOLFOX+ASC. The evaluation considered it inappropriate that the submission did not provide post matched characteristics. The ESCs noted the post matched characteristics of the included MAICs provided in the PSCR appear to be well balanced after matching, but do not explain why the population adjusted futibatinib arm would have better OS and PFS outcomes than the unadjusted futibatinib arm (discussed in paragraph 6.39). The ESCs considered that this raises questions around the reliability of the match adjustments given the unexpected direction of PFS and OS shift post adjustment.⁴
- 6.30 The submission identified the following potential cofounders that the submission did not account for in the MAIC: *FGFR2* alteration status, ethnicity, % of patients with TP53 alteration status, and proportion of patients with iCCA. The ESCs noted that matching

⁴ Note that the results presented in paragraphs 6.28 and 6.29 are derived from analyses conducted by the applicant 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.

for *FGFR2* and P53 alteration status was not possible as data was not available for the ABC-06 study.⁵

- 6.31 The submission considered that the prognostic value of *FGFR2* fusions or rearrangements for chemotherapy is uncertain. Noting that the evaluation considered the available evidence suggests that presence of *FGFR2* alterations may improve prognosis (see Claim of codependence section), the ESCs considered it probable that adjusting for *FGFR2* alterations would decrease the incremental benefit of futibatinib.⁵
- 6.32 Moreover, as previously noted (paragraph 6.15) there were two published studies which presented results from a MAIC (Paine 2022) and an STC (Borad 2022) which included an *FGFR2* fusion/rearrangement population in both futibatinib and chemotherapy arms, which the ESCs considered further supported the theory that the presence of *FGFR2* alterations improved prognosis.⁵
- 6.33 The submission considered that despite the limitation of not adjusting these variables in the MAIC, the comparative efficacy data from ABC-06 were the most appropriate evidence for decision making. Overall, the evaluation considered that given the differences in the two studies and the lack of adjustment for *FGFR2* alteration status, any estimated magnitude of benefit in the MAIC presented in the submission is highly uncertain. Moreover, the evaluation considered that it was unclear if this was the most appropriate evidence, because, as discussed above, Paine 2022 and Borad 2022 were able to adjust for *FGFR2* status in the FOLFOX arm.⁵
- 6.34 The submission also stated that the effective sample size (ESS) for futibatinib in the base case of the comparison with FOLFOX was 53 for PFS and OS, which was approximately 50% reduction from the trial sample size. The submission further claimed that this suggested moderate to good overlap in baseline characteristics between studies. The evaluation considered that this may not be reasonable, as rescaled patient weights show that the majority of patients had poor matches and subsequently heavily reduced weights. Rescaled patient weights showed a few patients received a large weighting. The evaluation noted that it appears that two patients had weighting of greater than four and five, respectively. The evaluation considered that given that the ESS was 53, this suggests that these two patients likely represented almost 20% of the entire population after adjustment. The evaluation and the ESCs considered that results are therefore heavily influenced by the performance of these two patients.⁵
- 6.35 The submission stated that the ESS for futibatinib in the base case of the comparison with ASC was 52 for OS. Similar to the MAIC between futibatinib and FOLFOX, three patients had weights above four, which the evaluation considered suggest that these

⁵ Note that the results presented in paragraphs 6.30 to 6.34 are derived from analyses conducted by the applicant 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.

three patients alone represented almost 25% of the total population of futibatinib patients, with the majority of patients having significantly reduced weights. The evaluation and the ESCs considered that results would be heavily influenced by the results of the three patients receiving high weights.⁶

- 6.36 The evaluation considered it inappropriate that no ESS for ORR was reported.⁶
- 6.37 Table 12 presents the adjusted and unadjusted results of the MAIC comparing futibatinib to FOLFOX for PFS. The evaluation noted that, only PFS by investigator was reported in ABC-06, therefore the base case comparison was PFS by independent review committee in FOENIX-CCA2 compared to PFS by investigator in ABC-06. The evaluation presented a comparison using futibatinib results for PFS by investigator as a sensitivity analysis.⁶

Table 12: Unadjusted and adjusted PFS model results: Futibatinib vs FOLFOX+ASC

Model	HR for PFS	95% CI; p value	RMST (months) for PFS tau=14.79 months	RMST difference (months) for PFS (95% CI; p value)	Notes
Cox-naïve/unadjusted (PFS-IRC)	0.43	0.31–0.59; p<0.0001	Futibatinib unadjusted (PFS-IRC): 8.88 FOLFOX+ASC: 5.32	3.56 (2.28–4.84); p<0.0001	No covariate adjustment
Cox-naïve/unadjusted (PFS-INV)	0.38	0.27–0.52; p<0.0001	Futibatinib unadjusted (PFS-INV): 9.45 FOLFOX+ASC: 5.32	4.14 (2.92–5.35); p<0.0001	
Adjusted Cox MAIC model analyses					
Base-case covariates (PFS-IRC)	0.30	0.22–0.41; p<0.0001	Futibatinib adjusted (PFS-IRC): 10.46	3.57 (2.55–4.64); p<0.0001	Adjusted for age, gender, ECOG status, prior surgery, baseline hypoalbuminemia status
Sensitivity covariates (PFS-INV)	0.31	0.23–0.41; p<0.0001	Futibatinib adjusted (PFS-INV): 10.34	4.14 (3.27–5.08); p<0.0001	Adjusted for age, gender, ECOG status, prior surgery, baseline hypoalbuminemia status

Source: Table 2.62, p161 of the submission.

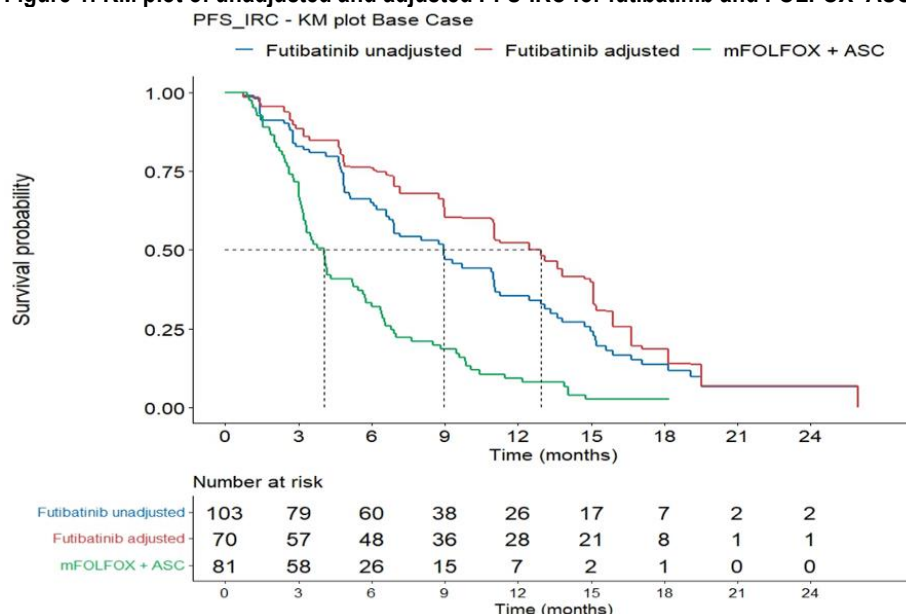
ASC = active symptom control; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; INV = by investigator; IRC = by independent review committee; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; RMST = restricted mean survival time.

Note that the results presented in Table 12 are derived from analyses conducted by the applicant 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.

- 6.38 Figure 1 shows the Kaplan-Meier (KM) plot of the MAIC for adjusted and unadjusted PFS based on independent review.⁶

⁶ Note that the results presented in paragraphs 6.35 to 6.38 are derived from analyses conducted by the applicant 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.

Figure 1: KM plot of unadjusted and adjusted PFS-IRC for futibatinib and FOLFOX+ASC



Source: Figure 2.21, p160 of the submission.

ASC = active symptom control; IRC = independent review committee assessed; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; FOLFOX = modified FOLFOX; PFS = progression-free survival.

Note: for a weighted estimate, the effective sample size (ESS) is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. The ESS is different to the number at risk at the start of a weighted KM plot for time-to-event outcomes, as the weighted number at risk is simply the sum of the weights.

Note that the results presented in Figure 1 are derived from analyses conducted by the applicant 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.

- 6.39 The evaluation considered it unclear why the population adjusted futibatinib arm (30.86% ECOG 0, mean/median age 65 years, from Table 1 in PSCR) had better PFS and OS outcomes than the unadjusted futibatinib arm (46.6% ECOG 0, mean/median age 55.7 years, from Table 1 in PSCR), given the poorer performance status and older age in the adjusted population. The ESC agreed with the evaluation that it was unclear why the adjustments improved PFS and OS but considered it possible that *FGFR2* fusions or rearrangements may confer improved prognosis. The ESCs also considered it may also be related to the high weights applied to a few patients in the MAIC (see paragraph 6.34), and the reliability of the matched adjustments may be questionable given the unexpected direction of PFS and OS shift post adjustment.⁷
- 6.40 Table 13 presents the OS results of futibatinib versus FOLFOX+ASC and futibatinib versus ASC from the unadjusted Cox model and covariate-adjusted MAIC analyses (adjusted for covariates outlined in paragraph 6.29). The submission considered that the MAIC base-case HR estimate shows a significantly reduced risk of death for

⁷ Note that the results presented in paragraph 6.39 are derived from analyses conducted by the applicant 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.

futibatinib patients (HR: 0.24; 95% CI: 0.18–0.32). The MAIC base-case HR estimate also indicated a significantly reduced risk of death for futibatinib patients versus ASC (HR: 0.18; 95% CI: 0.14–0.24, $p < 0.0001$).⁸

- 6.41 Based on a visual assessment of the log-cumulative hazard plot and the Schoenfeld residuals, the submission stated that the proportional hazards assumption holds in both comparisons. However, the decline in hazard with chemotherapy was quite steep and could be indicative of non-proportional hazard. Therefore, restricted mean survival time (RMST) analyses were also conducted. Based on RMST calculation, futibatinib showed an incremental benefit in OS of approximately 10 months over chemotherapy in both adjusted and unadjusted analysis at up to 27.24 months (the truncation time point of the RMST analysis) ($p < 0.0001$).⁸
- 6.42 In the submission's RMST analysis, futibatinib showed an incremental benefit in OS of approximately 10 months over ASC in both adjusted and unadjusted analysis at up to 23.66 months (the truncation time point of the RMST analysis), with a p value of < 0.0001 .⁸

⁸ Note that the results presented in paragraph 6.40 to 6.42 are derived from analyses conducted by the applicant 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 13: Unadjusted and adjusted OS model results: Futibatinib vs FOLFOX+ASC

Model	HR for OS	95% CI; p value	RMST (months) for OS	RMST difference (months) for OS (95% CI; p value)	Notes
Futibatinib versus ASC+FOLFOX					
Cox-naïve/unadjusted	0.26	0.18–0.37; p<0.0001	Futibatinib unadjusted:18.41 FOLFOX+ASC: 8.46	9.95 (7.70, 12.20); p<0.0001	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case covariates	0.24	0.18–0.32; p<0.0001	Futibatinib adjusted:19.33	9.85 (8.12, 11.54); p<0.0001	Adjusted for age, gender, ECOG status, prior surgery, baseline hypoalbuminemia status
Futibatinib versus ASC					
Cox-naïve/unadjusted	0.20	0.14–0.29; p<0.0001	Futibatinib unadjusted:18.41 Chemotherapy: 8.46	10.38 (8.50–12.27); p<0.0001	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case covariates	0.18	0.14–0.24; p<0.0001	Futibatinib adjusted:19.33	10.39 (8.90–11.74); p<0.0001	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status

Source: Table 2.64, p163 of the submission.

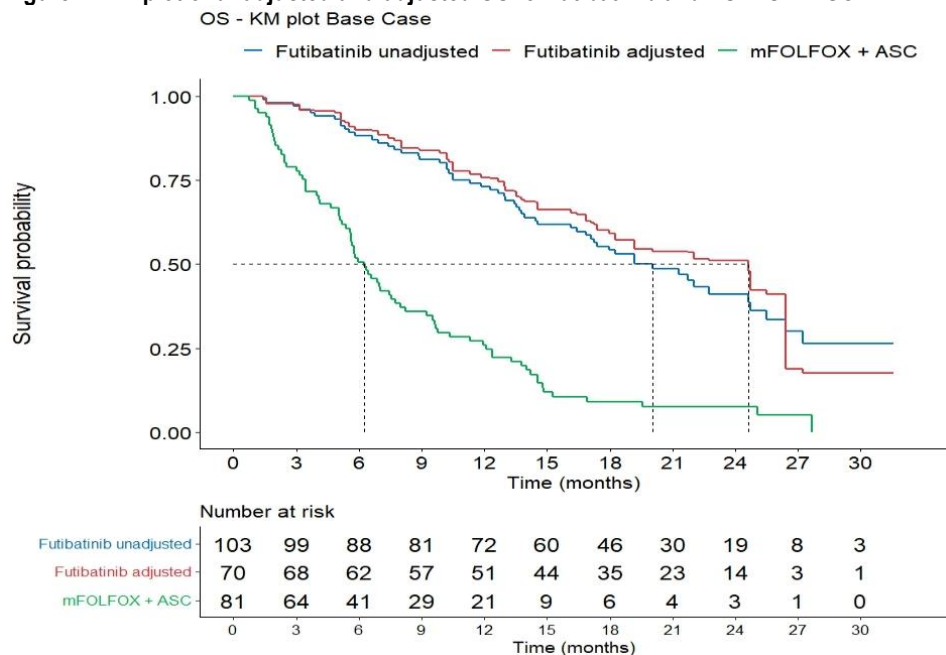
ASC = active symptom control; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPD = individual patient data; MAIC = matching-adjusted indirect comparison; FOLFOX = modified FOLFOX; OS = overall survival; RMST = restricted mean survival time

Note that the results presented in Table 13 are derived from analyses conducted by the applicant 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

6.43 Figure 2 and Figure 3 present the KM plots for OS of futibatinib versus FOLFOX+ASC and ASC in the MAIC, respectively.⁹

⁹ Note that the results presented in paragraph 6.43 are derived from analyses conducted by the applicant 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.

Figure 2: KM plot of unadjusted and adjusted OS for futibatinib and FOLFOX+ASC



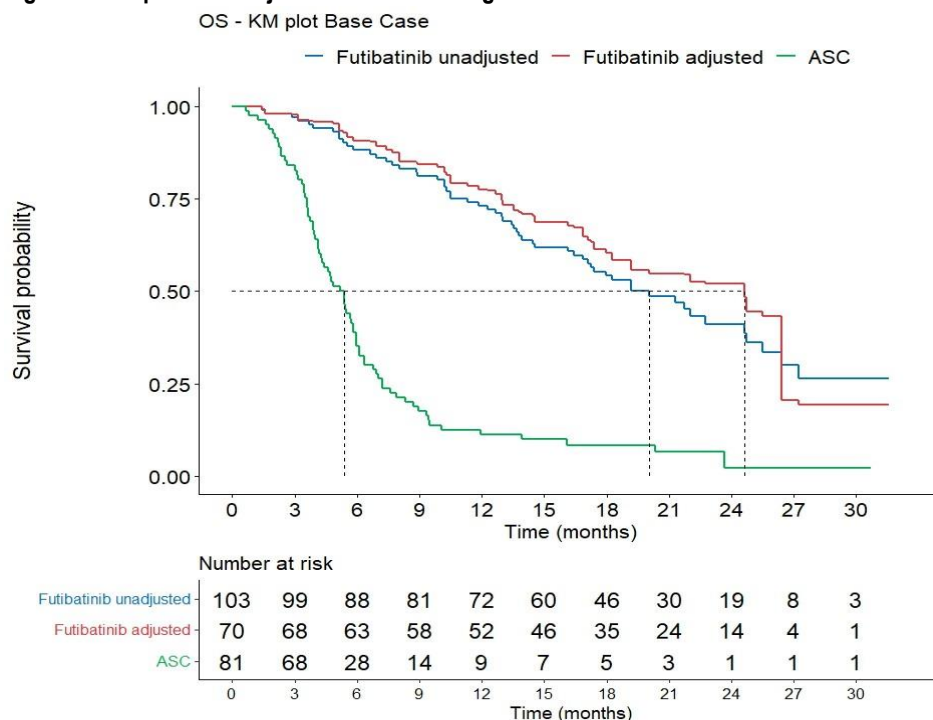
Source: Figure 2.23, p162 of the submission.

ASC = active symptom control; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; FOLFOX = modified FOLFOX; OS = overall survival

Note: for a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. The ESS is different to the number at risk at the start of a weighted KM plot for time-to-event outcomes, as the weighted number at risk is simply the sum of the weights.

Note that the results presented in Figure 2 are derived from analyses conducted by the applicant 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

Figure 3: KM plot of unadjusted and MAIC-weighted OS for futibatinib and ASC



Source: Figure 2.24, p165 of the submission.

ASC = active symptom control; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

Note: for a weighted estimate, the ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. The ESS is different to the number at risk at the start of a weighted KM plot for time-to-event outcomes, as the weighted number at risk is simply the sum of the weights.

Note that the results presented in Figure 3 are derived from analyses conducted by the applicant 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

6.44 As for PFS, the evaluation considered it unclear why the adjusted futibatinib arm would have a better OS than the unadjusted futibatinib arm, given that patients enrolled in FOENIX-CCA2 had better ECOG and were younger than patients enrolled in ABC-06.¹⁰

6.45 Table 14 presents the ORR results from the unadjusted binomial model and covariate-adjusted MAIC analyses. As with the survival outcomes, five base-case prognostic factors were included in the base-case adjusted model (age, gender, ECOG status, prior surgery, and baseline hypoalbuminemia status). In the base case, the odds ratio (OR) estimate shows an increased rate of ORR for futibatinib compared with FOLFOX+ASC patients (OR: 18.74; 95% CI: 7.20–61.31). This effect remained statistically significant when a comparison was made using ORR by investigator for futibatinib in the sensitivity analyses.¹⁰

¹⁰ Note that the results presented in paragraphs 6.44 and 6.45 are derived from analyses conducted by the applicant 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: Unadjusted and adjusted ORR model results: Futibatinib vs FOLFOX+ASC

Model	OR for ORR	95% CI; p value	Notes
Cox-naïve/unadjusted (ORR-IRC)	13.80	5.49–44.12; p<0.001	No covariate adjustment
Cox-naïve/unadjusted (ORR-INV)	11.73	4.65–37.57; p<0.001	
Adjusted Cox MAIC model analyses			
Base-case covariates (IRC)	18.74	7.20–61.31; p<0.001	Adjusted for age, gender, ECOG status, prior surgery, baseline hypoalbuminemia status
Base-case covariates (INV)	12.71	4.85–41.69; p<0.001	

Source: Table 2.66, p164 of the submission.

ASC = active symptom control; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; INV = investigator assessed; IPD = individual patient data; IRC = independent review committee; MAIC = matching-adjusted indirect comparison; OR = odds ratio; ORR = objective response rate

Note that the results presented in Table 14 are derived from analyses conducted by the applicant 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

6.46 Additional published indirect comparisons between futibatinib and FOLFOX were identified during the evaluation, with Paine 2022 reporting the results using a MAIC approach whereas Borad 2022 reported the results using a STC approach. In both studies, futibatinib results were informed by FOENIX-CCA2. However, the evaluation noted that instead of using ABC-06 (as in the submission) to inform chemotherapy outcomes, patients treated with second line chemotherapy in the Pre-FIGHT 202 study¹¹ (n=53) and Shroff 2022 (n=71) were used to inform chemotherapy PFS and OS outcomes, respectively. Unlike ABC-06, all patients in Pre-FIGHT 202 had *FGFR2* alterations (as these patients were subsequently enrolled in the FIGHT 202 study of pemigatinib). Similarly, only patients with *FGFR2* alterations from Shroff 2022 were used to inform the indirect comparison. As such, the evaluation considered that the results of Paine 2022 and Borad 2022 are likely to be much more comparable and applicable to the proposed Australian population, as there is evidence that *FGFR2* alterations have a positive prognostic effect. The PSCR (p7) contended that these comparisons are flawed and inappropriate sources of efficacy estimates given their limitations (including use of data from retrospective analyses to inform ITCs, uncertainty arising from statistical methods, and lack of information regarding treatments used in the chemotherapy arm). In Paine 2022, age, sex, ECOG PS, proportion of patients with ≥2 lines of prior chemotherapy, albumin ≤35 g/L and prior surgery were used as covariates in the MAIC. After matching, ESS for futibatinib was 48.5, and 65.3 for comparisons with pre-FIGHT-202 (for PFS) and Shroff 2022 (for OS), respectively.

6.47 In Borad 2022, regression models were applied to adjust for between-trial differences in baseline characteristics, though it was unclear which characteristics were adjusted

¹¹ Abou-Alfa G, et al. SO-4 Progression-free survival in patients with cholangiocarcinoma with *FGFR2* fusions or rearrangements: A FIGHT-202 post-hoc analysis of prior systemic therapy response. *Ann Oncol.* 2021;32:S203-4.

for. Population-adjusted Cox regression models were used for base case time-to-event outcomes (PFS, OS and DOR) and binomial-logistic regressions for binary outcomes (ORR).

6.48 The results from Paine 2022 and Borad 2022 as well as a comparison with the results of the MAIC presented in the submission are summarised in Table 15.

Table 15: 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)	0.30 (0.22-0.41, <0.0001)
OS	20.0 (16.4-24.6)	6.2 (5.4-7.6) ^e	0.26 (0.18-0.37, <0.0001)	0.24 (0.18-0.32, <0.0001)
ORR	NA	NA	13.8 (5.49-44.12, <0.001) ^f	18.74 (7.20-61.31, <0.001) ^f

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

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

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

6.49 The evaluation noted that compared to the submission’s estimates, Paine 2022 and Borad 2022 reported a less favourable adjusted PFS and OS HR for futibatinib compared to chemotherapy. The evaluation considered that this was likely related to better OS (and to a smaller extent, PFS) in the chemotherapy arm as only patients with *FGFR2* alterations were included in Paine 2022 and Borad 2022. Similarly, the evaluation noted that neither ORR nor duration of response were considered to be statistically significantly different in Borad 2022 (95% CI included the null of 1) whereas the submission’s MAIC reported a odds ratio of 13.8 (unadjusted) to 18.7 (adjusted) for ORR. The evaluation considered that this suggests that by not adjusting for *FGFR2* alterations, the submission likely overestimated the benefit associated with futibatinib in the *FGFR2* altered population.

6.50 The evaluation considered that given the lack of details regarding the methodology of Paine 2022 and Borad 2022 (which were only available as abstracts/ posters), as well as risks of bias inherent with indirect comparisons of single arm studies, these results

should also be interpreted with caution. The ESCs considered the comparisons were informative and considered it likely that they represent more reasonable estimates for PFS and OS benefits associated with futibatinib relative to chemotherapy in patients with *FGFR2* alterations.

Comparative harms

6.51 Table 16 presents a summary of adverse events (AEs) in FOENIX-CCA2.

Table 16: Safety overview for FOENIX-CCA2– Safety population, May 2021 cut-off

	All Treated Patients (N=103) n (%)
Adverse events	103 (100.0)
Adverse events of CTCAE Grade 3, 4, or 5	82 (79.6)
Serious adverse events	42 (40.8)
Deaths due to SAEs	6 (5.8)
Adverse events leading to study drug dose adjustment	80 (77.7)
Adverse events leading to study drug withdrawal	11 (10.7)
Adverse events leading to study drug dose reduction	61 (59.2)
Adverse events leading to study drug interruption	70 (68.0)
Treatment-related adverse events	102 (99.0)
Treatment-related adverse events of CTCAE Grade 3, 4, or 5	60 (58.3)
Treatment-related SAE	11 (10.7)
Treatment related deaths due to SAEs	0
Treatment-related adverse events leading to study drug dose adjustment	68 (66.0)
Adverse events leading to study drug withdrawal	4 (3.9)
Adverse events leading to study drug dose reduction	57 (55.3)
Adverse events leading to study drug interruption	53 (51.5)

Source: Table 2.52, p146 of the submission.

CTCAE = Common Terminology Criteria for Adverse Events; SAE: Serious adverse event.

Summary includes all events reported between first dose and 30 days after last dose of study drug

Treatment Related was deemed by the Investigator to be possibly or probably related to study drug or AEs with a missing causality.

For each row category, a patient with two or more adverse events in that category is counted only once.

Adverse events were graded using CTCAE Version 4.03 except for hyperphosphatemia and blood phosphorus increased.

6.52 Eighty two (79.6%) patients had grade 3 or greater AEs. Most frequent Grade 3 or greater AEs were hyperphosphataemia (30.1%), hyponatraemia (10.7%), and aspartate aminotransferase increased (9.7%). The ESCs considered that whilst TEAEs were frequent, they were mostly anomalies in laboratory values, and not symptomatic.

6.53 Adverse events of special interests (AESIs) in FOENIX-CCA2 were defined based on non-clinical data and prior clinical experience with futibatinib, as well as known class effects of FGFR inhibitors included hyperphosphatemia, retinal disorders, hepatotoxicity, nail disorders, Palmar-plantar erythrodysesthesia syndrome, and rash. Table 17 reports AESIs by grade in FOENIX-CCA2. Forty-three (41.7%) patients had an AESI of grade 3 or above.

Table 17: Summary of AEs of special interest by worst CTC Grade – FOENIX-CCA2, Safety Population, May 2021

AESI	Grade 1 (N %)	Grade 2 (N %)	Grade 3 (N %)	Grade 4 (N %)	Grade 5 (N %)	Total (N %)	>=Grade 3 (N %)
Patients with at least one AE	9 (8.7)	46 (44.7)	42 (40.8)	1 (1.0)	0	98 (95.1)	43 (41.7)
Hepatotoxicity	13 (12.6)	2 (1.9)	12 (11.7)	1 (1.0)	0	28 (27.2)	13 (12.6)
Hyperphosphataemia	8 (7.8)	54 (52.4)	32 (31.1)	0	0	94 (91.3)	32 (31.1)
Nail Disorders	27 (26.2)	25 (24.3)	2 (1.9)	0	0	54 (52.4)	2 (1.9)
Palmar-plantar erythrodysesthesia syndrome	4 (3.9)	13 (12.6)	6 (5.8)	0	0	23 (22.3)	6 (5.8)
Rash	8 (7.8)	1 (1.0)	0	0	0	9 (8.7)	0
Retinal Disorders	5 (4.9)	3 (2.9)	0	0	0	8 (7.8)	0

Source: Table 2.57, p150 of the submission.

AESI = adverse events of special interest; CTC = Common Terminology Criteria

Summary includes all events reported between first dose and 30 days after last dose of study drug

If a patient had two or more adverse events in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that patient.

- 6.54 In the most recent Periodic Benefit-Risk Evaluation report, important identified risk for futibatinib included serious retinal detachment, and important potential risk included Embryo-Foetal Toxicity/Teratogenicity. The ESCs noted that whilst retinal detachment is an important risk, only Grade 1-2 retinal disorders were reported. The PBAC noted that the ACM did not advise routine retinal screening with the use of futibatinib (ACM minutes, February 2025).
- 6.55 In ABC-06, Grade 3-5 adverse events were reported in 56 (69%) of 81 patients in the ASC+FOLFOX group and 42 (52%) of 81 patients in the ASC alone group. Three chemotherapy-related deaths (one each due to infection, acute kidney injury, and febrile neutropenia) were reported in the ASC+FOLFOX group. All other deaths reported in both groups were cancer related, with the exception of ten deaths associated with intercurrent illness (eight in the ASC+FOLFOX group and two in the ASC-only group); cause of death was not reported for one patient in the ASC alone group.
- 6.56 Thirty-one patients (38%) in the ASC+FOLFOX treatment group reported a chemotherapy-related AE that was at least Grade 3 in severity. The most frequently reported Grade 3–5 chemotherapy-related adverse events were neutropenia (ten [12%] patients), fatigue or lethargy (nine [11%] patients), and infection (eight [10%] patients).
- 6.57 The submission did not conduct an indirect treatment comparison of safety outcomes. The evaluation noted that in the economic model, AEs from the unanchored unadjusted results of FOENIX-CCA2 and ABC-06 were used for futibatinib and FOLFOX, respectively.
- 6.58 Overall, the evaluation considered that as no comparative safety evidence was presented, assessing a safety claim of futibatinib versus ASC+FOLFOX is challenging. The FDA, in its consideration of futibatinib for CCA, concluded that the observed safety profile of futibatinib in this patient population was generally consistent with the

known toxicity profile of the pharmacological class. The evaluation considered that the risks of futibatinib are largely manageable with safety monitoring, treatment modifications, and supportive care.

Benefits/ harms

6.59 The unanchored MAIC presented in the submission did not allow for a meaningful comparison of the relative benefits of futibatinib and FOLFOX as the results were not adjusted for *FGFR2* alteration status and were likely to be overestimated. Additionally, the submission did not present a comparison of safety outcomes. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.60 The submission described futibatinib as superior in terms of effectiveness compared with FOLFOX and superior in terms of safety compared to FOLFOX. The submission also described futibatinib as superior in terms of effectiveness compared to ASC, with a different safety profile that is manageable.

6.61 With regards to the effectiveness claim versus FOLFOX, the ESCs considered that the submission's MAIC indicated a greater magnitude of benefit associated with futibatinib compared to FOLFOX in both the adjusted and unadjusted comparison; however, the magnitude of benefit is highly uncertain, and likely overestimated, due to:

- Differences in the baseline characteristics of patients enrolled in these studies, such as tumour site (FOENIX-CCA2 was 100% iCCA, whereas ABC-06 included iCCA, eCCA, gallbladder cancers and ampullar cancers), and *FGFR2* alteration status (100% *FGFR2* alterations in FOENIX-CCA2, with unknown status in ABC-06), that would likely have affected transitivity and were unadjusted for (see paragraph 6.30).
- 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 OS, PFS and ORR, which the ESCs considered suggest that the submission's estimates may be overestimated. The ESCs noted the issues raised regarding these studies (see paragraphs 6.48, 6.50) but considered they were informative.
- The ESCs considered the unanchored nature of the comparison conferred a high risk of bias to unknown treatment effect modifiers. The PSCR reiterated consideration that the presented MAIC was the 'best available evidence' in the absence of comparative trial data for this very small patient population and requested that the limitations of the evidence be considered in the context of the rarity of CCA.

6.62 With regards to the claim of superior safety, the submission did not present comparative safety data between futibatinib and FOLFOX to support a claim of

superior safety. The ESCs considered that given the known toxicity of FOLFOX treatment, a claim of superiority may be plausible but remained unsupported in the submission.

- 6.63 The evaluation and the ESCs considered that the submission's claim of superior efficacy versus ASC generally had the same limitations as that versus FOLFOX. The evaluation considered that logically, given the improved outcomes associated with the addition of FOLFOX to ASC in ABC-06, the benefit of futibatinib versus ASC should be greater than futibatinib compared to FOLFOX. However, the claim of superior efficacy was only based on OS, and not PFS or ORR.
- 6.64 In terms of safety, the evaluation considered that a claim of inferior (but manageable) safety versus ASC would be appropriate given the risk of hyperphosphatemia, nail toxicities and eye toxicities with futibatinib treatment. The ESCs considered a claim of inferior but manageable safety compared to ASC was reasonable.
- 6.65 The PBAC considered that the claim of superior comparative effectiveness was reasonable; however that the magnitude of effect is highly uncertain and likely overestimated due to differences in baseline characteristics (tumour site, *FGFR2* status), less favourable HR in other indirect comparisons, and the unanchored MAIC.
- 6.66 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data, but that it is theoretically plausible. The PBAC considered that the claim of inferior comparative safety compared to ASC was reasonable.

Claim of codependence

- 6.67 The ESCs agreed with the evaluation that the available evidence suggests that the presence of *FGFR2* alterations improve prognosis, regardless of treatment.
- 6.68 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.

Economic analysis

- 6.69 The submission presented an economic evaluation based on the results of the MAIC described above. The evaluation and the ESCs considered that given concerns

regarding the results of the MAIC, the underlying clinical benefit used to inform the economic evaluation was uncertain. As such, the evaluation and the ESCs considered that the economic model presented was likely not reflective of the true cost effectiveness of futibatinib and may not be informative for decision making. The PSCR) reiterated the sponsor’s consideration that it is appropriate and provides a sufficiently robust estimate of magnitude of effect. The ability to run sensitivity analyses using alternative MAIC results from Paine 2022 or Borad 2022 was not included in the model operability. The PSCR acknowledged the lack of flexibility in the model but considered it not to be a flaw insofar as it claimed the comparator data from ABC-06 is the best available and to use other results would introduce additional uncertainty and biases against futibatinib. The ESCs considered that the more conservative results from Paine 2002 and Borad 2022 are likely more appropriate.

6.70 The type of economic evaluation presented was a cost utility analysis. Table 18 summarises the key component of the economic evaluation.

Table 18: Key components of the economic evaluation

Component	Description	Justification/comments
Comparison modelled	Futibatinib 20mg versus FOLFOX chemotherapy ^a every 14 days for up to 12 cycles	Noting 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	
Time horizon	10 years versus median follow-up of 25.0 months at final data cut off in FOENIX-CCA2	May be too optimistic, as in its consideration of ivosidenib for CCA, the PBAC had requested a re-specification to a 5-year time horizon. The ESC noted the median OS was 20 months in FOENIX-CCA2.
Methods used to generate results	Partitioned survival analysis	
Health states	PFS, PD, death	
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 <i>FGFR2</i> testing using NGS on RNA it was 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. The ESCs noted that these were likely more appropriate as they were more conservative..

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Component	Description	Justification/comments
Extrapolation method	<p>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.</p> <p>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.</p>	<p>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. The ESCs noted that the OS curves did not converge in the model.</p>
Health related quality of life	<p>Futibatinib PFS: 0.796 based on EQ-5D-3L of FOENIX CCA-2</p> <p>FOLFOX PFS: 0.70 based on ABC-06 supplement</p> <p>Futibatinib PD: 0.68 (based on NICE 474)</p> <p>FOLFOX PD: 0.584 (based on applying same decrement from PFS to PD as futibatinib)</p>	<p>The submission did not present a clinical comparison of QoL outcomes to justify treatment-based utilities in the PF or PD health state. The evaluation and the ESCs noted that utilities for these states are much lower than the ivosidenib submission, and considered that the utilities for FOLFOX may have been underestimated as it was informed by a single value at month 4 in ABC-06 (as opposed to change over time). 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.</p>

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

- 6.71 The model did not account for the impact of potential false positives and false negatives in the testing population, which the evaluation considered may have underestimated the ICER. However, the evaluation noted that 100% sensitivity and specificity was also included in the base case of the ivosidenib July 2024 submission though there may be differences in the evidence around testing between the two submissions.
- 6.72 The evaluation considered it inappropriate that the submission applied a half cycle correction to drug acquisition costs. The evaluation considered that as these costs will be accrued at the beginning of the cycle regardless of when a patient stops taking them (futibatinib is expected to be dispensed on 28-day intervals), this was inappropriate. Additionally, the evaluation considered that the half cycle correction was incorrectly applied and the half cycle corrected results in a given cycle were actually based on the averages of the two cycles preceding, leading to an overestimate of the patient flow probabilities. During the evaluation, the half cycle correction error was corrected for costs and outcomes, and the half cycle correction was removed for drug acquisition costs. This reduced the base case ICER from \$95,000 to <\$115,000/QALY to \$95,000 to <\$115,000/QALY. All presented results below are reflective of these corrections.

- 6.73 The submission assumed a time horizon of 10 years, noting that median survival among subjects in FOENIX-CCA2 who were treated with futibatinib was 20.0 months at final OS analysis (25 months follow up), and that those treated with FOLFOX in the ABC-06 study experienced lower median survival of 6.2 months. The evaluation considered that given the limited duration of follow-up of the two studies and the general uncertainty regarding the adjusted survival from the MAIC, a 10-year time horizon is highly uncertain.
- 6.74 In its consideration of ivosidenib for *IDH1* positive CCA, the PBAC considered that a 5-year time horizon would appropriately capture benefits in this population (paragraph 7.11, ivosidenib PSD, July 2024 PBAC meeting). However, it should be acknowledged that there may be evidence to support better prognosis in patients with *FGFR2* fusions or rearrangements, whereas the MSAC had previously considered that *IDH1* variant status may be associated with a poorer prognosis, though the evidence was too heterogenous for any strong conclusion to be made (p12, Application 1750 PSD, MSAC August 2024 meeting). Shortening the time horizon to 5-years and 7-years increased the ICER by █████% and █████%, respectively.
- 6.75 The submission fitted the extrapolation in each treatment arm with gamma extrapolation selected in base case for PFS in both arms, and loglogistic for OS in both arms. The choice of extrapolation function was not based on statistical fit, but a mix of statistical fit, visual fit and clinical plausibility. The evaluation considered it unclear if this was appropriate, as statistical fit would be the most objective measure for use in a base case. The submission fitted the distributions separately for each treatment arm. The evaluation noted that no convergence of OS was assumed by the submission. The model was sensitive to assumptions around the extrapolation of OS in futibatinib (see Table 22). As discussed in paragraph 6.69, the evaluation considered that given the likely overestimate of OS in the submission's MAIC, the results of sensitivity analyses around the OS extrapolations were unlikely to be informative in terms of providing a more accurate estimate of the cost effectiveness of futibatinib compared to FOLFOX.
- 6.76 The evaluation noted that the values of the Akaike information criteria (AIC) and Bayesian Information Criteria (BIC) scores for the OS extrapolation presented in the submission were identical in both model arms, which appeared to be an error. The sponsor, in the PSCR, provided confirmation that the AIC and BIC values in the model were correct for futibatinib, but incorrect for FOLFOX OS, and updated the values in the PSCR. However these appear to be the FOLFOX PFS AIC and BIC values and not the OS AIC and BIC values, as claimed.
- 6.77 The timepoint to switch from KM data to extrapolation was estimated based on GebSKI 2006. The switch occurred at 22 months for OS, and 14 months for OS for futibatinib and 11 months for OS and 7 months for PFS for FOLFOX.
- 6.78 The submission did not model time to treatment discontinuation (TTD) separately, but rather assumed that patients in the futibatinib arm of the model are treated until

progression. During the evaluation it was noted that the median PFS in the model was 12.4 months, and that the mean (estimated by summing the PFS 3-week transition probabilities) was 57.78 weeks (13.3 months) (after correcting for the half cycle correction errors as described in paragraph 6.72). As discussed in paragraph 3.5, 13% of patients in FOENIX-CCA2 used futibatinib beyond progression. The ESCs noted that using PFS instead of TTD would underestimate the treatment duration, and therefore the cost, of futibatinib. The Pre-PBAC response contended that not all remaining patients would be treated until progression due to AEs, withdrawal of consent, and investigator driven discontinuation.

- 6.79 The submission estimated treatment specific health state utilities (see Table 19). The difference in PFS health state utilities was based on the assumption of greater toxicity associated with FOLFOX. The evaluation considered that using the unadjusted utility values (rather than change from baseline) biased the results in favour of futibatinib given the lower baseline value in ABC-06 (0.77) compared to FOENIX CCA2 (0.796). For example, the change from baseline to month 4 values for PFS in ABC-06 was 0.07 (0.77 – 0.70), if the baseline value was 0.796 (as in FOENIX-CCA2) the PFS utility for FOLFOX would be 0.726 instead of the 0.70 reported. The ESCs considered that the application of treatment-specific utilities was not supported and favoured futibatinib.

Table 19: Utility values used in the model

Health state or event	Mean utility	Instrument	Source
PFS - futibatinib	0.796	EQ-5D-3L	FOENIX-CCA2
PFS - FOLFOX	0.70	EQ-5D	ABC-06 supplementary, month 4 visit results ^a
PD - futibatinib	0.68 (this is a decrement of 0.116 vs the PFS state)	Not reported	NICE 474, as used by Chueh 2023, Chen 2023 and Chen 2024
PD - FOLFOX	0.584 (calculated as 0.70 – 0.116)	Not reported	Calculation applying the progression decrement from futibatinib to FOLFOX based on advisory board advice
Death	0	-	-

Source: Table 3.11, p210 of the submission.

PD = progressed disease; PFS = progression free survival; QALY = quality-adjusted life year

^a Baseline utility in ABC-06 was 0.77.

- 6.80 The submission stated that the utility values for the progressed disease (PD) health state could not be informed by FOENIX-CCA2 due to low patient numbers/surveys completed. Instead, the futibatinib PD state (0.68) was based on an estimate used in NICE TA 474 (sorafenib for advanced hepatocellular carcinoma). The FOLFOX PD state (0.584) was calculated by applying same decrement from PFS to PD as futibatinib. The ESC considered that it was unclear why there would be any difference in post-progression utilities given both futibatinib and FOLFOX would have been ceased.
- 6.81 In its previous consideration of ivosidenib in CCA, the PBAC noted that “(a)lthough utility weights based on trial outcomes are generally preferred, the PBAC considered that, given the lack of face validity and likely impact of limited trial QoL data, in this case the values used in the durvalumab submission (PF=0.857, PD=0.766) would be more reasonable” (Paragraph 7.13, ivosidenib PBAC PSD July 2024). However, the Pre-

PBAC response contended that the durvalumab PF values (0.857) bias against futibatinib, due to the worse safety profile for FOLFOX assumed by the sponsor, and proposed that “at a minimum, a value of 0.735 should be applied to the FOLFOX disutility, OR the utility decrement of -0.025 NICE accepts for IV administration (NICE TA722) should be applied to FOLFOX treatment”. Whereas, the sponsor, in the Pre-PBAC response accepted the change to the durvalumab PD value (0.766). During the evaluation these utilities were tested for both arms of the model and led to a decrease in the ICER by █████% to \$95,000 to < \$115,000. This was due to the model assuming that patients in the futibatinib arm will have a longer time in both progression free and progressed health states, compared to the FOLFOX arm.

- 6.82 The dosing regimen for futibatinib was based on the TGA draft PI for futibatinib and FOENIX-CCA-2. The dose for futibatinib was 20 mg daily with 21 days per cycle. The submission applied the mean FOENIX-CCA2 relative dose intensity (RDI) of 83.26% to the cost of futibatinib. The submission noted that the RDI also flows into the financial estimates. The evaluation considered that the use of this estimate of RDI was highly uncertain, given it was unclear how the RDI in the matched population may differ in futibatinib use compared to the whole study population. A more conservative assumption of assuming 100% RDI increased the ICER by █████%.
- 6.83 It was not possible to inform the impact of omitting post progression *FGFR2* inhibitor use in the futibatinib arm from the cost side as the duration of post progression treatment in FOENIX-CCA2 was unknown. Overall, the evaluation considered it likely that the cost of futibatinib was underestimated, or in the case of post progression *FGFR2* inhibitor use, the efficacy of futibatinib on OS may be overestimated.
- 6.84 The evaluation noted that the submission did not account for the elements of listing being based on 4-weekly scripts of futibatinib, which was inconsistent with the 3-weekly cycle of the model. Consequently, the evaluation considered that although not technically wastage, it would be expected that the cost of a full month of treatment would be borne by the PBS regardless of when a patient discontinued in that 4-week cycle. The assumption that futibatinib costs will be incurred based on the proportion of patients remaining on treatment every three weeks would likely underestimate futibatinib drug costs.
- 6.85 The submission noted that the draft futibatinib product information states: Ophthalmological examination should be performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. As such one MBS item 11219, optical coherence tomography (OCT) at cycle 1 was included, and conservatively included an additional OCT every 12 weeks for futibatinib patients (0.25 every 3-week cycle).
- 6.86 The submission considered that patients treated with FOLFOX are offered a choice of a peripherally inserted central catheter (PICC) or port, which are both central venous access devices (CVAD). A PICC is radiologically inserted under anaesthetic, and hangs out of a patient which makes it more prone to infection and means a patient’s

activities of daily living are limited. A port is inserted under the skin under anaesthetic and has fewer infections. Both the PICC or port remain in the patient for the entire FOLFOX treatment course (up to 24 weeks). MBS costs associated with administering FOLFOX as well as pre-medication (Netupitant + palonosetron and dexamethasone) were included as costs in the model for the FOLFOX arm. The model applied a one-off cost of \$697.93 per patient and a per cycle cost of \$495.41 to account for administration of FOLFOX.

- 6.87 Overall, the evaluation considered that the submission's approach to costing FOLFOX administration appears consistent with the eviQ guidelines for FOLFOX administration in biliary cancer. During the evaluation a sensitivity analysis was conducted in which administration costs for FOLFOX only included MBS item 13950 for chemotherapy infusion (\$123.05). This increased the ICER by █████% to \$95,000 to < \$115,000/QALY.
- 6.88 The submission did not explicitly include the cost of post progression anti-cancer therapy in the model. The submission considered that this may favour futibatinib as 19% of discontinued patients used a chemotherapy in FOENIX-CCA2. The submission, however, considered that this was adequately accounted for in end-of-life costs. The evaluation considered that this may not be reasonable, as 8.7% of patients in FOENIX-CCA2 used an *FGFR2* inhibitor (including erdafitinib, pemigatinib, derazantinib and futibatinib) post progression.
- 6.89 An end-of-life (terminal care) cost was derived from Reeve 2018, adjusted using ABS health inflation values to derive a 2024 value of \$51,605.07. This value was then reduced by \$464.80 ($\53.45×8.7 cycles in 6 months) to avoid double counting post progression pain management over the last 6 months of life. Overall, the submission estimated a cost associated with end-of-life care of \$51,140. Removing end of life costs from both arms increased the ICER by █████%. The PBAC it may not be reasonable to include terminal care costs as differences in the model were driven by the time horizon and all patients would eventually accrue terminal care costs.
- 6.90 The submission estimated a cost of NGS testing for *FGFR2* fusion or rearrangement testing from tumour tissue of \$1,050 per identified patient. 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.
- 6.91 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 █████% of testing would be conducted by Omico. The evaluation considered that this was inappropriate as once *FGFR2* testing becomes available on the MBS, it was unlikely that current testing by Omico would continue at this rate. Moreover, the evaluation noted that 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). The evaluation considered that 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.

- 6.92 The cost per patient identified was also based on assumption of 20% prevalence of *FGFR2* alteration in advanced disease. The evaluation considered that this was consistent with the prevalence presented by the submission, but noted the substantial variation in estimates of prevalence, with a weighted average prevalence of 10% in all CCA settings (reflective of testing at diagnosis).
- 6.93 Consistent with the MBS item descriptor, the submission assumed only one test per lifetime. The evaluation considered that this was reasonable. However, given concerns regarding the stability of the biomarker, the evaluation and the ESCs considered that it is possible that some patients may benefit from later testing, especially if they were first tested in an earlier setting. Doubling *FGFR2* test costs and assuming 100% of tests were conducted on the MBS had only a small impact (+ [REDACTED] %) on the ICER.
- 6.94 Grade 3 or higher treatment related AEs with a frequency greater than 5% in either treatment arm were applied in the model. Grade 2 or higher AEs for hyperphosphatemia were also considered due to their frequency in patients treated with FGFR inhibitors. The model used the probability of an AE to estimate a one-off cost which is applied in the first cycle of the model.
- 6.95 The evaluation noted that these differences in adverse events are based on unanchored unadjusted results of two different studies with substantial differences in study populations (ABC-06 and FOENIX-CCA-2). Consequently, the evaluation considered it unclear how accurate these estimates of AE rates would be in the requested population.
- 6.96 Overall, the ESC considered that the key issue with the model was the validity of the clinical OS and PFS estimates on which it was based. The ESCs considered that the submission's MAIC provided a highly uncertain estimate of magnitude of effect due to not adjusting for *FGFR2* status, was likely overestimated and favoured futibatinib to a substantial degree, that cannot be addressed through parametric extrapolation. The ESCs noted that given the structure of the model it was not possible to test the model using results from Paine 2022 and Borad 2022. The Pre-PBAC response attributed this to insufficient data available in the Borad and Paine abstracts to create Kaplan Meier (KM) curves to insert into the model rather than a limitation of the model, and presented an additional sensitivity analysis including scenarios the ABC-06 KM curves are shifted by [REDACTED] %, [REDACTED] % and [REDACTED] % (Table 1, Pre-PBAC Response).
- 6.97 Table 20 presents the key drivers of the model.

Table 20: Key drivers of the model

Description	Method/Value	Impact (Corrected base case: █████ ¹ /QALY gained.)
Use of data from submission's MAIC	OS and PFS health states were informed by ABC-06 KM data in a group of patients in whom <i>FGFR2</i> status was unknown, and matched adjusted KM data from FOENIX-CCA2 in patients who have <i>FGFR2</i> fusion/rearrangement.	Unknown, but likely high, favouring futibatinib
OS extrapolation	Log logistic function chosen for both arms in base case. No convergence of OS assumed.	High, likely favours futibatinib. Use of Loglogistic for FOLFOX and generalised gamma for futibatinib increased the ICER by █████% to █████ ² /QALY gained. However, given uncertainty in the inputs of the MAIC, may not be informative.
Time horizon	10-year time horizon assumed in base case. The PBAC considered that a 5-year time horizon was appropriate in its consideration of ivosidenib in <i>IDH1</i> variant CCA.	Moderate, favours futibatinib. Use of a 5-year time horizon increased the ICER by █████% to █████ ³ /QALY gained.

Source: attached economic model to the submission.

KM = Kaplan-Meier; MAIC = matching adjusted indirect comparison, OS = overall survival, PFS = progression free survival

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$155,000 to < \$255,000

³ \$115,000 to < \$135,000

6.98 Table 21 presents the results of the stepped economic evaluation. Over the 10 year time horizon, the model estimated an undiscounted life year gained (LYG) of 2.48 (1.08 in PFS and 1.40 in PD) for futibatinib compared to 0.81 LYG (0.44 in PFS and 0.37 in PD) for FOLFOX, with an incremental difference of 1.66 LYG. The ESCs also noted the implausibly large survival gain (0.76 LYG) in Step 1 of the model over a two year time horizon.

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Table 21: 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	█	\$8,298	█
LYG	1.50	0.74	0.76
Incremental cost/extra LYG gained			█ 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	█	\$60,226	█
LYG	2.32	0.84	1.48
Incremental cost/extra LYG gained			█ 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	█	\$59,994	█
LYG	2.33	0.84	1.49
Incremental cost/extra LYG gained			█ ²
Step 4: Transformation of LYs to QALYs. Costs: As in Step 3. Outcomes: QALYs over the modelled time horizon			
Costs	█	\$59,994	█
QALYS	1.72	0.55	1.17
Incremental cost/extra LYG gained			█ ³
Step 5: Evaluation- correct half cycle correction and remove half cycle correction from drug acquisition costs.			
Costs	█	\$59,481	█
QALYS	1.67	0.51	1.16
Incremental cost/extra LYG gained			█ ³

Source: Table 3.19 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:

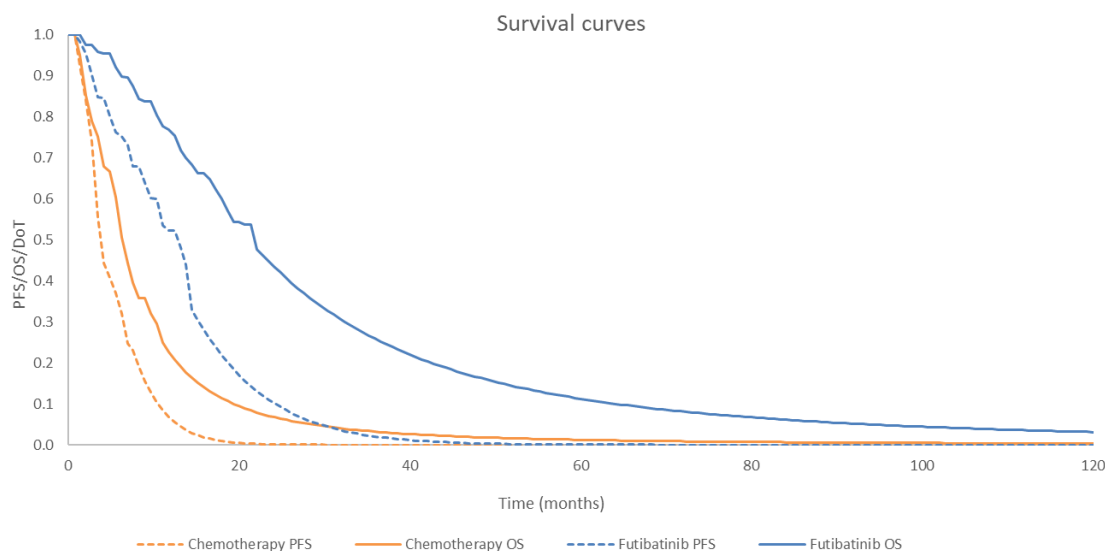
¹ \$155,000 to < \$255,000

² \$75,000 to < \$95,000

³ \$95,000 to < \$115,000

6.99 Figure 4 presents the survival curves (model trace) of the economic model's base case.

Figure 4: Survival curves of the base case economic model



Source: 'Results' sheet, attached economic evaluation

6.100 The results of key sensitivity analyses are summarised in Table 22.

Table 22: Results of the sensitivity analyses (corrected for half cycle correction)

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% Change
Base case	█	1.16	█ ¹	-
Discount rate (BC: 5% costs and outcomes)				
0%	█	1.28	█ ¹	- █%
3.5%	█	1.20	█ ¹	- █%
Time horizon (BC: 10 years)				
7 years	█	1.11	█ ¹	- █%
5 years	█	1.03	█ ²	- █%
Extrapolation from median follow up of FOENIX-CCA2 (25 months) and ABC-06 (21.7 months) (BC: 22 months for OS and 14 months for PFS for futibatinib and 11 months for OS and 7 months for PFS for FOLFOX)	█	1.17	█ ¹	- █%
Remove KM data (extrapolation from cycle 1)	█	1.15	█ ¹	- █%
PFS extrapolation (BC: gamma in both arms)				
Exponential in both arms	█	1.18	█ ²	- █%
Weibull in both arms	█	1.16	█ ¹	- █%
Gompertz in both arms	█	1.15	█ ¹	- █%
Log-Logistic in both arms	█	1.18	█ ²	- █%
Log normal in both arms	█	1.18	█ ²	- █%
Generalised gamma in both arms	█	1.15	█ ¹	- █%
Best fitting in both arms (Gompertz for FUTI and Lognormal for FOLFOX)	█	1.15	█ ¹	- █%
Best fitting (Gompertz) for FUTI	█	1.16	█ ¹	- █%
Best fitting (Lognormal) for FOLFOX	█	1.16	█ ¹	+ █%
OS extrapolation (Log-logistic both arms)				
Exponential in both arms	█	1.30	█ ¹	- █%
Weibull in both arms	█	0.93	█ ³	- █%
Gompertz in both arms	█	0.82	█ ³	- █%

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Analyses	Incremental cost (\$)	Incremental QALY	ICER	% Change
Log normal in both arms		1.25	█ ¹	█%
Generalised gamma in both arms		0.78	█ ⁴	█%
Gamma in both arms		1.01	█ ²	█%
Best fitting in both arms (Log normal for FUT1 and Gompertz for FOLFOX)		1.27	█ ¹	█%
Most conservative OS extrapolation combination (Loglogistic for FOLFOX and Generalised Gamma for FUT1)		0.74	█ ⁴	█%
Costs				
Futibatinib RDI 100% (83.26% in BC)		1.16	█ ²	█%
Testing assumed 100% MBS/ 0% Omico (BC: 60%)		1.16	█ ¹	█%
Testing assumed 100% MBS and test cost doubled (\$700)		1.16	█ ¹	█%
FOLFOX admin costs only include MBS item 13950 ^b		1.16	█ ¹	█%
Remove EOL costs		1.16	█ ¹	█%
Quality of Life (BC: FUT1 PFS = 0.796, PD = 0.68; FOLFOX PFS = 0.70, PD=0.584)				
PF Utility by state (not drug) - FUT1 values		1.12	█ ¹	█%
PD Utility by state (not drug) - FUT1 values		1.13	█ ¹	█%
Change utilities to those from durvalumab PBAC submission (PF 0.857; PD 0.766)		1.20	█ ¹	█%
Change utilities to those from durvalumab PBAC submission - After IV decrement (-0.025) in PF state (futibatinib: PF 0.857; PD 0.766; FOLFOX: PF 0.832, PD 0.766) ^a		1.22	█ ¹	█%

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; FUT1 = 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 provided in Pre-PBAC response

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$115,000 to < \$135,000

³ \$135,000 to < \$155,000

⁴ \$155,000 to < \$255,000

6.101 The evaluation noted that the model was most sensitive to choice of OS extrapolation. Using the generalised gamma extrapolation instead of the base case log logistic model in both arms increased the ICER by █% to \$155,000 to < \$255,000/QALY. However, the evaluation considered that the sensitivity analyses around OS extrapolation are of limited informativeness given the high degree of uncertainty regarding the MAIC used as the basis for estimates of clinical benefit, and the ESCs agreed. The evaluation considered that given the sensitivity in the parametric extrapolations of OS, it is reasonable to assume that a more modest benefit as reported in Paine 2022 and Borad 2022 would increase the ICER. Moreover, the evaluation noted that the model does not include any convergence of OS benefit which the evaluation considered was likely to be optimistic and favours futibatinib, particularly as the model is estimating longer life years in both progression free (38.6% of all incremental life years) and progressed disease (61.4% of all incremental life years) in the futibatinib arm (see paragraph 6.98).

6.102 The evaluation noted that shortening the time horizon from 10 years to 5 years, as recently recommended by the PBAC in its consideration of ivosidenib for CCA,

increased the ICER by █████% to \$115,000 to < \$135,000/QALY. The ESCs noted that the evidence from FOENIX-CCA2 had a median follow-up of only 25 months, and considered a 5 year time horizon to be more appropriate.

- 6.103 The PSCR acknowledged a reduction to the time horizon and/or a more conservative choice of extrapolated survival curves would increase the ICER and noted that this has been an accepted method to mitigate any residual uncertainty in previous decision making. However, the Pre-PBAC response contended that if the survival curves for FOLFOX are changed to account for *FGFR2* prognostic benefit, then also shortening the time horizon to 5 years would be double counting uncertainty.
- 6.104 The evaluation noted that the model was also sensitive to inputs that affected futibatinib drug acquisition costs. The evaluation noted it was not possible to simply adjust the costing to account for four weekly dispensing in the model with its three-weekly cycle. It was also not possible to inform the impact of omitting utilisation of futibatinib post progression or subsequent *FGFR2* inhibitor use in the futibatinib arm from the cost side, as the duration of post progression treatment in FOENIX-CCA2 was unknown. Nonetheless, the evaluation considered it likely that the cost of futibatinib was underestimated, or in the case of post progression *FGFR2* inhibitor use, the efficacy of futibatinib on OS may be overestimated.
- 6.105 The evaluation noted that the model was not sensitive to test cost assumptions, chemotherapy administration cost assumptions, or disease management cost assumptions. Additionally, the model was minimally sensitive to changes in utility values. The evaluation considered that this may be attributable to the model assuming patients in the futibatinib arm would spend more time in both PFS and PD health states compared to patients in the FOLFOX arm, which may not be reasonable or supported by evidence.
- 6.106 Overall, the ESCs considered that it was extremely likely that the submission's ICER was underestimated due to overestimated incremental futibatinib benefit and underestimated futibatinib drug costs.

Drug cost/patient/course

Table 23: Drug cost per patient for proposed drug

	Futibatinib			FOLFOX		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
DPMQ/ (cost/dose for FOLFOX)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	F		\$143.56
				O		\$150.77
				Cf		\$3.89
				Total 2-week cycle		\$298.22
Relative dose intensity	83.26%	83.26%	83.26%	NR	100%	100%
Adjustment for 3-week model cycle	NA	3/4	NA	NA	3/2	NA
Cost per model cycle	NA	\$ [REDACTED]	NA	NA	\$447.34	NA
Average model cycles on treatment	NA	19.26	NA	NR	5.91	
Average weeks on treatment	NR ^a	57.78	56.05	NR	17.74	17.83
Cost per course per patient	-	\$ [REDACTED]	\$ [REDACTED]	-	\$2,645.36	\$2,658.63

Source: Table 26, of the trial report, Section 3 workbook, sheet 3a of the utilisation-and-cost-model.

DPMQ = Dispensed price per maximum quantity; Cf = calcium folate; F = Fluorouracil; NA = not applicable; NR = not reported; O = oxaliplatin
Text in italics indicate values calculated during the evaluation

^a The submission did not provide a mean duration of treatment in the MAIC dataset. The mean dose duration for the whole study population was 10.65 months (46.15 weeks) which corresponds to a cost of \$ [REDACTED]

Note: estimates of cost per course per patient may not exactly match the product of the presented inputs due to rounding.

6.107 The evaluation noted that the drug cost per course per patient of \$ [REDACTED] is based on a DPMQ of \$ [REDACTED] (28-days), a relative dose intensity of 83.26% and an average of 57.78 weeks on treatment. The submission stated that the mean duration of treatment was not available for the matched adjusted population of FOENIX-CCA2. Consequently, the duration of futibatinib treatment was based on the modelled mean PFS. The evaluation considered that the submission’s financial estimates were largely consistent, except they were based on 56.05 weeks of treatment. FOLFOX was estimated to have a cost of \$2,645.36 per patient per course based on a total two-week cycle cost of fluorouracil, oxaliplatin and calcium folate of \$298.22 and an average duration of treatment of 17.74 weeks.

Estimated PBS usage & financial implications

6.108 This submission was considered by DUSC.

6.109 Table 24: presents the key inputs use for the financial estimates. The submission took an epidemiological approach to derive the financial estimates.

Table 24: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian Population	Estimated Australian population from 18 -100 years of age	ABS Adult population	The incidence rates taken from the March 2023 submission (and applied below) were from ‘All age-specific incidence (crude)’ therefore the DUSC noted exclusion of the population <18 may not be reasonable.

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Data	Value	Source	Comment
Liver Cancer Incidence (per 100,000)	Yr 1: 11.5 Yr 2: 11.8 Yr 3: 12.1 Yr 4: 12.3 Yr 5: 12.6 Yr 6: 12.9	AIHW 2022	Same as that used in March 2023 Durvalumab submission. The ivosidenib submission in July 2024 (Table 16, ivosidenib PSD, July 2024 PBAC meeting) based these estimates on commissioned incidence data from AIHW in 2015-2019. The DUSC noted eCCA estimates were obtained from the AIHW, whereas estimates for iCCA were estimated based on the incidence of liver cancer. The DUSC noted more granular information on incidence of eCCA and iCCA was available via AIHW ¹² . In 2020, Under ICD-10 codes C24.8-C24.9 (Overlapping lesions of biliary tract and biliary tract, unspecified), C22.1 (intrahepatic bile duct carcinoma), both representing iCCA, there were 164 and 638 cases respectively, for a total of 802 iCCA cases. Representing eCCA, in ICD-10 code C24.0 (Extrahepatic bile duct) there were 397 cases.
EHCC (eCCA) incidence (per 100,000)	Yr 1-2: 1.7 Yr 3-4: 1.8 Yr 5-6: 1.9	AIHW 2022	
IHCC (iCCA) incidence (per 100,000)	Yr 1: 1.725-2.53 Yr 2: 1.77-2.596 Yr 3: 1.815-2.662 Yr 4: 1.845-2.706 Yr 5: 1.89-2.772 Yr 6: 1.935-2.838	Durvalumab March 2023 PSD	In the durvalumab March 2023 submission, it was assumed that 15% of liver cancer patients have iCCA based on advisory board opinion and a "literature review" that was not detailed. This was increased to 22% in the durvalumab PSCR. However, the PBAC considered the 15% value to be more plausible (paragraph 5.9, durvalumab PSD, July 2023 PBAC meeting). The base case of the submission used the higher proportion value of 22%. As noted above, iCCA data is available from AIHW.
Patients (%) diagnosed with advanced BTC (locally advanced, metastatic, recurrent)	80%	DUSC estimate in Durvalumab March 2023 PSD.	This input was also used in the ivosidenib July 2024 estimates (Table 16, ivosidenib PSD, July 2024 PBAC meeting), and appeared reasonable. DUSC noted approximately 70-90% of patients with CCA present with either locally advanced or metastatic disease at the time of diagnosis. ^{13,14,15}
% of patients taking 1st line durvalumab	70%	Advisory board.	The ivosidenib PSD from the July 2024 PBAC meeting did not indicate the proportion used for this parameter. The uptake of first line durvalumab was uncertain. DUSC considered the eligible population for futibatinib could have been derived from the market share of durvalumab. DUSC noted that most patients would be treated with durvalumab with chemotherapy in the first line setting, unless contraindicated.

¹² <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/stage>

¹³ Valle JW, Borbath I, Khan SA, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v28-v37. doi:10.1093/annonc/mdw324

¹⁴ Ilyas SI, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology*. 2013;145(6):1215-1229. doi:10.1053/j.gastro.2013.10.013

¹⁵ Razumilava N, Gores GJ. Classification, diagnosis, and management of cholangiocarcinoma. *Clin Gastroenterol Hepatol*. 2013;11(1):13-e4. doi:10.1016/j.cgh.2012.09.009

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Data	Value	Source	Comment
Durvalumab patients progressing to 2L	60%	Advisory board	Uncertain and likely to be overestimated. In the consideration of ivosidenib (Table 16, ivosidenib PSD, July 2024 PBAC meeting) the DUSC noted prior studies where patients experience a rapid decline in performance status following progression on 1L therapy and only 15- 25% receive 2L therapy. The DUSC considered this to be likely overestimated given that a limited number of patients progress to second line therapy due to issues with liver failure and performance status.
FGFR2 aberrations/alterations	20%	Average of prevalence studies from submission's diagnostic section	The PBAC considered it was likely a prevalence of 20% was an overestimate, noting the prevalence in eCCA (which accounted for ~80% of CCA cases) was <1%.
Test utilisation			
Number of tests	5.2 tests per patient treated	Calculation	Based on multiplying number of patient-years of futibatinib in incident patients by 500% (assuming 20% diagnostic yield). DUSC noted that the proposed MBS Item Descriptor for the test is applicable only once per lifetime and commented that it would be more appropriate to assume the number of tests be based on the population eligible for second line therapy rather than based on the number of patients treated with futibatinib. Additionally, DUSC commented that it would be likely that reflex testing would occur at diagnosis or before progression to first line therapy.
Treatment utilisation			
Patients electing treatment	█%	Advisory board	With regard to ivosidenib (Table 16, ivosidenib PSD, July 2024 PBAC meeting), DUSC considered this input was inappropriate. DUSC considered that adjusting for patients progressing to 2L treatment incorporates these patients who elect treatment and applying both inputs unnecessarily decreases the population.
Duration of futibatinib treatment	56.05 weeks	Calculation	Based on median duration of treatment from the 70 futibatinib patients included in the MAIC (12.5 months/380.5 days) adjusted to mean duration based on the proportional duration of treatment between mean (284.6 days) and median (276 days) duration for treatment in the whole trial population (difference of 3.1%), such that 380.5 days × 103.1% = 392.3 days, or 56.05 weeks The economic model based its estimate of drug acquisition cost on mean extrapolated PFS, which was 57.78 weeks. DUSC considered the treatment duration applied in the economic model and financial estimates should align.
Costs			
MBS costs			
FGFR2 RNA testing	\$350	Proposed	The financial estimates do not account for Omico testing. This was reasonable, as 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. Consistent with the economic evaluation.
Ophthalmological monitoring	\$45.50	MBS 11219	
Chemotherapy admin	\$123.05	MBS 13950	

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Data	Value	Source	Comment
Insertion of CVAD	\$310.35	MBS 34528	
Removal of CVAD	\$232.60	MBS 34530	
Anaesthesia	\$90.20	MBS 20400+23010	
Cleaning of CVAD	\$59.80	MBS 14221	

Source: Tables 4.1-4.4, pp229-233 of the submission and attached financial spreadsheet.

BTC = biliary tract cancer; CVAD = central venous access device; DUSC = drug utilisation sub-committee; EHCC/eCCA = extra-hepatic cholangiocarcinoma; *FGFR2* = fibroblast growth factor receptor 2; IHCC/iCCA = intra-hepatic cholangiocarcinoma; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document. RNA = ribonucleic acid

- 6.110 The submission assumed that in addition to the < 500 incident patients treated in Year 1, < 500 grandfathered patients would be treated. For the < 500 grandfathered patients, it was estimated that time on PBS funded futibatinib would be six months (26.09 weeks).
- 6.111 The submission noted that in the economic model, time to treatment discontinuation was set to PFS, and thus the median duration of treatment is 12.5 months (380.5 days) using the population from the MAIC (n=70), however the mean duration of treatment is not available from the MAIC population. The submission noted that the duration of treatment for all treated patients (N=103), was a median of 276.0 days and the mean was 284.6 days, a 3.1% difference. As such, the submission assumed a similar relationship between the mean and median duration of treatment in the MAIC and estimated a mean duration of 392.3 days (56.05 weeks) by multiplying median days by 103.1% (380.5 * 103.1%).
- 6.112 However, the economic evaluation was based on mean PFS not median duration of treatment. During the evaluation, this was back calculated by summing all of the per cycle PFS probabilities in the futibatinib arm and estimated to be 19.26 three-week cycles, or 57.78 weeks (404.46 days). Consequently, the evaluation considered that the duration of treatment was underestimated relative to that estimated in the economic evaluation.
- 6.113 Consistent with the economic model, the RDI of futibatinib was assumed to be 83.26% in the financial estimates, applied to both incident and grandfathered patients.
- 6.114 The submission's estimated average scripts per incident patient was 11.67 scripts/patient after adjusting for duration of treatment and RDI.
- 6.115 The submission assumed that testing will only occur once patients progress after first line durvalumab, and only in patients who will consider futibatinib (█% uptake rate). This was at a later time point than proposed in the submission, where the test population was proposed to be 'adult patients with locally advanced or metastatic CCA', and as such, the evaluation and the DUSC considered the number of tests may be underestimated. Moreover, if testing was to occur at diagnosis (as proposed by the PASC), the cost of testing will increase further. As such, the evaluation considered that the submission's estimates of the cost of *FGFR2* testing may be underestimated.
- 6.116 Consistent with the economic model (see paragraph 6.85), in the financial estimates, two OCTs (MBS item 11219) were included for each patient treated with futibatinib.

6.117 Table 25 presents the estimated use and financial implications.

Table 25: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated patient numbers						
Australian Population over 18 years of age	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Liver cancer incident population	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
IHCC (22% of liver cancer)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
EHCC	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Total incident population	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
80% Patients diagnosed with advanced CCA (locally advanced, metastatic)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
█% 1st line treatment (durvalumab) for CCA	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
60% Progress to 2L ECOG PS 0 or 1	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated extent of use of FGFR2 testing						
Number of patients tested ^a	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Number of patients likely to receive a positive test result	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated extent of use of futibatinib						
Number of patients likely to be treated with proposed drug	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Number of scripts dispensed ^b	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of futibatinib to the PBS/RPBS						
Cost to PBS/RPBS less copayments	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications for reduction in FOLFOX use to the PBS/RPBS						
Cost to PBS/RPBS less copayments	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Net cost to PBS/RPBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications of the FGFR2 testing to the MBS						
Cost to MBS less co-payments (80% rebate)	█ ⁶	█ ⁶	█ ⁷	█ ⁷	█ ⁷	█ ⁸
Estimated financial implications of the Optical Coherence tomography (ophthalmological monitoring) to the MBS						
Cost to MBS less co-payments (80% rebate)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications for FOLFOX associated costs to the MBS						
Cost to MBS less co-payments (80% rebate)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Net cost to MBS	█ ⁵	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net financial implications						
Net cost to PBS/RPBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to MBS	█ ⁵	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Net cost to PBS/RPBS/MBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴

Source: Attached financial spreadsheet.

^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 11.67 scripts per patient per year for incident patients and 5.43 per patient for year for grandfathered patients. The numbers do not equal the scripts multiplied by the patient numbers because the financial spreadsheet adjusts the eligible patients for duration of treatment longer than 12 months

CCA = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group performance score; EHCC = extra-hepatic 2L = second line; cholangiocarcinoma; FGFR2 = fibroblast growth factor receptor 2; IHCC = intra-hepatic cholangiocarcinoma

The redacted values correspond to the following ranges:

¹ > 10,000,000

² 500 to < 5,000

³ <500

⁴ \$0 to < \$10 million

⁵ net cost saving

6.118 The total net cost to the PBS/RPBS of listing futibatinib was estimated to be \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, and a total of \$50 million to < \$60 million in the first six years of listing.

6.119 The DUSC provided the following advice with regards to drug utilisation:

- it noted more granular information regarding the incidence estimates are available from the AIHW.
- it considered the number of patients progressing to second line therapy to be overestimated.
- it considered the number of tests per patient to be underestimated.
- it considered that the inclusion of treatment uptake rate for futibatinib patients double counts the proportion of patients who progress to second line therapy with ECOG PS 0 or 1.
- it considered the treatment duration applied in the economic model and financial estimates should align.

Quality use of medicines

6.120 The submission described the risk management plan (RMP) developed for futibatinib for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

6.121 The plan identifies a number of important risks and missing information to be addressed. In addition to the measures to address these risks, the submission noted that information about adverse reactions is continuously collected and regularly analysed so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. DUSC noted that the most recent Periodic Benefit-Risk Evaluation report identified risks for futibatinib included serious retinal detachment, and the costs associated with ophthalmological monitoring were accounted for in the submission.

6.122 The submission considered that the Australian Product Information (PI) is the primary tool to communicate the benefits and risks with futibatinib use.

6.123 The PBAC noted that although the submission claimed the risk management plan was developed with focus on serious retinal detachment and teratogenicity, no health care professional, nor patient education has been proposed regarding retinal detachment, and considered that this should be addressed.

- 6.124 DUSC considered it unlikely that futibatinib would be used beyond the requested restriction, and noted the dosing and administration schedule of futibatinib and considered it would improve treatment access for patients in rural and remote areas.

Financial management – risk sharing arrangements

- 6.125 The submission considered that due to the small and identifiable population (through testing for *FGFR2* fusions or rearrangements) and the minor cost to PBS budgets, no risk sharing arrangement was proposed.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of futibatinib for the treatment of patients with locally advanced or metastatic cholangiocarcinoma (CCA) who have previously progressed on systemic therapy and have a fibroblast growth factor receptor 2 (*FGFR2*) fusion or rearrangement. The PBAC considered that there was a high clinical need for treatments for patients with CCA, particularly those with locally advanced or metastatic disease, where the prognosis is generally poor. The PBAC noted that based on the available clinical evidence the magnitude of clinical benefit was highly uncertain. The PBAC considered the economic model would need to be amended to include a more conservative and realistic estimate of clinical benefit to increase the reliability of the incremental cost-effectiveness ratio (ICER). The PBAC considered futibatinib would be cost-effective with an ICER less than \$55,000 to < \$75,000 per QALY. The PBAC noted the estimated number of patients that would be treated with futibatinib was uncertain and would need revision to more accurately reflect the prevalence of CCA and the number of patients with a *FGFR2* fusion or rearrangement. The PBAC considered the outstanding issues could be addressed in an early re-entry submission. However, the PBAC noted that if MSAC is not of a mind to recommend the proposed testing component, an integrated resubmission would be required, which would not be suitable for the early re-entry pathway.
- 7.2 The primary reason for this outcome was due to the economic evaluation.
- 7.3 The PBAC noted that survival outcomes for patients with CCA are very poor, with a 2% 5-year survival rate for patients with metastatic disease. The PBAC considered there is a high clinical need for more effective therapies for CAA and noted that futibatinib is targeted to the small subset of patients whose tumours have a *FGFR2* fusion or rearrangement.
- 7.4 The PBAC noted the integrated codependent submission requested: 1) the Medicare Benefits Schedule (MBS) listing of testing of tumour tissue to detect *FGFR2* fusions or rearrangements, and 2) the PBS listing of futibatinib for the treatment of locally advanced or metastatic cholangiocarcinoma (CCA) in patients with *FGFR2* fusion or rearrangement.

- 7.5 The PBAC considered it is likely that there is a codependency between futibatinib and *FGFR2* testing based on the biological rationale as described in paragraph 6.67 and there is therefore a reasonable rationale for restricting the use of futibatinib to patients with tumours with *FGFR2* fusions or rearrangements. The PBAC noted that consideration of the proposed MBS item for *FGFR2* testing for patients with CCA, to determine access to futibatinib was a matter for MSAC consideration.
- 7.6 The PBAC considered it would be appropriate for futibatinib to be listed for patients with locally advanced or metastatic CCA who have previously progressed on systemic therapy and who have evidence of an *FGFR2* fusion or rearrangement. The PBAC agreed with the ESCs that it can be difficult to differentiate between intrahepatic and extrahepatic CCA and it was likely futibatinib would provide benefit in the small population of patients with non-iCCA who have an *FGFR2* fusion or rearrangement.
- 7.7 The submission nominated FOLFOX chemotherapy (as modified FOLFOX6) as the primary comparator in the first-line setting, and palliative care with active symptom control (ASC) in the second- and subsequent line settings for patients with poor performance status, or those who elect no further treatment. The PBAC noted ivosidenib (recommended for CCA in November 2024) is not a comparator, as *IDH1* and *FGFR2* variants are generally considered to be mutually exclusive, but that pemigatinib, an inhibitor of *FGFR* with provisional TGA approval may be considered a near market comparator. The PBAC noted no comparison to pemigatinib was provided in the submission.
- 7.8 The submission was based on FOENIX-CCA2 (n=103), an open-label, single-arm, phase 2 trial of futibatinib in patients with unresectable or metastatic *FGFR2* fusion-positive or *FGFR2* rearrangement-positive iCCA, and disease progression after one or more previous lines of systemic therapy; and ABC-06 (n=81), an open-label randomised phase 3 trial of ASC and FOLFOX in patients with locally advanced or metastatic biliary tract cancer (including CCA and gallbladder or ampullary carcinoma). These trials formed the basis of an unanchored matched adjusted indirect comparison (MAIC) of futibatinib versus FOLFOX. The PBAC noted the improvements in efficacy with futibatinib compared to FOLFOX based on the MAIC: adjusted PFS HR = 0.30 (95% CI: 0.22, 0.41) and OS HR = 0.24 (95% CI: 0.18, 0.32). However, the PBAC considered that the magnitude of clinical benefit was likely overestimated due to differences in baseline characteristics (in particular *FGFR2* status which may be a prognostic factor), and the unanchored nature of the MAIC, which confers a high risk of bias to unknown treatment effect modifiers. The PBAC noted that the adjustments applied as part of the MAIC increased the estimated PFS and OS for futibatinib, despite it accounting for the FOLFOX trial patients being older and having a worse performance status compared with the patients in the futibatinib trial, which further raised questions regarding the reliability of the MAIC. The PBAC considered that the clinical claim of superiority for futibatinib compared to FOLFOX was reasonable, but that the magnitude of benefit was highly uncertain.

- 7.9 Additional indirect comparisons identified during the evaluation (Paine 2022, Borad 2022), comparing futibatinib and FOLFOX for patients with *FGFR2* alterations (both arms, which accounted for the potential prognostic influence of *FGFR2* status) reported a less favourable adjusted HR for PFS (0.48-0.53 vs 0.30) and OS (0.48-0.49 vs 0.24) for futibatinib compared to chemotherapy vs those presented in the submission. The PBAC noted this supported its consideration that the MAIC likely overestimated the magnitude of clinical benefit of futibatinib.
- 7.10 The submission also presented a MAIC of futibatinib compared to ASC for OS. The PBAC considered that the submission's claim of superior efficacy versus ASC was reasonable but that it was not well supported by the evidence as the MAIC generally had the same limitations as that versus FOLFOX, and the claim of superior efficacy was only based on OS, and not PFS or ORR.
- 7.11 The submission did not present any comparative safety data between futibatinib and FOLFOX. The PBAC noted AEs reported in FOENIX-CCA2: although frequent (80%), lab abnormalities in the FOENIX-CCA2 trial were mostly asymptomatic (e.g., hyperphosphatemia (11%) and elevated AST (10%)), and that although grade 1-2 retinopathy occurred in 8% of patients, the TGA ACM advised that retinal detachment is rare and occurs slowly, so can be picked up in screening of patients reporting symptoms (e.g., flashes, floaters, or decreased vision). The PBAC also noted the known toxicity of FOLFOX treatment, and issues associated with IV administration. The PBAC considered the clinical claim of superior safety for futibatinib compared with FOLFOX may be plausible although there was limited evidence to support this. The PBAC considered that the claim of inferior comparative safety compared to ASC was reasonable.
- 7.12 The submission presented an economic evaluation based on the results of the MAIC. The PBAC agreed with the ESCs that as the underlying clinical benefit used to inform the economic evaluation was uncertain, the economic model presented was likely not reflective of the true cost effectiveness of futibatinib. The PBAC noted the economic model resulted in an undiscounted life year gain of 2.48 over the 10 year time horizon of the model and considered that was implausibly large. The PBAC agreed with the ESC that the economic model should include a more conservative estimate of the modelled clinical benefit but noted the model did not include this operability. The PBAC noted that the MAIC results from Paine 2022 or Borad 2022 were more conservative, and considered that the model should be aligned with that OS HR: 0.48-0.49 (vs 0.24).
- 7.13 The PBAC noted the economic model assumed a time horizon of 10 years with no convergence of OS modelled. The PBAC agreed with the evaluation that a 10-year time horizon increased the uncertainty in the model results given the limited duration of follow-up of the two studies and the general uncertainty regarding the incremental survival. The PBAC considered that a 5-year time horizon, in line with the PBAC's consideration of ivosidenib for *IDH1* positive CCA (paragraph 7.11, ivosidenib PSD, July 2024 PBAC meeting), would result in a more reliable estimate of the benefits.

- 7.14 The submission estimated treatment-specific health state utilities, with different progression free (PF) and progressive disease (PD) health state utilities based on the assumption of greater toxicity associated with FOLFOX. However, the PBAC agreed with the evaluation and the ESCs that that difference between treatment arms in post-progression utilities was not supported given both futibatinib and FOLFOX would have been ceased, and this biased the results in favour of futibatinib. The PBAC considered it would be more appropriate to apply the same utilities to the PF and PD health states in each treatment arm.
- 7.15 The PBAC noted a number of other issues with the model, including use of PFS curves instead of time to treatment discontinuation to estimate treatment duration (see paragraph 6.78), inclusion of terminal care costs (see paragraph 6.89) and uncertainties regarding the extrapolation functions applied (see paragraph 6.101). However, the PBAC noted the main limitation of the model remained the implausible clinical benefit modelled and it was difficult to interpret the sensitivity analyses related to these issues.
- 7.16 The submission took an epidemiological approach to derive the financial estimates. The PBAC agreed with the DUSC that a number of inputs needed to be revised as outlined in paragraph 6.119. Additionally, the PBAC considered the prevalence of *FGFR2* fusion or rearrangements was likely overestimated and should be revised to account for the low prevalence ($\leq 1\%$) in eCCA patients.
- 7.17 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for futibatinib using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.
- Revision of the economic model as outlined in paragraphs 7.12 to 7.14.
 - Reduced price to give an ICER less than \$55,000 to < \$75,000 per QALY gained (consistent with other treatments for CCA) using the revised model.
 - Revision of the financial estimates, as outlined in paragraph 7.16.
- 7.18 The PBAC noted that if MSAC is not of a mind to recommend the proposed testing component, an integrated resubmission would be required, which would not be suitable for the early re-entry pathway. The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.
- 7.19 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

The Sponsor is pleased that the PBAC has acknowledged the high clinical need for treatments in the proposed patient population and is committed to working with the PBAC and the Department to facilitate sustainable patient access to futibatinib as soon as possible.