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Matching-Adjusted Indirect Comparison of Futibatinib Versus Chemotherapy and Pemigatinib in Cholangiocarcinoma Patients with *FGFR2* Fusions/Rearrangements

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Background

- Intrahepatic cholangiocarcinoma (iCCA) is an aggressive, molecularly heterogenous malignancy with poor survival outcomes.[1]
- Futibatinib is a covalently binding fibroblast growth factor receptor (FGFR) 1-4 inhibitor and has demonstrated efficacy among previously treated iCCA patients with *FGFR2* fusions/rearrangements, in the FOENIX-CCA2 (NCT02052778) pivotal phase 2 trial, leading to accelerated approval in the US in September 2022.[2-4]
- While there are other approved FGFR inhibitors for the treatment of advanced iCCA, including pemigatinib and infigratinib,[5,6] futibatinib differs from these in its mechanism of binding and spectrum of activity against FGFR mutations (**Box 1**).
- To date, only single-arm studies have been reported with FGFR inhibitors in the iCCA patient population; no head-to-head trials have been conducted and no direct comparisons made with chemotherapy.
- In the absence of head-to-head trials, indirect treatment comparisons are informative to support health technology assessment. Unanchored matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) are methods for indirect comparison using single-arm studies. However, there are conflicting simulation studies on the relative performance of MAIC and STC in the anchored setting.[7,8] Simulations in the unanchored setting have evaluated only MAIC.[9]

Objective

- To conduct an indirect treatment comparison, using MAIC, of efficacy outcomes for futibatinib with published data for chemotherapy and the FGFR inhibitor pemigatinib in previously treated iCCA patients with *FGFR2* fusions/rearrangements.

Box 1. Futibatinib mechanism of action and inhibitory activity

- Most FGFR inhibitors in clinical development, including pemigatinib and infigratinib, are reversible, ATP-competitive kinase inhibitors. In contrast, futibatinib binds covalently to a conserved cysteine residue in the FGFR kinase domain P-loop and leads to irreversible inhibition of FGFR signalling.[3,16]
- The covalent nature of binding makes futibatinib less susceptible to drug resistance, with robust activity against several *FGFR2* kinase domain mutations that confer resistance to ATP-competitive inhibitors demonstrated in vitro.[3,16–18]

Inhibitory activity against FGFR2 kinase domain mutations

FGFR2 WT or mutants	Phospho-FGFR2 inhibition, IC_{50} (nmol/L)		
	Futibatinib	Infigratinib	Pemigatinib
WT	2	4	2
N549D	4	345	153
N549K	17	288	246
V564I	8	>1000	62
V564L	92	>1000	502
E565A	7	49	12

Values in cells with yellow and red shading represent 5- to 15-fold and >15-fold attenuation relative to WT, respectively.

- Futibatinib has shown broad activity against various types of genomic *FGFR* alterations,[2,3] with similar response rates observed in iCCA patients with *FGFR2* fusions versus rearrangements and with *BICC1* versus non-*BICC1* fusions in FOENIX-CCA.[2,4]
- Clinical responses in the pivotal FOENIX-CCA2 study were consistent for iCCA patients irrespective of commonly co-occurring genomic alterations, including those associated with poor prognosis and resistance to ATP-competitive FGFR inhibitors, such as *TP53*.[4] In contrast, the pemigatinib FIGHT-202 study revealed lower-efficacy outcomes among the small patient cohort with *TP53* co-alterations compared with those without co-alterations.[5,19,20]
- Studies to further explore the mechanisms underlying these differences are ongoing, and further genomic-profiling studies are required.

ATP, adenosine triphosphate; FGFR2, fibroblast growth factor receptor 2; IC_{50}, half maximal inhibitory concentration; WT, wild-type.

Methods

- A systematic literature review (SLR) was conducted to identify clinical trials for FGFR inhibitors published 01/2015–02/2021, with additional targeted searches to identify chemotherapy data in a population of previously treated patients with CCA and *FGFR* fusions/rearrangements.
- As the studies were not connected via a common comparator, unanchored MAIC was conducted to avoid making parametric assumptions required by STC.[8,10]
  - MAIC is a propensity score weighting method that can be used to reweight patients receiving futibatinib so that they match the distribution of patient characteristics receiving comparator treatments.[10]
- Individual-level patient data for futibatinib from FOENIX-CCA2 (data cutoff October 2020) and published aggregate data from comparator trials were used in the analyses; propensity score weights were applied to futibatinib patients using logistic regression models to adjust for their over- or under-representation relative to the comparator treatment populations.
- As recommended by the UK National Centre for Health and Care Excellence (NICE) and other published guidelines, all available baseline characteristics were used for matching, and potential stability of the analysis estimates was determined by approximating effective sample size (ESS).[11,12]
- Base-case covariates used for matching were age, gender, Eastern Cooperative Oncology Group performance status, prior lines of therapy, prior surgery (primary tumor resection), and baseline hypoalbuminemia status.
- Sensitivity analyses were conducted adjusting for additional covariates including *TP53* status, alternative surgery definition (prior cancer surgery), race (or region, if race data are unavailable), and including age and gender covariates only.
- Cox regression models were used for base-case time-to-event outcomes (progression-free survival [PFS], overall survival [OS], and duration of response [DOR]), and binomial-logistic regressions were used for binary outcomes (odds ratio for objective response rate [ORR]).

Results

Included studies and baseline characteristics

- Two FGFR-inhibitor studies in patients with CCA (>98% iCCA) and *FGFR2* fusions/rearrangements were identified with sufficient data for analysis (at the time of conducting the SLR):
  - FOENIX-CCA2: futibatinib, n=103.[4]
  - FIGHT-202: pemigatinib, n=107.[5,13]
- Two chemotherapy studies in patients with CCA (>94% iCCA) and *FGFR2* fusions/rearrangements were included:
  - An analysis of prior systemic therapy in FIGHT-202, n=53.[14]
  - A natural history study in a clinicogenomic database, n=71.[15]
- Baseline characteristics of these study populations, used as covariates in the model, are provided in **Table 1**. After matching, ESS for futibatinib was 91.3, 48.5, and 65.3 for comparisons with pemigatinib, pre-FIGHT-202, and the natural history study, respectively.

Futibatinib versus chemotherapy

- Futibatinib demonstrated significantly longer PFS and OS versus chemotherapy; adjusted hazard ratios (HRs; 95%CI) were 0.48 (0.30–0.76; p=0.002) for PFS and 0.48 (0.31–0.74; p=0.001) for OS (**Figure 1**).
- Results of sensitivity analyses were consistent with the base case.

Futibatinib versus pemigatinib

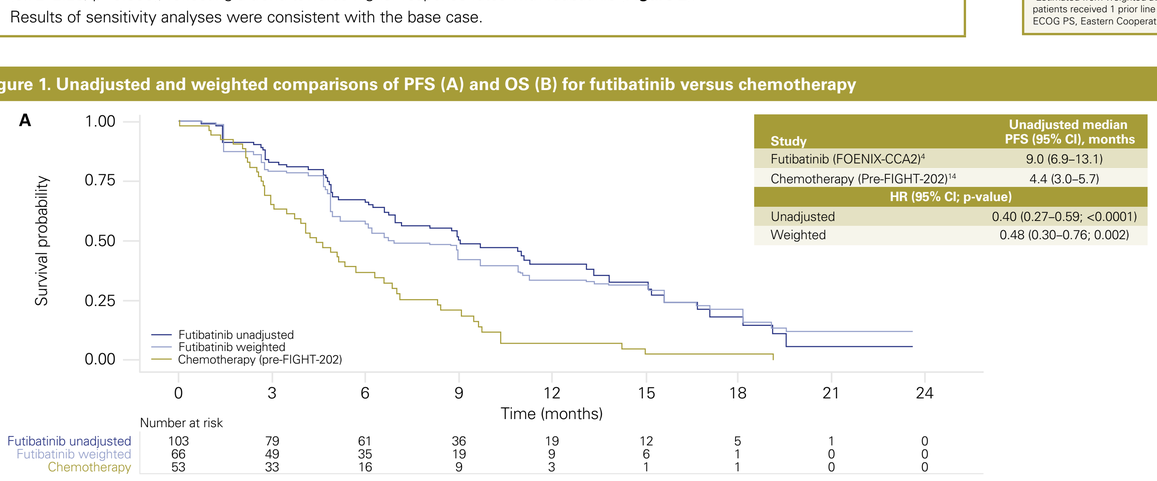
- Similar treatment effects were seen between futibatinib versus pemigatinib, although HRs numerically favoured futibatinib: 0.83 (0.58–1.17; p=0.287) for PFS, 0.88 (0.58–1.34; p=0.564) for OS, 0.80 (0.42–1.50; p=0.489) for DOR; odds ratio for ORR was 1.28 (0.72–2.25; p=0.399), reflecting a trend towards higher response rates with futibatinib (**Figure 2**).
- Results of sensitivity analyses were consistent with the base case.

Table 1. Baseline characteristics used as covariates (unadjusted)

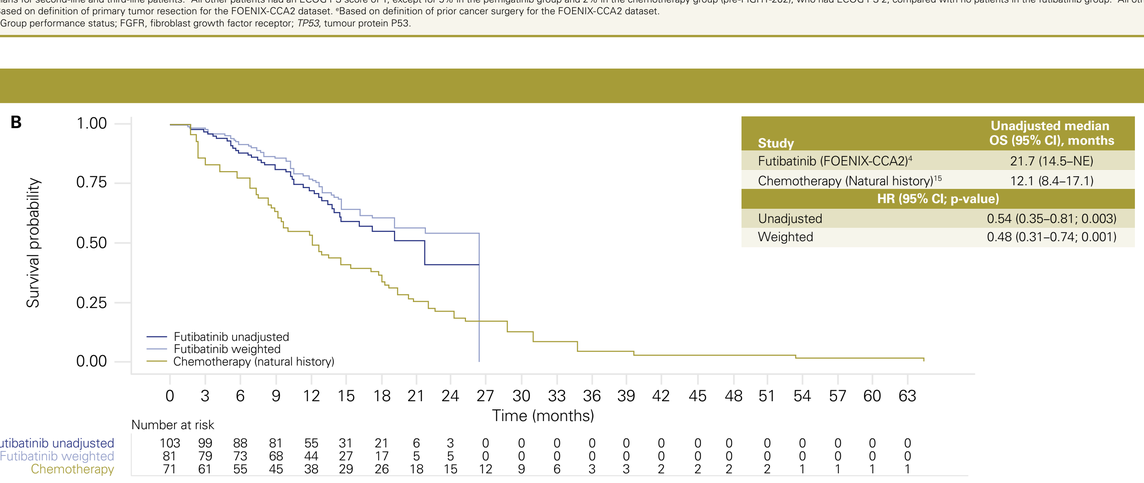
Characteristic	FGFR inhibitors		Chemotherapy	
	Futibatinib (FOENIX-CCA2)[4] N=103	Pemigatinib (FIGHT-202)[5,13] N=107	Pre-FIGHT-202 cohort[14] N=53	Natural history study[15] N=71
Base case				
Mean/median age, years	55.7	56.0	51.3[a]	63.0
Male, %	43.7	39.3	32.1	36.0
ECOG PS 0[b], %	46.6	42.0	45.3	–
≥2 prior lines[c], %	53.4	39.3	24.5	–
Albumin <35 g/L, %	19.4	19.6	–	–
Prior surgery[d], %	20.4	35.5	50.9	–
Sensitivity analyses				
White, %	49.5	73.8	–	74.7
Region: North America/Europe, %	72.8	–	94.3	–
Prior surgery (alternative)[e], %	39.8	35.5	50.9	-
TP53 status (altered), %	12.6	8.4	–	–

[a]Estimated from weighted average of medians for second-line and third-line patients. [b]All other patients had an ECOG PS score of 1, except for 5% in the pemigatinib group and 2% in the chemotherapy group (pre-FIGHT-202), who had ECOG PS 2, compared with no patients in the futibatinib group. [c]All other patients received 1 prior line of therapy. [d]Based on definition of primary tumor resection for the FOENIX-CCA2 dataset. [e]Based on definition of prior cancer surgery for the FOENIX-CCA2 dataset.
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *TP53*, tumour protein P53.

Figure 1. Unadjusted and weighted comparisons of PFS (A) and OS (B) for futibatinib versus chemotherapy



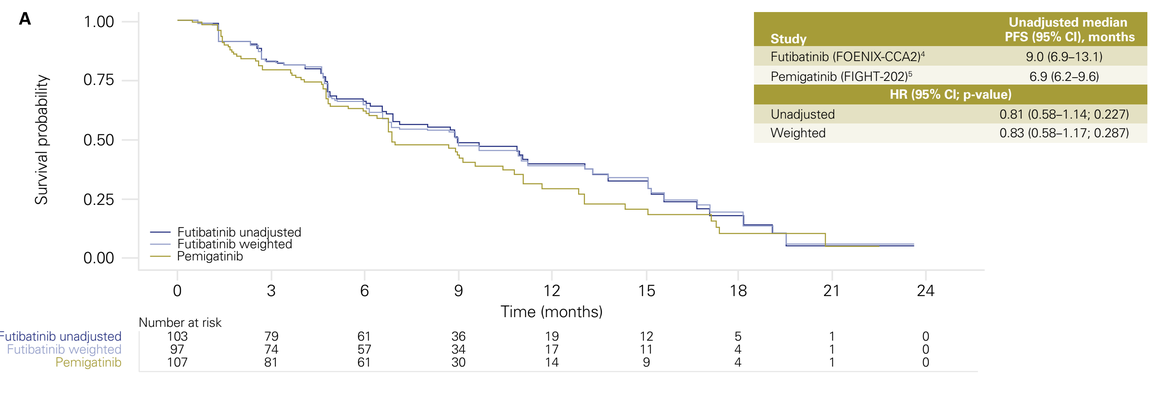
Study	Unadjusted median PFS (95% CI), months
Futibatinib (FOENIX-CCA2)[4]	9.0 (6.9–13.1)
Chemotherapy (Pre-FIGHT-202)[14]	4.4 (3.0–5.7)
HR (95% CI; p-value)	
Unadjusted	0.40 (0.27–0.59; <0.0001)
Weighted	0.48 (0.30–0.76; 0.002)



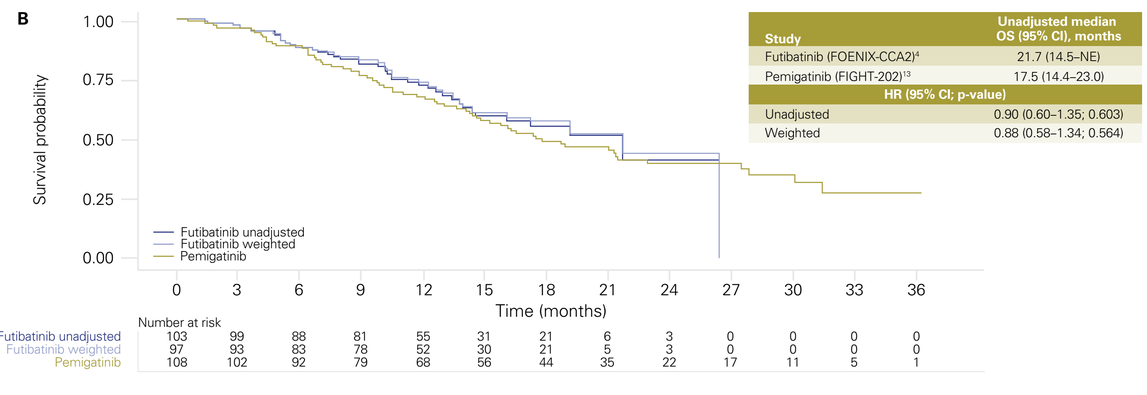
Study	Unadjusted median OS (95% CI), months
Futibatinib (FOENIX-CCA2)[4]	21.7 (14.5–NE)
Chemotherapy (Natural history)[15]	12.1 (8.4–17.1)
HR (95% CI; p-value)	
Unadjusted	0.54 (0.35–0.81; 0.003)
Weighted	0.48 (0.31–0.74; 0.001)

Note: The drop at the end of the futibatinib OS Kaplan–Meier curves are due to a single patient with follow-up >25 months experiencing an event at that time; with longer patient follow-up, the futibatinib curves will be updated.
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.
CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

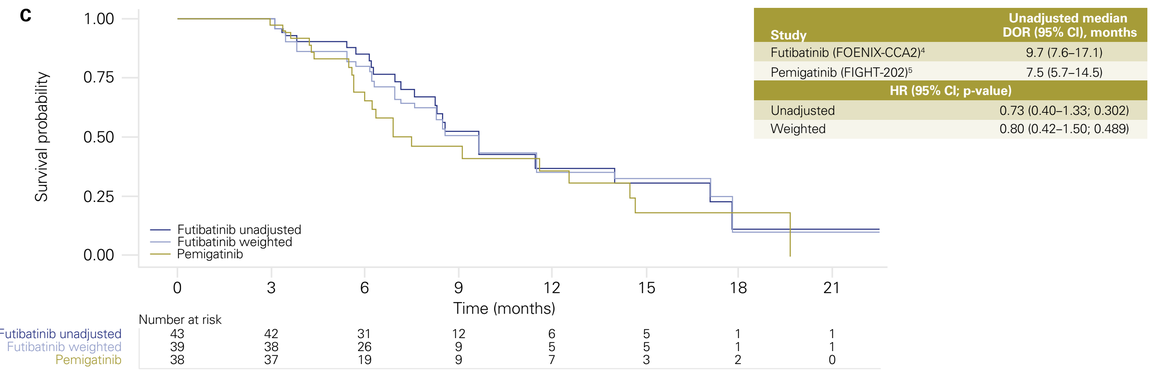
Figure 2. Unadjusted and weighted comparisons of PFS (A), OS (B), DOR (C), and ORR (D) for futibatinib versus pemigatinib



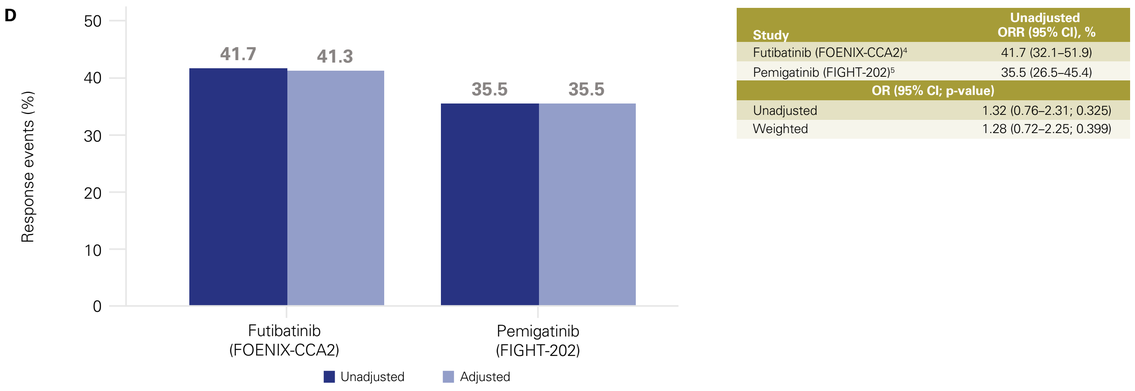
Study	Unadjusted median PFS (95% CI), months
Futibatinib (FOENIX-CCA2)[4]	9.0 (6.9–13.1)
Pemigatinib (FIGHT-202)[5]	6.9 (6.2–9.6)
HR (95% CI; p-value)	
Unadjusted	0.81 (0.58–1.14; 0.227)
Weighted	0.83 (0.58–1.17; 0.287)



Study	Unadjusted median OS (95% CI), months
Futibatinib (FOENIX-CCA2)[4]	21.7 (14.5–NE)
Pemigatinib (FIGHT-202)[13]	17.5 (14.4–23.0)
HR (95% CI; p-value)	
Unadjusted	0.90 (0.60–1.35; 0.603)
Weighted	0.88 (0.58–1.34; 0.564)



Study	Unadjusted median DOR (95% CI), months
Futibatinib (FOENIX-CCA2)[4]	9.7 (7.6–17.1)
Pemigatinib (FIGHT-202)[5]	7.5 (5.7–14.5)
HR (95% CI; p-value)	
Unadjusted	0.73 (0.40–1.33; 0.302)
Weighted	0.80 (0.42–1.50; 0.489)



Study	Unadjusted ORR (95% CI), %
Futibatinib (FOENIX-CCA2)[4]	41.7 (32.1–51.9)
Pemigatinib (FIGHT-202)[5]	35.5 (26.5–45.4)
OR (95% CI; p-value)	
Unadjusted	1.32 (0.76–2.31; 0.325)
Weighted	1.28 (0.72–2.25; 0.399)

Note: The drop at the end of the futibatinib OS Kaplan–Meier curves are due to a single patient with follow-up >25 months experiencing an event at that time; with longer patient follow-up, the futibatinib curves will be updated.
CI, confidence interval; DOR, duration of response; HR, hazard ratio; NE, not evaluable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Limitations

- These analyses are subject to common limitations associated with indirect treatment comparisons made without a common comparator (eg, availability of sufficient literature for analysis, identifying all potential confounding factors); however, the findings are consistent across the unadjusted and MAIC analyses (including the base-case and sensitivity analyses), suggesting validity of the MAIC results.

Conclusions

- These analyses provide evidence that futibatinib improves survival outcomes versus chemotherapy among previously treated iCCA patients with *FGFR2* fusions/rearrangements.
- While efficacy outcomes were similar for futibatinib versus pemigatinib, numerical trends favoured futibatinib in these analyses.
- Futibatinib's covalent mode of binding with activity against resistance mutations, in the FGFR2 kinase domain and in the presence of co-mutations (**Box 1**), may explain such trends.
- Future work in this setting will further explore both MAIC and STC approaches.

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Disclosures

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