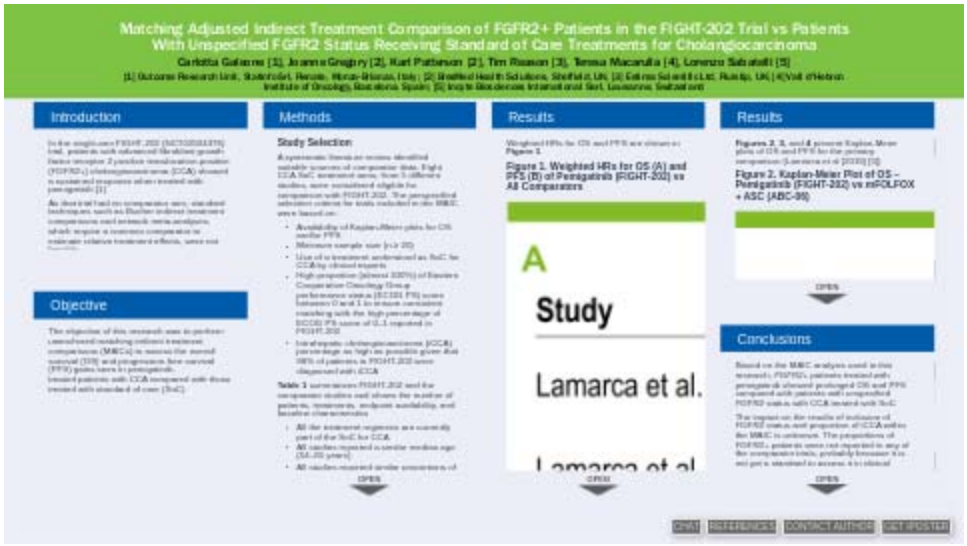
Matching Adjusted Indirect Treatment Comparison of FGFR2+ Patients in the FIGHT-202 Trial vs Patients With Unspecified FGFR2 Status Receiving Standard of Care Treatments for Cholangiocarcinoma



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INTRODUCTION

In the single-arm FIGHT-202 (NCT02924376) trial, patients with advanced fibroblast growth factor receptor 2 positive translocation-positive (*FGFR2*+) cholangiocarcinoma (CCA) showed a sustained response when treated with pemigatinib [1]

As that trial had no comparator arm, standard techniques such as Bucher indirect treatment comparisons and network meta-analyses, which require a common comparator to estimate relative treatment effects, were not feasible

OBJECTIVE

The objective of this research was to perform unanchored matching indirect treatment comparisons (MAICs) to assess the overall survival (OS) and progression-free survival (PFS) gains seen in pemigatinib-treated patients with CCA compared with those treated with standard of care (SoC)

METHODS

Study Selection

A systematic literature review identified suitable sources of comparator data. Eight CCA SoC treatment arms, from 5 different studies, were considered eligible for comparison with FIGHT-202. The prespecified selection criteria for trials included in the MAIC were based on:

- Availability of Kaplan-Meier plots for OS and/or PFS
- Minimum sample size ($n \geq 20$)
- Use of a treatment understood as SoC for CCA by clinical experts
- High proportion (almost 100%) of Eastern Cooperative Oncology Group performance status (ECOG PS) score between 0 and 1 to ensure consistent matching with the high percentage of ECOG PS score of 0–1 reported in FIGHT-202
- Intrahepatic cholangiocarcinoma (iCCA) percentage as high as possible given that 98% of patients in FIGHT-202 were diagnosed with iCCA

Table 1 summarizes FIGHT-202 and the comparator studies and shows the number of patients, treatments, endpoint availability, and baseline characteristics

- All the treatment regimens are currently part of the SoC for CCA
- All studies reported a similar median age (54–65 years)
- All studies reported similar proportions of male patients (39.0–63.3%)
- The proportion of patients with iCCA varied across the trials (42–98%)
- All studies reported a similar proportion of patients with ECOG PS of 0–1 at baseline (83.6–100%)

Table 1. Comparison of Baseline Characteristics and Endpoint Availability

Study Name	N	Treatment	OS	PFS	FGFR2+, %	Median Age, Years	Men, %	Intrahepatic CCA, %	ECOG PS 0–1, %	Albumin Levels ≥35 g/L, %
Abou-Alfa et al (2020) [1]	107	Pemigatinib	Yes	Yes	(100)	56	39	98	95	79
Lamarca et al (2019) [5]	81	ASC + mFOLFOX	Yes	Yes	NR	65	53	42	100	77
Lamarca et al (2019) [5]	81	ASC	Yes	No	NR	65	46	47	100	74
Kim et al (2017) [6]	255	Fluoropyrimidine alone	Yes	Yes	NR	60	57.3	43.9	91.3	NR
Kim et al (2017) [6]	66	Fluoropyrimidine plus platinum	Yes	Yes						NR
Zheng et al (2018) [7]	30	Irinotecan plus capecitabine	Yes	Yes	NR	54	53.3	67	100	NR
Zheng et al (2018) [7]	30	Irinotecan	Yes	Yes	NR	55	63.3	70	100	NR
Lowery et al (2019) [8]	198	SoC (chemotherapy)	Yes	No	NR	62.0	43.4	NR	NR	NR
Schweitzer et al (2019) [9]	144	SoC (chemotherapy)	Yes	No	NR	59.6	56.9	NR	83.6	NR

ASC, active symptom control; CCA, cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR2, fibroblast growth factor receptor 2; mFOLFOX, oxaliplatin, L-folinic acid, and fluorouracil; NR, not reported; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

MAIC Methodology

Unanchored MAIC analyses were conducted. They complied with the National Institute for Health and Care Excellence Decision Support Unit Technical Support Document 18 (NICE DSU TSD 18) [2]

Patient-level data from FIGHT-202 were assigned statistical weights that adjust for their over- or underrepresentation relative to that observed in each comparative evidence source

- Based on opinion elicited from clinical experts and availability in published studies, the covariates with a potential prognostic and/or treatment effect–modifying impact used for the weighting were age, sex, ECOG PS, and albumin levels
- Retrospective studies suggest *FGFR2* translocation status may be associated with positive prognosis in the patient population of interest. However, this biomarker was not reported in any of the identified comparator studies [3]

Using the Guyot algorithm, we created pseudo patient-level data from the Kaplan-Meier plots in the comparator publications [4]

Weighted Cox proportional hazards regression models were implemented to derive an adjusted hazard ratio (HR) and 95% bootstrapped confidence intervals (CIs) for OS and PFS

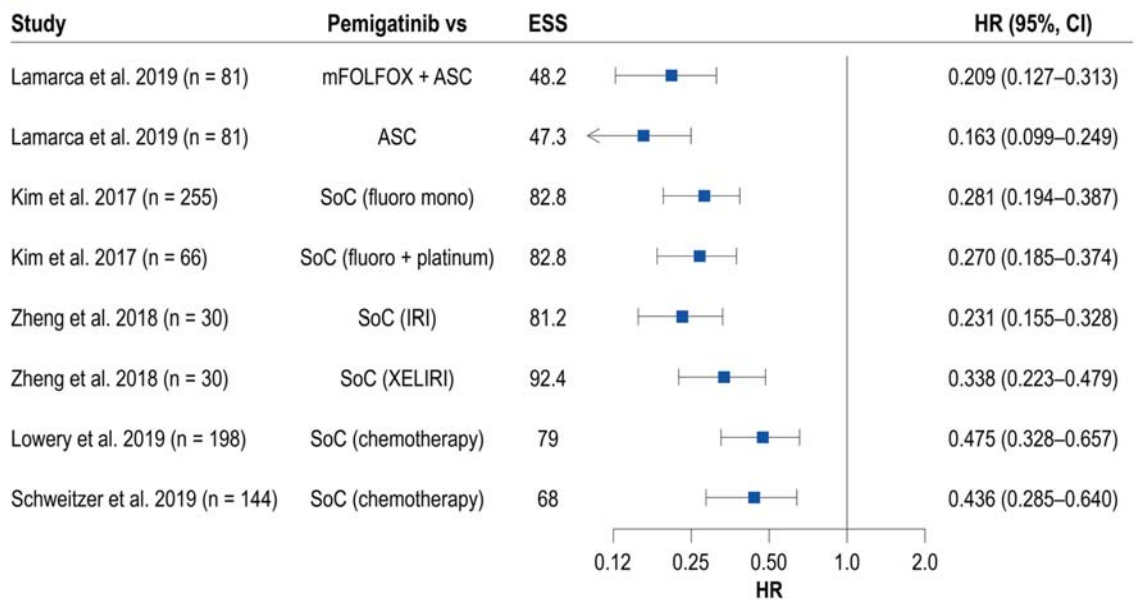
The effective sample size was derived and represents the number of independent nonweighted individuals who would be required to provide an estimate with the same precision as the weighted sample estimate

RESULTS

Weighted HRs for OS and PFS are shown in **Figure 1**

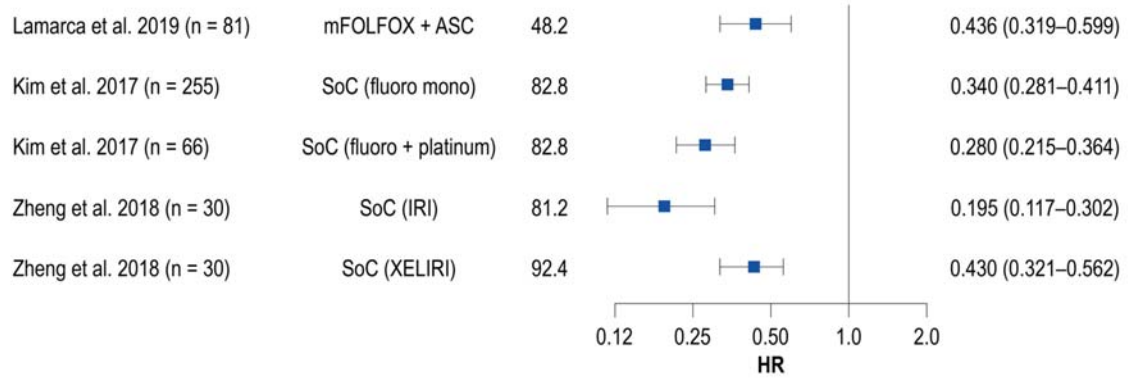
Figure 1. Weighted HRs for OS (A) and PFS (B) of Pemigatinib (FIGHT-202) vs All Comparators

A



ASC, active symptom control; CI, confidence interval; ESS, effective sample size; FOLFOX, oxaliplatin, L-folinic acid, and fluorouracil; HR, hazard ratio; IRI, irinotecan; OS, overall survival; PFS, progression-free survival; SoC, standard of care; XELIRI, irinotecan + capecitabine.

B



ASC, active symptom control; CI, confidence interval; ESS, effective sample size; FOLFOX, oxaliplatin, L-folinic acid, and fluorouracil; HR, hazard ratio; IRI, irinotecan; OS, overall survival; PFS, progression-free survival; SoC, standard of care; XELIRI, irinotecan + capecitabine.

For OS and PFS, the MAIC results showed that pemigatinib significantly ($P < 0.05$) reduced the hazard of progression or death compared with all other treatments, as the HRs were all less than 1.0 with tight CIs with most of the values in the range of 0.1 to 0.4

- For OS, the weighted HRs of pemigatinib vs SoC ranged from 0.163 (95% CI, 0.099–0.249) when compared with the active symptom control arm from Lamarca et al (2019) [5] to 0.475 (95% CI, 0.328–0.657) when compared with the chemotherapy arm from Lowery et al (2019) [8]
- For PFS, the weighted HRs of pemigatinib vs SoC ranged from 0.195 (95% CI, 0.117–0.302) when compared with the irinotecan arm from Zheng et al (2018) [7] to 0.436 (95% CI 0.319–

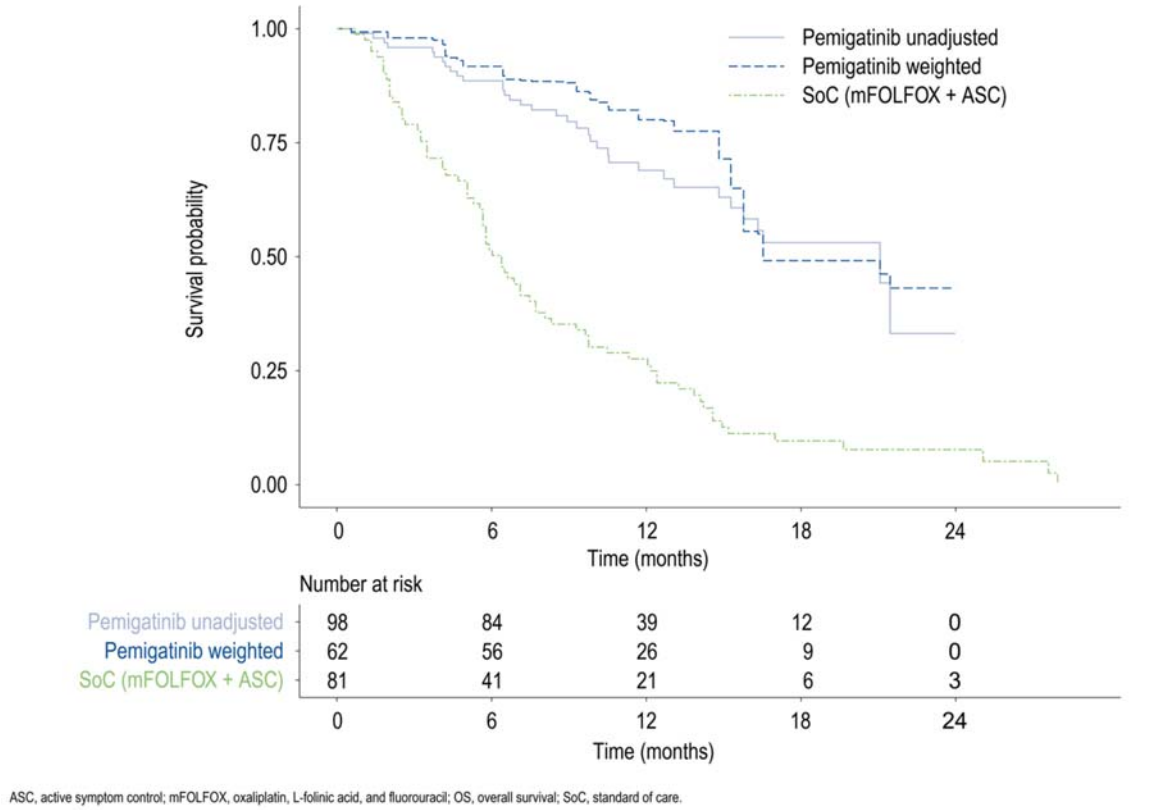
0.599) when compared with the mFOLFOX plus active symptom control arm from Lamarca et al (2019) [5]

- The effective sample size ranged from 47.3 to 92.4

RESULTS

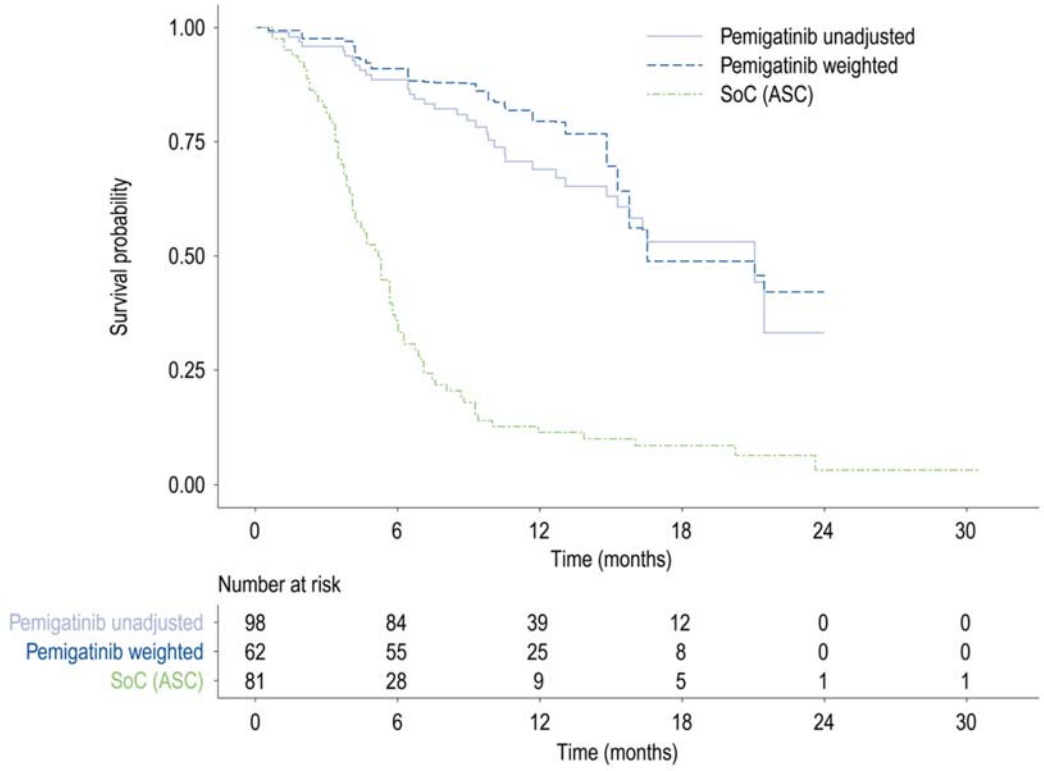
Figures 2, **3,** and **4** present Kaplan-Meier plots of OS and PFS for the primary comparison (Lamarca et al [2019] [5])

Figure 2. Kaplan-Meier Plot of OS – Pemigatinib (FIGHT-202) vs mFOLFOX + ASC (ABC-06)



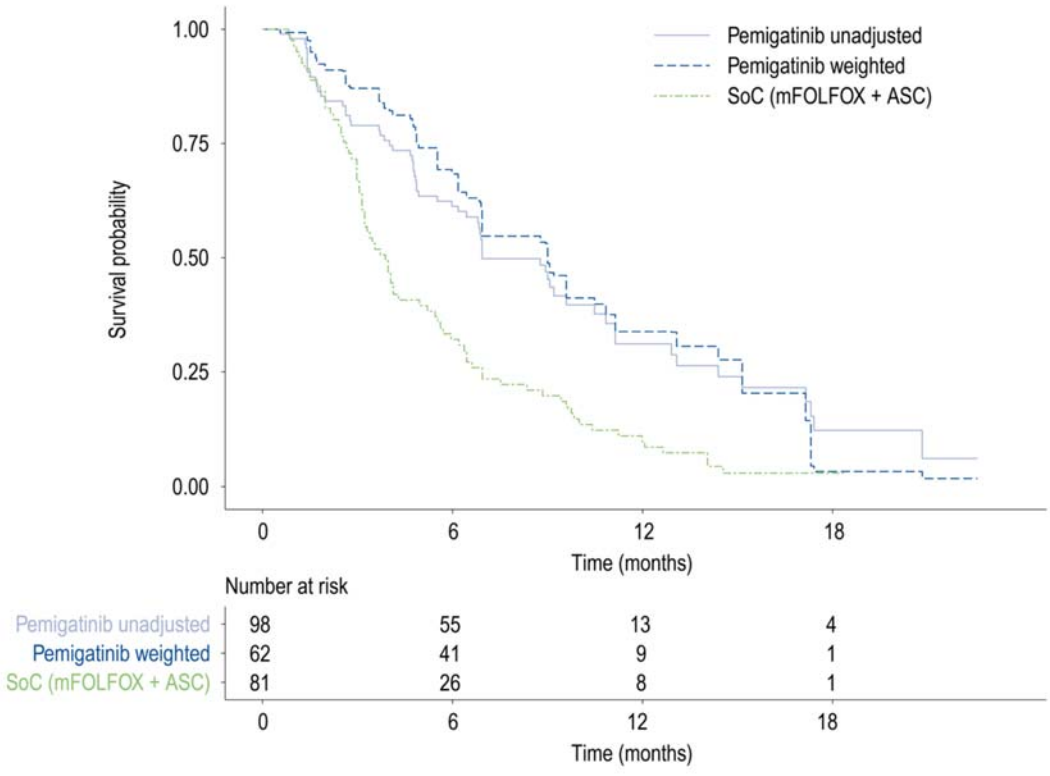
ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid, and fluorouracil; OS, overall survival; SoC, standard of care.

Figure 3. Kaplan-Meier Plot of OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)



ASC, active symptom control; OS, overall survival; SoC, standard of care.

Figure 4. Kaplan-Meier Plot of PFS – Pemigatinib (FIGHT-202) vs mFOLFOX + ASC (ABC-06)

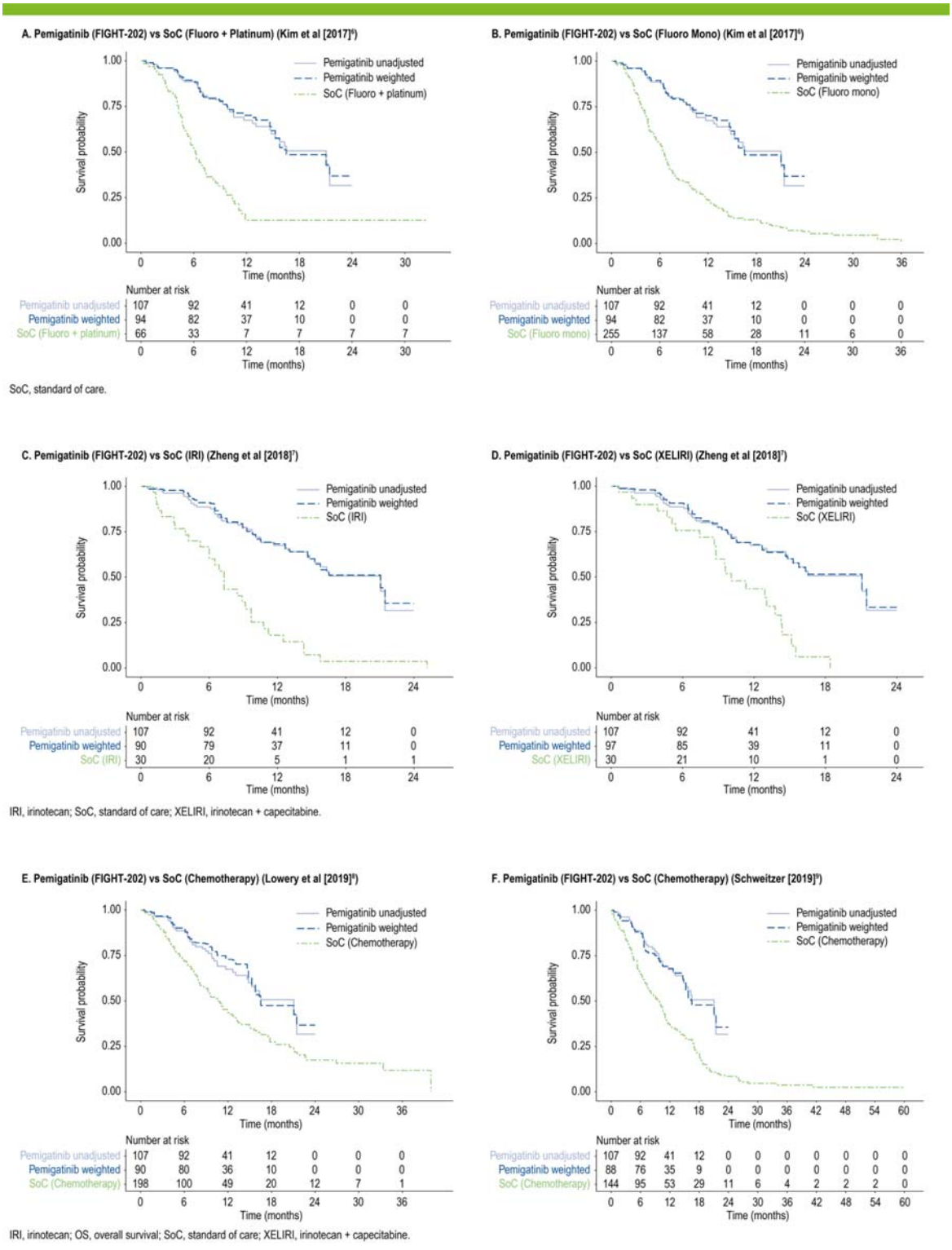


ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid, and fluorouracil; PFS, progression-free survival; SoC, standard of care.

As shown by the Kaplan-Meier survival analyses, treatment with pemigatinib showed prolonged OS and PFS compared with SoC for the Lamarca et al study

Similar results were seen by Kaplan-Meier survival analyses for OS (**Figure 5**) and PFS (data not shown) for all other studies

Figure 5. Kaplan-Meier Plots of OS for Pemigatinib (FIGHT-202) vs SoC in Other Studies



CONCLUSIONS

Based on the MAIC analysis used in this research, *FGFR2*+ patients treated with pemigatinib showed prolonged OS and PFS compared with patients with unspecified *FGFR2* status with CCA treated with SoC

The impact on the results of inclusion of *FGFR2* status and proportion of iCCA within the MAIC is unknown. The proportions of *FGFR2*+ patients were not reported in any of the comparator trials, probably because it is not yet a standard to assess it in clinical practice. Therefore, it was not possible to assess the impact of this factor on the relative effectiveness of pemigatinib vs SoC treatments. Further research and data on the strength of *FGFR2* as a prognostic factor in CCA are warranted

Whereas the MAIC methodology assumes that all prognostic factors and treatment effect modifiers are adjusted for, there may be unknown or unobserved prognostic factors, treatment effect modifiers, or other differences between studies. This is a known limitation of population adjustment methods, which should be considered when interpreting results. However, the present analyses are the most robust assessment that could be performed, given the available data

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