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Pemigatinib for patients with previously treated, locally advanced or metastatic cholangiocarcinoma harboring FGFR2 fusions or rearrangements: A joint analysis of the French PEMI-BIL and Italian PEMI-REAL cohort studies

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ABSTRACT

Background: Pemigatinib is approved for patients with pretreated, locally advanced or metastatic CCA harboring FGFR2 rearrangements or fusions. We aim to assess the effectiveness and safety of pemigatinib in real-world setting.

Material and methods: A joint analysis of two multicentre observational retrospective cohort studies independently conducted in France and Italy was performed. All consecutive FGFR2-positive patients affected by CCA and treated with pemigatinib as second- or further line of systemic treatment in clinical practice, within or outside the European Expanded Access Program, were included.

Results: Between July 2020 and September 2022, 72 patients were treated with pemigatinib in 14 Italian and 25 French Centres.

Patients had a median age of 57 years, 76% were female, 81% had ECOG-PS 0–1, 99% had intrahepatic CCA, 74% had $\geq$ 2 metastatic sites, 67% had metastatic disease at diagnosis, while 38.8% received $\geq$ 2 previous lines of systemic treatment.

At data cut-off analysis (April 2023), ORR and DCR were 45.8% and 84.7%, respectively. Median DoR was 7 months (IQR: 5.8–9.3).

Over a median follow-up time of 19.5 months, median PFS and 1-year PFS rate were 8.7 months and 32.8%. Median OS and 1-year OS rate were 17.1 months and 60.6%.

Fatigue (69.4%), ocular toxicity (68%), nail toxicities (61.1%), dermatologic toxicity (41.6%) hyperphosphataemia (55.6%), stomatitis (48.6%), and diarrhea (36.1%) were the most frequent, mainly G1-G2 AEs. Overall incidence of G3 AEs was 22.2%, while no patient experienced G4 AE. Dose reduction and temporary discontinuation were needed in 33.3% and 40.3% of cases, with 1 permanent discontinuation due to AEs.

Conclusions: These results confirm the effectiveness and safety of pemigatinib in a real-world setting.

1. Introduction

Cholangiocarcinoma (CCA) accounts for 3% of all gastrointestinal tumors and includes rare heterogeneous tumors that can arise anywhere in the bile ducts. CCAs are classically classified by tumor location into intrahepatic (iCCA) and extrahepatic (eCCA) (perihilar and distal) forms. Although these are rare diseases, their incidence is increasing worldwide, as well as their mortality, with an overall 5-year survival rate of less than 20% in Europe and around 4% for locally advanced and metastatic stages [1].

Surgery remains the cornerstone of the curative treatment for CCA although unfortunately only one third of patients present with resectable disease and among those who undergo surgery, approximately 70% experience a disease relapse, 35% of whom within the first two years [2]. The standard of care first-line treatment for locally advanced or metastatic CCA was chemotherapy with the association of cisplatin + gemcitabine [3]. Two recent studies have confirmed the efficacy of adding immunotherapy with immune checkpoint inhibitors (ICI) in combination with chemotherapy as first-line treatment. Durvalumab first showed an improved survival and activity benefit compared to chemotherapy alone in the randomized phase III TOPAZ-1 trial, becoming the new standard of care as first line treatment [4]. Later, pembrolizumab showed similar survival benefit in the KEYNOTE 966 trial [5]. Until recently, according to data from the ABC-06 trial, second line treatment consisted of chemotherapy with the FOLFOX regimen, which provided a modest OS improvement compared to active symptom control (ASC) [6].

Molecular profiling studies have shown the presence of targetable molecular alterations in 45–50% of CCAs, particularly in iCCAs where *IDH1* mutations are present in 10–15% of cases and *FGFR2* alterations in 10% of cases [7]. These two alterations can be targeted by targeted therapies available in Europe: pemigatinib, infigratinib, and futibatinib for *FGFR2* fusions or rearrangements and ivosidenib for *IDH1* mutations [8–12].

Pemigatinib is a selective, potent, oral competitive inhibitor of *FGFR1*, *FGFR2* and *FGFR3*. In the multicenter, single-arm, open-label, multicohort FIGHT-202 trial, previously treated locally advanced inoperable or metastatic CCA patients with or without *FGFR* genetic aberrations received pemigatinib (13.5 mg orally once daily, on days 1–14 of 21-day cycles) [8]. The trial included 107 patients with *FGFR2* fusions/rearrangements, 20 with other *FGF/FGFR* aberrations, and 18 CCA patients without alterations.

At the first analysis at a median follow-up of 17.8 months, in the FIGHT-202 patients harboring *FGFR2* gene fusions and/or rearrangements, ORR and DCR were 35.5% and 82%, respectively, with three cases of complete response and a median duration of response of 7.5 (95%CI: 5.7–14.5) months. In the same group, the median PFS was 6.9

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(95%CI: 6.2–9.6) months and the median OS was 21.1 (95%CI: 14.8-NE) months. On the contrary, no responses were reported in the other two cohorts of CCA patients; in patients harboring other *FGF/FGFR* alterations and in *FGFR* wild type, median PFS was 2.1 and 1.7 months, while median OS was 6.7 and 4.0 months, respectively.

These results led to FDA approval and an Expanded Access Program (EAP) was made available in Europe since July 2020, before EMA approval of pemigatinib on January 2021.

At the final analysis, objective response rate (ORR) and disease control rate (DCR) were 37.0% and 82.4%, respectively, with a median duration of response (DoR) of 9.1 months. Median PFS was 7.0 months and the median OS was 17.5 months. All patients reported treatment-emergent adverse events (TEAEs); the most common were hyperphosphataemia (58.5%), alopecia (49.7%), and diarrhea (47.6%). Most TEAEs were grade (G)1–2; the most common G$\geq$ 3 TEAE was hypophosphatemia (14.3%). Additionally, 91.8% of patients had a treatment-related AE (TRAEs), 4.1% had a fatal TEAE (all considered unrelated to pemigatinib treatment), and 10.2% discontinued pemigatinib due to a TEAE [12].

No phase 3–4 data are currently available to date and, to the best of our knowledge, no previous studies have assessed the effectiveness and safety of pemigatinib in a real-world setting.

2. Materials and methods

2.1. Study population

This multicentre, observational, retrospective study included consecutive patients with unresectable, locally advanced or metastatic FGFR2-positive CCA, treated with pemigatinib as second- or further line of systemic treatment, within or outside the European EAP for pemigatinib (Incyte - Wilmington, DE, USA), according to the drug reimbursement policy and timing of each country. Incyte had no role in planning this study, nor in collecting or analyzing patient data.

Medical records of patients referred to 14 Italian and 25 French Oncology Units from July 2020 to September 2022 were evaluated.

The main inclusion criteria for both cohorts were: a) adult patients with proven locally advanced or metastatic CCA harboring *FGFR2* fusion or rearrangement; b) availability of clinico-pathological characteristics, treatment patterns and outcomes; c) patients should have received at least a first-line systemic treatment for the advanced/metastatic disease and at least one cycle of pemigatinib. Patients could have had previous surgery with curative intent for early disease or locoregional treatment (i.e. TARE or RT or HAIC) for locally advanced or metastatic disease.

The present study was approved by the local Ethics Committee for each participating institution, complies with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfills Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data. More specifically, this analysis is a joint analysis of two observational retrospective studies which were independently approved by the respective local Ethical Committee in Italy (PEMI-REAL study, approved by "Comitato Etico Regione Marche" on December 2022, protocol number 325–2022) and in France (PEMI-BIL study, protocol number RnIPH 2022–105).

2.2. Study endpoints

The primary endpoint of the study was to assess clinician-reported ORR. Treatment responses were evaluated in accordance with RECIST 1.1. ORR was defined as the proportion of patients experiencing an objective response (complete response – CR, or partial response - PR) as the best response, according to RECIST 1.1, and as reported by the local investigator. DCR was defined as the proportion of patients experiencing CR, PR or stable disease (SD) according to RECIST 1.1, as per local investigator assessment. Responders were defined as patients achieving a PR or CR as best response during treatment with pemigatinib, while non-responders were defined as patients achieving a SD or PD (progressive disease) as best response during treatment with pemigatinib, according to the above mentioned criteria.

Secondary endpoints of the study included the assessment of PFS, OS, and safety during treatment with pemigatinib. Moreover, exploratory analyses were performed to estimate and eventually compare PFS during previous (first and second) lines of treatment in the overall population.

PFS was defined as the time from the beginning of treatment to the first evidence of objective disease progression or death of the patient for any cause, whichever occurred first. Determination of disease progression was based on the measurements reported by the investigator. OS was defined as the time from the start of treatment to the date of death for any cause. For patients still alive at the time of analysis, OS was censored at the last date of follow-up.

Safety was assessed through analysis of AEs, which were measured and collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

2.3. Statistical analysis

Patients' characteristics and treatment data were summarized in a descriptive manner. Categorical variables were presented in the form of frequencies and percentages; while continuous variables by mean, standard deviation, minimum and maximum value (if normal/gaussian distribution); or using median and interquartile range (if not normal/gaussian distribution). Differences between categorical variables were analyzed by exact Fisher test or chi-square, as appropriate, while differences between continuous variables were evaluated by Student T-test or Mann-Whitney U-test as applicable. Survival outcomes were calculated by the Kaplan-Meier method. The median follow-up time was calculated with the reverse Kaplan-Meier method. Cox proportional hazards regression was used for the univariate analysis of PFS and OS and estimation of the Hazard ratios (HRs) with 95% confidence intervals (CIs). The alpha level for all analyses was set to a p value < 0.05. Statistical analyses were conducted by using R software (version 4.3.0).

3. Results

3.1. Patients and disease characteristics

From July 2020 to September 2022, 72 patients were enrolled at 14 Italian and 25 French Oncology Units (CONSORT diagram of patients' selection and inclusion in Supplementary File - Figure 1). The main patients' and disease characteristics are summarized in Table 1. In brief, the median age was 57 years with a majority of female patients (numbering, 55 in total 76%); 28 (39%) patients had BMI $>$ 30Kg/m2; 71 (99%) patients had iCCA; 48 (67%) patients had metastatic disease at diagnosis; 53 (74%) patients had 2 or more metastatic sites, particularly with liver (78%), lymph node (54%), and lung (49%) involvement; baseline CA19–9 level was $>$ 200 UI/ml in 12 (16.6%) patients, and *BICC1* was the most frequent *FGFR2* fusion co-partner in 22 (31%) patients.

3.2. Clinical outcomes

Over a median follow-up time of 19.5 months (95%CI: 15.0–30.5), the investigator-assessed ORR was 45.8% (CR: 2.7%, PR: 43.1%) and DCR was 84.7%, while median DoR was 7 months (95%CI: 5.8 - 9.3). Main activity results are summarized in Table 2. Univariate analysis revealed no clinical, biological or molecular predictive factors of response (Supplementary File - Table 1).

The median PFS was 8.7 months (95%CI: 7.3–11.8; 41/72 events), and the median OS was 17.1 months (95%CI: 12.7-NA; 27/72 events) (Figures 1 and 2).

Six- and 12-month PFS rates were 63.3% and 32.8%, respectively; 6-

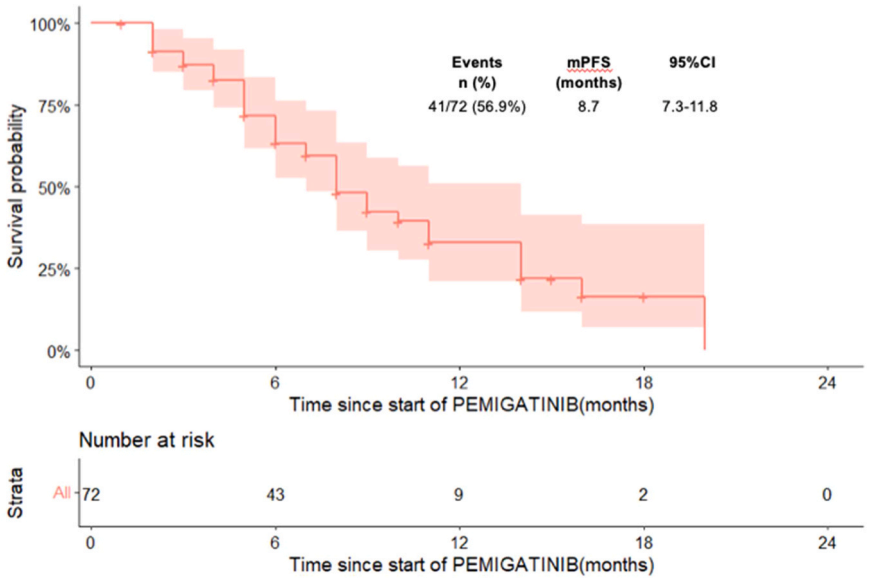

Fig. 1. PFS during treatment with pemigatinib.

and 12-month OS rates were 79.8% and 60.6% respectively.

There was a statistically significant OS benefit in favor of patients who achieved objective response to pemigatinib (mOS=18.7 [95%CI: 17.1 – NA]) compared to non-responders (mOS = 12.7 [95% CI: 7.7 – NA]) (HR: 0.38 [95%CI: 0.17 – 0.87], p = 0.016). The 1-year OS rate was 77.6% [63%– 95.6%] among responders compared to 46.3% [30.9%– 69.6%] for non-responders (Figure 3).

Median PFS was 8.7 (95%CI: 6.6 – NA) and 9.7 (95%CI: 7 – 14.9) months for patients treated with pemigatinib as second or further line of systemic treatment, respectively, with no statistically significant difference (HR = 0.8 [95% CI:0.5 – 1.6]; p = 0.61) (Supplementary file - Figure 2).

Median PFS of patients who needed dose reduction or discontinuation was 14.9 (95%CI: 8 – NA) months, while PFS of patients who did not need of dose reduction or discontinuation was to 8.7 (95%CI: 6.2 – 11.8) months, with no statistically significant difference (HR = 1.5 [95% CI:0.8 – 3.02]; p = 0.21) (Supplementary file - Figure 3).

At an exploratory analysis conducted among patients undergoing second-line treatment, a statistically significant survival benefit in terms of PFS was found in favor of patients treated with pemigatinib compared to those treated with chemotherapy (8.6 [95%CI: 6.6-NA] vs 3.4 [2.1-NA] months, HR=3.88 [95%CI: 1.81–8.31], p < 0.001) (Figure 4).

3.3. Safety analysis

The median number of administered cycles was 8 (range 1–28; IQR 13–5). Any grade AEs occurred in 70/72 patients (97.2%). The most common any grade AEs were fatigue (69.4%), ocular toxicity (68%, including dry eye, keratitis and retinal detachment), nail toxicities (61.1%), dermatologic toxicity (41.6%, including erythema and palmar-plantar erythrodysesthesia), hyperphosphataemia (55.6%), stomatitis (48.6%), diarrhea (36.1%) (Table 3).

Grade 3 AEs affected 16 (22.2%) patients. No G4 AEs and no deaths due to AEs occurred.

Temporary discontinuation was needed for 29 (40.3%) patients while dose reduction was necessary for 24 (33.3%) patients. Only 1 patient (1.4%) required permanent discontinuation as a result of AEs.

3.4. Molecular assessment

Assessment of *FGFR2* status was performed on formalin-fixed paraffin-embedded samples from primary tumors or metastasis via Next Generation Sequencing (NGS) or Fluorescent In Situ Hybridization (FISH), according to the local clinical practice for each participating centre.

In the whole cohort, patients were most commonly tested for *FGFR* alterations using DNA NGS platforms (31/72 patients, 42.5%) (predominantly FoundationOne® CDx platform in 26 patients, or others in 5 patients) or NGS fusion platforms (28/72 patients, 38.4%) (Archer® Fusion Plex NGS assay in 27 patients, other in 1 patient), followed by FISH (7 patients, 9.6%), the method used was not available for 4 patients.

BICC1 was the most frequent fusion/rearrangement partner of *FGFR2* (30.1%), followed by *KIAA12* (13.6%), and others in a lower percentage, which were almost unique for each patient.

Among patients who underwent a NGS evaluation, the most frequent (>5%) concomitant molecular alterations were: *BAP1* mutation (9.6%), *TP53* mutation (8.2%), *CDKN2A* loss or mutation (8.2%), *CDKN2B* loss (5.5%). Concomitant *IDH1* mutation was present in 4.2% of patients. All the other available individual alterations are described in Supplementary File - Table 2.

3.5. Prior line treatments

Overall, 57/72 (79.1%) patients received cisplatin-gemcitabine, oxaliplatin-gemcitabine (7/72, 10%) or other chemotherapy regimen (8/72, 11%) as first-line treatment; 29/72 (40.3%) patients received a second-line treatment with: FOLFOX (9/29, 31%), cisplatin-gemcitabine (6/29, 20.7%), Regorafenib (3/29, 10.3%), FOLFIRI (2/29, 6.9%), or other (9/29, 31.1%); 16/72 (22.2%) patients received a third-line treatment with: FOLFOX (7/16, 43.75%), FOLFIRI (4/16, 25%), or other (5/16, 31.3%). Prior treatment outcomes are described in Table 4.

Median PFS during first-line treatment with platinum-based regimen (cisplatin or oxaliplatin) in combination with gemcitabine was 7.7 months (95%CI: 6.9–9.9), with a 6-month and 12-month PFS rate of 56.2% and 18.7%, respectively (Supplementary File - Figure 4).

Median OS since first-line treatment with platinum-based regimen (cisplatin or oxaliplatin) in combination with gemcitabine was 37 months (95%CI: 35-NA), with a 12-month and 24-month OS rate of 88.4% and 70.1%, respectively (Supplementary File - Figure 5).

3.6. Post-progression treatments

Among the 42 patients who discontinued pemigatinib due to disease

Table 1
Clinical and molecular patients' features in the overall, PEMI-BIL, and PEMI-REAL cohort.

Demographics and disease characteristics	Overall (N = 72) N (%)	PEMI-BIL cohort (N = 49) N (%)	PEMI-REAL cohort (N = 23) N (%)
Age mean (SD, years)	56.9 (13.6)	56.7 (14.6)	57.4 (11.4)
Sex			
Female	55 (76)	36 (73.5)	19 (82.6)
Male	17 (24)	13 (26.5)	4 (17.4)
ECOG performance status			
0	28 (38)	18 (36.7)	10 (43.5)
1	31 (43)	19 (38.7)	12 (52.2)
2	12 (16)	11 (22.4)	1 (4.3)
Comorbidities			
BMI $\geq$ 25	28 (39)	21 (42.8)	13 (56.5)
Viral hepatitis	6 (8)	2 (4)	4 (17.4)
Smoking	7 (10)	6 (12.2)	1 (4.3)
Diabetes	7 (10)	7 (14.3)	-
Cholangiocarcinoma location			
Intrahepatic	70 (98.6)	48 (98)	22 (95.6)
Extrahepatic (proximal/perihilar)	1 (1.4)	0	1 (4.4)
Missing data	1 (1.4)	1 (2)	0
Grading			
Well differentiated	12 (17)	11 (22.4)	1 (4.3)
Moderately differentiated	24 (33)	20 (40.8)	4 (17.4)
Poorly differentiated	13 (18)	8 (16.3)	5 (21.7)
Missing data	23 (32)	10 (20.4)	13 (56.5)
Tumour size (cm). mean (SD)	8.18 (3.57)	8.18 (3.57)	NA
FGFR2 fusion partner			
BICC1	22 (31)	16 (32.6)	6 (26.1)
Disease stage at systemic treatment			
Locally advanced	3 (4.2)	3 (6.1)	0
Metastatic	69 (96)	46 (93.8)	23 (100)
Number of metastatic sites			
Locally advanced	3 (4.2)	3 (6.1)	0
1	16 (22)	9 (18.4)	7 (30.4)
2	28 (39)	17 (34.7)	11 (47.8)
$\geq$ 3	25 (35)	20 (40.8)	5 (21.7)
Sites of disease			
Liver	56 (78)	38 (77.5)	18 (78.3)
Lymph nodes	39 (54)	28 (57.1)	11 (47.8)
Lung	35 (49)	26 (53.1)	9 (39.1)
Ascites	14 (19)	11 (22.4)	3 (13)
Other	16 (22)	13 (26.5)	4 (17.4)
Previous surgery with curative intent for early disease*	19 (26.4)	10 (20.4)	9 (39.1)
Previous locoregional treatment (TARE or RT or HAIC) for locally advanced or metastatic disease	7 (9.7)	6 (12.2)	1 (4.4)
Number of previous systemic treatment for locally advanced or metastatic disease			
1	43 (59.7)	29 (59.2)	14 (60.8)
2	15 (20.8)	10 (20.4)	5 (21.7)
$\geq$ 3	14 (19.4)	10 (20.4)	4 (17.4)

SD: standard deviation; * 2 metastatic patients performed palliative surgery

progression, 24/42 (57.1%) received a post-pemigatinib first line of systemic treatment with: FOLFOX (7/24, 29.2%), FOLFIRI (2/24, 8.3%), RLY-4008 (7/24, 29.2%), futibatinib (5/24, 20.8%), or others (3/24, 12.5%). Among patients who progressed to a post-pemigatinib first line treatment, 5/24 (20.8%) patients received a post-pemigatinib second line of treatment with: FOLFOX (2 patients), FOLFIRI (one patient), cisplatin + gemcitabine (one patient), RLY-4008 (one patient). 2/42 patients received a post-pemigatinib third-line of treatment.

Table 2
Activity and effectiveness outcomes during treatment with pemigatinib.

	Patients (N = 72) N (%)
Best overall response	
Complete response (CR)	2 (2.7)
Partial response (PR)	31 (43.1)
Stable disease (SD)	28 (38.8)
Progressive disease (PD)	9 (12.5)
Not evaluable (NE)	2 (2.7)
Objective response rate (ORR)	33 (45.8)
Disease control rate (DCR)	61 (84.7)
Median Duration of Response (DoR, months)	7 (95%CI: 5.8 - 9.3)
Mean DoR (months)	8.2 (SD: 3.9)
Median follow-up time (months)	19.5 (95%CI: 15 - 30.5)
Progression-free survival (PFS)	
Median PFS (months)	8.7 (95%CI: 7.3-11.8)
12-month PFS rate	32.8%
Overall survival (OS)	
Median OS (months)	17.1 (95%CI: 12.7-NA)
12-month OS rate	60.6%

4. Discussion

The treatment landscape of CCA is rapidly evolving thanks to a better understanding of tumor biology [7,13]. Both an anatomical and a molecular heterogeneity characterize iCCA, eCCA, and gallbladder cancer.

Specifically, rearrangements/fusions of FGFR2 are almost exclusively found in about 10% of patients affected by iCCA.

Following the results of the FIGHT-202 trial, the FDA granted accelerated approval to pemigatinib for pretreated patients with metastatic CCA harboring *FGFR2* fusions/rearrangements after a positive FoundationOne® CDX (Foundation Medicine, Inc., Cambridge, MA, USA) test. Thereafter, EMA approved the use of pemigatinib for the same indication.

Based on this data, a randomized phase III trial (FIGHT-302) is currently ongoing to compare pemigatinib versus cisplatin- gemcitabine as first-line of systemic treatment in patients affected by CCA and harboring FGFR2 fusions/rearrangements [14].

Results of pivotal randomized trials are essential to bring new treatment options; on the other hand, real-life data may be useful to assess efficacy and safety of new agents in a less clinically selected population, thus helping to optimize the treatment management.

In this regard, to assess effectiveness and safety of pemigatinib in a real-world setting, we conducted a retrospective study on a multicentre international population of patients affected by unresectable advanced or metastatic CCA and treated with pemigatinib after disease progression with at least one previous line of systemic treatment.

Similarly to findings from the FIGHT-202 trial, the probability of *FGFR2* positivity seems to correlate with particular clinico-pathological features: female patients aged younger than 60 years affected by "de novo" metastatic iCCA with liver, lymph node and/or lung disease involvement. Moreover, the incidence of co-infection by hepatotropic viruses (HBV and HCV), a known risk factor for iCCA [15] was relatively low in our cohorts as well as in the registration trial. On the other hand, it is fascinating to underline the relatively higher incidence of obesity and diabetes as concomitant comorbidities in this particular cohort of patients with iCCA in where alterations of the FGF/FGFR pathway might play a particularly relevant role [16,17].

Consistent with previous findings, the most common *FGFR2* partner gene in this cohort was *BICC1*, which did not seem to affect the proportion of patients who achieved a disease response compared to any other FGFR2 rearrangement partner [18]. On the other hand, as previously reported, most *FGFR2* fusion or rearrangement partners identified were almost exclusive to each patient [8,19,20]. Taking into consideration the wide molecular heterogeneity of biliary tract cancers, these results further highlight the importance of implementing DNA-based and RNA-based NGS assays with proper diagnostic accuracy into

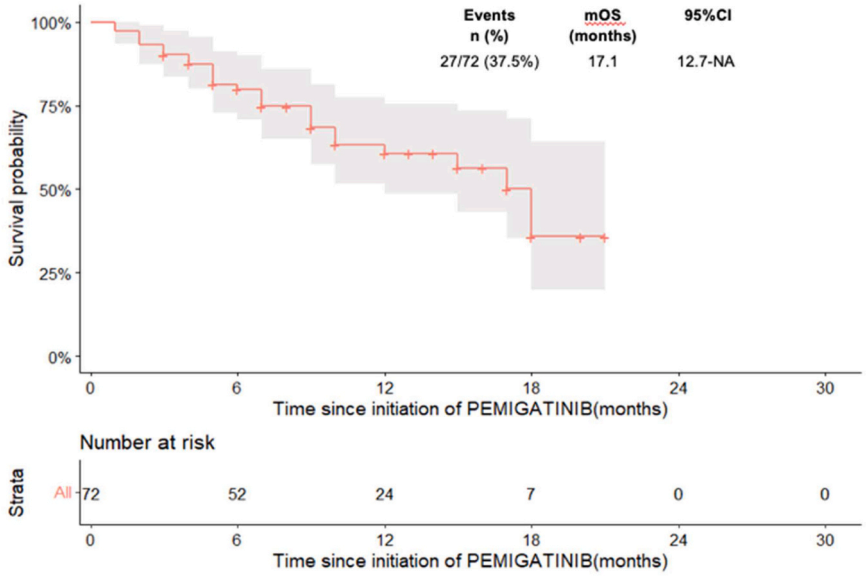

Fig. 2. OS during treatment with pemigatinib.

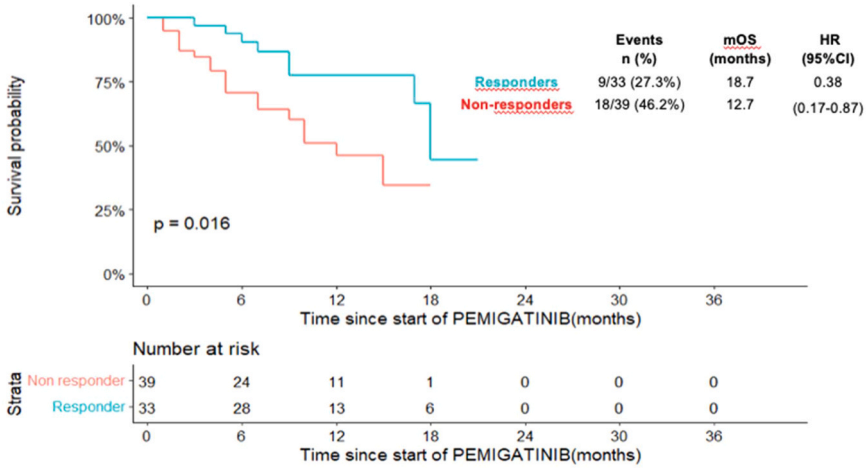

Fig. 3. OS according to response to treatment with pemigatinib.

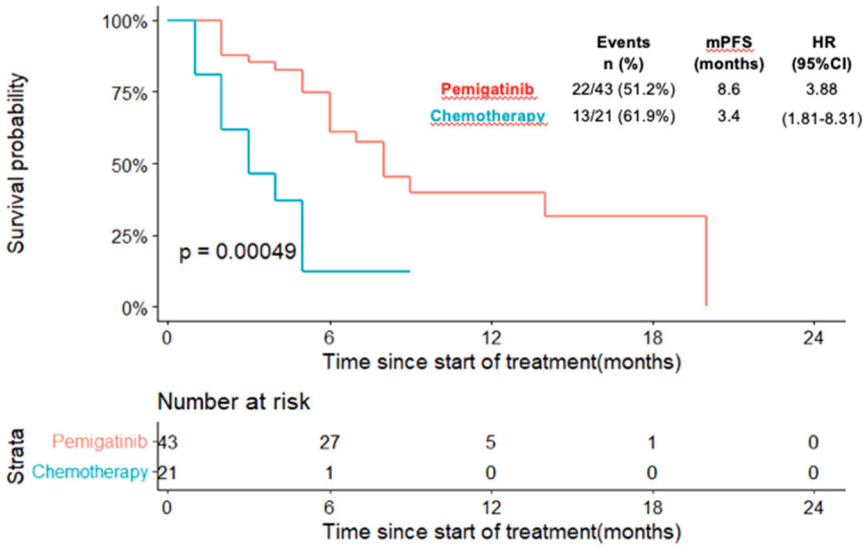

Fig. 4. PFS according to the type of second line treatment received.

Table 3
Safety profile of pemigatinib and treatment modification.

Adverse events (N = 72)	All grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Overall incidence of AEs	70 (97.2)	70 (97.2%)	55 (76.3%)	16 (22.2%)
Hyperphosphatemia	40 (55.6)	17 (23.6)	23 (31.9)	-
Nail toxicities	44 (61.1)	25 (34.7)	15 (20.8)	4 (5.6)
Dry eye	29 (40.3)	21 (29.2)	8 (11.1)	-
Keratitis	14 (19.4)	10 (13.9)	2 (2.8)	2 (2.8)
Retinal detachment	6 (8.3)	4 (5.6)	2 (2.8)	-
Fatigue	50 (69.4)	28 (38.9)	18 (25)	5 (6.9)
Weight decreased	20 (27.8)	18 (25)	2 (2.8)	-
Erythema	6 (8.3)	5 (6.9)	1 (1.4)	-
Palmo-plantar erythrodysesthesia	24 (33.3)	15 (20.8)	7 (9.7)	2 (2.8)
Myalgia	26 (36.1)	19 (26.4)	6 (8.3)	1 (1.4)
Dysgueusia	18 (25)	11 (15.3)	7 (9.7)	-
Stomatitis	35 (48.6)	218 (25)	17 (23.6)	1 (1.3%)
Diarrhea	26 (36.1)	20 (27.8)	5 (6.9)	1 (1.4)
Nausea/ vomiting	11 (15.3)	10 (13.9)	1 (1.4)	-
Alopecia	23 (31.9)	9 (12.5)	14 (19.4)	-
Anemia	32 (44.4)	16 (22.2)	14 (19.4)	2 (2.8)
Hypertransaminasemia	14 (19.4)	8 (11.1)	4 (5.6)	2 (2.8)
Hypophosphatemia	16 (22.2)	15 (20.8)	1 (1.4)	-
Treatment modification	**N (%)**			
Temporary discontinuation	29 (40.3)			
Dose reduction	24 (33.3)			
Permanent discontinuation	1 (1.4)			

Table 4
Activity results during previous lines of systemic treatment for locally advanced/metastatic disease.

Previous treatments	Patients N (%)
First line treatment (N = 72)	56.9 (13.6)
CISGEM	57 (79)
GEMOX	7 (10)
Other	8 (11)
Best overall response to first line	
Complete response	1 (1)
Partial response	20 (28)
Stable disease	30 (42)
Progressive disease	17 (24)
Not evaluable	2 (3)
Second line treatment (N = 29)	
Chemotherapy (5FU, CISGEM)	21 (72.4)
Immunotherapy	3 (10.3)
TKI FGFR	1 (0.03)
Other TKI	4 (13.7)
Best overall response to second line	
Complete response	0 (0)
Partial response	2 (6.8)
Stable disease	9 (31)
Progressive disease	17 (58.6)
Not evaluable	1 (0.03)

clinical practice, in order to detect concomitant or "de novo" molecular alterations able to predict benefit from *FGFR* inhibitors [21].

Due to the limitation of the small sample size, the activity results in our real-world cohort were similar to those found in the FIGHT-202 trial, even though the absence of a centralized radiological assessment of the response might have overestimated our activity results.

Interestingly, pemigatinib seemed to be active regardless of the number of previous lines of systemic treatment received, taking into consideration that the present population of patients with iCCA was heavily pretreated. Moreover, the median PFS in patients with *FGFR2* fusions/rearrangements who received pemigatinib as their second-line treatment was longer than that observed in patients who received chemotherapy as second-line treatment (8.6 vs 3.4 months). These results are consistent with those deriving from a FIGHT-202 post hoc analysis (7.0 vs 4.2 months, respectively) [22]. Taken together, these results are in line with the ESMO guidelines recommending the use of *FGFR2* inhibitors for second and further lines in patients with advanced/metastatic CCA [1].

The length of the follow-up as well as the survival results in terms of PFS, and OS in this population are consistent with previous findings and confirm the efficacy of pemigatinib in a real-life setting. On the other hand, the relevant OS benefit since first-line treatment in this population, together with the finding of a first-line PFS comparable to the historical control with no anatomical and molecular patient selection of the ABC-02 trial, seems to support the positive prognostic effect of *FGFR2* alterations [4,23] as well as that of primary tumor location. In this respect, a retrospective analysis reported longer OS in patients with tumors with *FGFR* alterations than in those without *FGFR* alterations [18], and a previous report from a post hoc analysis of data from the ABC-01, ABC-02, and ABC-03 trials conducted in patients receiving first-line cisplatin plus gemcitabine combination suggested that patients with iCCA, and particularly those with liver-only disease, might have longer OS compared to those with other CCA [24].

The relatively high rate of patients eligible for subsequent lines of systemic treatment after disease progression on pemigatinib further underlines the better prognosis of this group of patients compared to extra-hepatic CCA and *FGFR2*-negative tumors.

In terms of safety, hyperphosphataemia, ocular and dermatologic side effects (including nail toxicity) were the most frequent class-specific AEs. The large majority of the AEs were mainly G1-G2 and were managed with dietary modifications, specialist consultations, and pharmacological therapy, without clinically relevant sequelae, and an overall incidence almost similar to previous findings [25]. However dose reductions or temporary discontinuations were needed in about one third of the patients. This might indirectly underline the potential impact on everyday quality of life of patients treated with FGFR inhibitors, an aspect which probably needs to be better addressed in a real-world setting in a prospective manner. On the other hand, the next-generation, covalently binding *FGFR1–4* inhibitor futibatinib and the highly selective, irreversible *FGFR2* inhibitor RLY-4008 provided even superior activity and efficacy results, with a better safety profile if indirectly compared to second-generation *FGFR* inhibitors such as pemigatinib or infigratinib [10,26].

Moreover, a further aspect which will require investigation is the relationship between specific co-occurring genomic alterations and clinical outcomes, particularly the presence of predictive resistance factors to treatment with pemigatinib. Indeed, about 10% and 15% of *FGFR2*-positive patients within our cohort and FIGHT-202 cohort, respectively, were primary refractory to pemigatinib. In this respect, co-occurring genomic alterations of known tumor-suppressor genes, such as *CDKN2A/B*, *PBRM1*, and *TP53* seemed to be related to a lower response rate and shorter PFS compared to those without alterations in these genes [27]. One of the planned subsequent analyses of the present study, to be conducted on a larger number of patients at an updated follow-up, will investigate clinical and molecular factors potentially predictive of resistance to treatment with pemigatinib.

FGFR2 kinase domain mutations, most commonly N550 and V565 mutations, seem to be the most common mechanism of acquired resistance to systemic treatment with second-generation *FGFR* inhibitors such as pemigatinib and infigratinib [28]. Circulating tumor-DNA (ct-DNA) assays could be a way to comprehensively genomically profile biliary tract malignancies in the absence of tumor tissue data and can be used for longitudinal testing, in order to characterize the emergence of putative resistance mechanisms upon treatment with targeted agents [29]. Future clinical studies are needed to further investigate the role of ct-DNA in acquired resistance to systemic treatment.

Our research presents several limitations. The retrospective nature of the study could account for potential selection or under-reporting bias and represent a limitation, since tumor assessment modalities, as well as time points, were at the treating physician's discretion. This variability could have influenced PFS as well as activity evaluation. Moreover, the

present study arises from the analysis of datasets from two independently conducted observational studies, not originally intended to be aggregated. Lastly, despite the large number of even tertiary cancer centers involved in the study, the average number of patients enrolled is relatively low (less than 2 patients/center). This aspect could be related to the presence of the concomitantly enrolling first-line FIGHT-302 trial, but it could also underline the need to reduce the risk of not evaluable sample or false-negative tests in clinical practice, optimizing the workflow from pre-analytical to analytical procedure and using validated targeted DNA and RNA NGS-based genomic profiling platforms adopting hybrid capture and amplicon-based approaches [21].

In conclusion, we reported the first large-scale multicenter international real-world experience of using pemigatinib in a previously treated cohort of patients with *FGFR2*-positive CCA managed in clinical practice.

These results almost confirm the activity, efficacy and safety outcomes achieved in the FIGHT-202 trial.

5. Ethics approval and consent to participate

The study was conducted in accordance with the precepts of Good Clinical Practice and Declaration of Helsinki and was approved by the ethics committees of each participating institution. Written informed consent to participate to the observational study was obtained from each alive patient from each cohort.

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CRediT authorship contribution statement

Conceptualization: AP, BD, NF, Data collection, acquisition and curation: All authors, Formal analysis: AP, NF, MCPD, GP, BD, Funding acquisition; JV, Investigation: All authors, Methodology: AP, FN, MCPD, Project administration: AP, FN, Resources: AP, FN, Software: AP, FN, MCPD, Supervision: FN, RB, Validation: All authors, Writing – original draft: AP, BD, GP, Writing – review & editing: FN, JV, LR, RG, RB, Final approval of the manuscript: All authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data collected for this study could be available in a de-identified form after reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113587.

References

[1] Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. ESMO guidelines committee. Electronic address: clinicalguidelines@esmo.org. Biliary tract cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34(2):127–40. https://doi.org/10.1016/j.annonc.2022.10.506.

[2] Lepage C, Capocaccia R, Hackl M, Lemmens V, Molina E, Pierannunzio D, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999–2007: results of EUROCARE-5. Eur J Cancer 2015;51(15):2169–78.

[3] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. ABC-02 Trial Investigators. cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273–81. https://doi.org/10.1056/NEJMoa0908721.

[4] Oh DY, He AR, Qin S, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. NEJM Evid 2022;1(8). https://doi.org/10.1056/EVIDoa2200015.

[5] Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 3 juin 2023;401(10391):1853–65.

[6] Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, 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 mai 2021;22(5):690–701.

[7] Kendre G, Murugesan K, Brummer T, Segatto O, Saborowski A, Vogel A. Charting co-mutation patterns associated with actionable drivers in intrahepatic cholangiocarcinoma. J Hepatol 2023;78(3):614–26. https://doi.org/10.1016/j.jhep.2022.11.030.

[8] Abou-Alfa GK, Sahai V, Hollebecque A, et al. pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21(5):671–84.

[9] Javle M, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol 2021;6(10):803–15.

[10] Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med 2023;388(3):228–39.

[11] Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol 2021;7(11):1669–77. https://doi.org/10.1001/jamaoncol.2021.3836.

[12] Vogel, A. et al. pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: Final results from FIGHT-202. Annals of Oncology, Volume 33, S379 doi:10.1016/j.annonc.2022.04.443.

[13] Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. Clin Cancer Res 2018;24:4154–61.

[14] Bekaii-Saab TS, Valle JW, Van Cutsem E, Rimassa L, Furuse J, Ioka T, et al. FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. Future Oncol 2020;16(30):2385–99. https://doi.org/10.2217/fon-2020-0429.

[15] Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 2012;57(1):69–76.

[16] Xie Y, Su N, Yang J, et al. FGF/FGFR signaling in health and disease. Sig Transduct Target Ther 2020;5:181. https://doi.org/10.1038/s41392-020-00222-7.

[17] Petrick JL, Thistle JE, Zeleniuch-Jacquotte A, et al. Body mass index,diabetes and intrahepatic cholangiocarcinoma risk: the liver cancerpooling project and meta-analysis. Am J Gastroenterol 2018;113(10):1494–505.

[18] Jain A, Borad MJ, Kelley RK, et al. Cholangiocarcinoma with FGFR genetic aberrations: a unique clinical phenotype. JCO Precis Oncol 2018;2:1–12.

[19] Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology 2014;59:1427–34.

[20] Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growthfactor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol 2014;45:1630–8.

[21] Bekaii-Saab TS, Bridgewater J, Normanno N. Practical considerations in screening for genetic alterations in cholangiocarcinoma. Ann Oncol 2021;32(9):1111–26. https://doi.org/10.1016/j.annonc.2021.04.012. Epub 2021 Apr 28.

[22] Bibeau K, Féliz L, Lihou CF, Ren H, Abou-Alfa GK. Progression-free survival in patients with cholangiocarcinoma with or without *FGF/FGFR* alterations: a FIGHT-202 post hoc analysis of prior systemic therapy response. JCO Precis Oncol 2022;6:e2100414. https://doi.org/10.1200/PO.21.00414.

[23] Rizzato M, Brignola S, Munari G, Gatti M, Dadduzio V, Borga C, et al. Prognostic impact of FGFR2/3 alterations in patients with biliary tract cancers receiving systemic chemotherapy: the BITCOIN study. Eur J Cancer 2022;166:165–75. https://doi.org/10.1016/j.ejca.2022.02.013.

[24] Lamarca A, Ross P, Wasan HS, et al. Advanced intrahepatic cholangiocarcinoma: post-hoc analysis of the ABC-01, -02 and -03clinical trials. J Natl Cancer Inst 2020;112:200–10.

[25] Mahipal A, Tella SH, Kommalapati A, Yu J, Kim R. Prevention and treatment of FGFR inhibitor-associated toxicities. Crit Rev Oncol Hematol 2020;155:103091. https://doi.org/10.1016/j.critrevonc.2020.103091. Epub 2020 Sep 1. PMID: 32961472.

[26] Subbiah V, Sahai V, Maglic D, Bruderek K, Toure BB, Zhao S, et al. RLY-4008, the first highly selective FGFR2 inhibitor with activity across FGFR2 alterations and resistance mutations. Cancer Discov 2023;13(9):2012–31.
[27] Silverman IM, Hollebecque A, Friboulet L, Owens S, Newton RC, Zhen H, et al. Clinicogenomic analysis of FGFR2-rearranged cholangiocarcinoma identifies correlates of response and mechanisms of resistance to pemigatinib. Cancer Discov 2021;11(2):326–39. https://doi.org/10.1158/2159-8290.CD-20-0766. Epub 2020 Nov 20. PMID: 33218975.
[28] Wu Q, Ellis H, Siravegna G, Michel AG, Norden BL, Fece de la Cruz F, et al. Landscape of clinical resistance mechanisms to FGFR inhibitors in FGFR2-altered cholangiocarcinoma. Clin Cancer Res 2024;30(1):198–208. https://doi.org/10.1158/1078-0432.CCR-23-1317. PMID: 37843855; PMCID: PMC10767308.
[29] Lee MS, Kaseb AO, Pant S. The emerging role of circulating tumor DNA in non-colorectal gastrointestinal cancers. Clin Cancer Res 2023;29(17):3267–74. https://doi.org/10.1158/1078-0432.CCR-22-3626. PMID: 37092904.