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Efficacy and Safety of Pemigatinib in European Patients With Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma: a FIGHT-202 Subgroup Analysis

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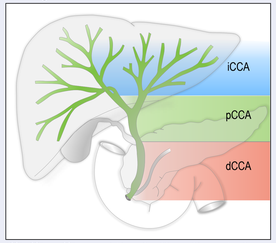
Background

Cholangiocarcinoma



iCCA, pCCA, and dCCA correspond to intrahepatic, perihilar, and distal cholangiocarcinoma, respectively. Cholangiocarcinoma: current knowledge and new developments. Blechacz B. *Gut Liver*. 2017;11(1):13–26, is licensed under CC BY-NC 4.0.

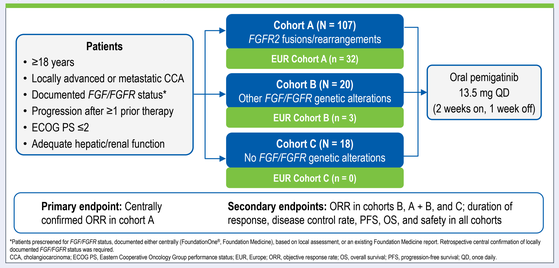
- Cholangiocarcinoma (CCA) is the most common primary malignancy of the bile duct[1]
  - Worldwide incidence varies regionally (0.3–3.4 per 100,000 in North America and Europe)[2]
    - Substantially higher incidence in certain regions of Asia, particularly in Thailand
- First-line treatment for locally advanced or metastatic CCA is gemcitabine plus cisplatin[3]
- Second-line chemotherapies have shown limited efficacy[4–7]
  - Progression-free survival (PFS): median, 2.6–3.2 months
  - Overall survival (OS): median, 6.2–7.2 months
  - Objective response rate (ORR): 7.7–9.5%
- Several actionable oncogenic alterations have been identified in CCA, including alterations involving fibroblast growth factor receptor 2 (FGFR2)[8–11]
- *FGFR2* fusions or rearrangements are:
  - Almost exclusively found in intrahepatic CCA (iCCA)
  - Generally reported to be present in 10–15% of patients with iCCA[8,12–16]
- Pemigatinib, a potent and selective oral FGFR1-3 inhibitor,[17] is approved for the treatment of adults with previously treated unresectable locally advanced or metastatic CCA with *FGFR2* fusion/rearrangements (in the United States and Europe) or unresectable biliary tract cancer with *FGFR2* fusion, worsening after cancer chemotherapy (in Japan)[18]
- Approval was based on phase 2 results from FIGHT-202 (NCT02924376)[19]
  - In the 107 patients with *FGFR2* fusions/rearrangements, pemigatinib monotherapy yielded an ORR of 35.5%, a disease control rate of 82%, and median duration of response, PFS, and estimated OS (not mature) of 7.5, 6.9, and 21.1 months, respectively

Methods

Patients and Study Design

- FIGHT-202 (NCT02924376) is a phase 2, open-label, single-arm, multicenter, global study conducted in 146 sites in the United States, Europe, the Middle East, and Asia[18]
- This post hoc analysis evaluated the efficacy and safety of pemigatinib in patients from Europe (EUR) enrolled in FIGHT-202 **(Figure 1)**

Figure 1. FIGHT-202 Study Design



*Patients prescreened for *FGF/FGFR* status, documented either centrally (FoundationOne®, Foundation Medicine), based on local assessment, or an existing Foundation Medicine report. Retrospective central confirmation of locally documented *FGF/FGFR* status was required.
CCA, cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EUR, Europe; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

Statistical Analyses

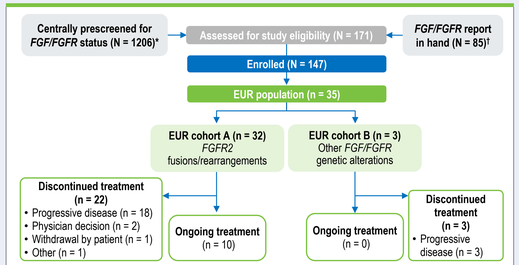
- Efficacy population: all patients with centrally confirmed *FGF/FGFR* status who received ≥1 dose of pemigatinib
- Safety population: all patients who received ≥1 dose of pemigatinib
- Survival analyses were conducted using Kaplan-Meier method; 95% confidence interval (CI) for ORR was estimated using the Clopper-Pearson method
- For the primary endpoint, patients with insufficient baseline or on-study data for adequate assessment of response status were considered nonresponders
- The data cutoff (March 22, 2019) used for this analysis was identical to that of the published primary analysis[18]
- *The study was not designed to make statistical comparisons between cohorts; no formal hypothesis testing or inferential analyses were conducted*

Results

Patients

- Thirty-five patients from EUR enrolled in FIGHT-202 were included in this analysis
  - Twenty-five patients (71%) had discontinued treatment, most commonly owing to disease progression (n = 21 [60%]) **(Figure 2)**
  - Ten patients (all EUR cohort A) were receiving ongoing treatment
  - Thirty-two patients (91%) analyzed had *FGFR2* fusions/rearrangements
- In EUR cohorts A and B, respectively
  - The median follow-up was 10.2 (range, 7.3–19.0) and 19.6 (19.4–20.1) months
  - The median duration of treatment was 7.6 (range, 0.3–15.4) and 1.7 (1.0–8.4) months

Figure 2. Patient Disposition



*FoundationOne®, Foundation Medicine. †Most patients with report in hand had undergone FoundationOne® testing for *FGF/FGFR* status.
EUR, Europe.

- Patient demographics and clinical characteristics are summarized in **Table 1**
- Across all EUR cohorts, the median age (range) was 59 (34–77) years; most patients (66%) were women; 46% had received ≥2 prior therapies
- Patient characteristics of the EUR cohort were generally consistent with the FIGHT-202 total study population[18]

Table 1. Patient Demographics and Clinical Characteristics

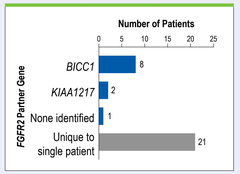
Variable	EUR Cohort A (n = 32) *FGFR2* Fusions/ Rearrangements	EUR Cohort B (n = 3) Other *FGF/FGFR* Genetic Alterations
Age, median (range), years	57 (34–77)	67 (67–70)
<65, n (%)	24 (75)	0
65–<75, n (%)	6 (19)	3 (100)
≥75, n (%)	2 (6)	0
Sex, n (%)		
Men	11 (34)	1 (33)
Women	21 (66)	2 (67)
Country, n (%)		
France	10 (31)	0
Italy	8 (25)	0
United Kingdom	6 (19)	0
Germany	5 (16)	0
Belgium	2 (6)	0
Spain	1 (3)	3 (100)
ECOG PS, n (%)		
0	17 (53)	1 (33)
1	13 (41)	2 (67)
2	2 (6)	0
Number of prior systemic therapies, n (%)	32 (100)	3 (100)
1	17 (53)	2 (67)
2	9 (28)	1 (33)
≥3	6 (19)	0
Prior cancer surgery, n (%)	17 (53)	0
Prior radiation, n (%)	9 (28)	0
CCA location, n (%)		
Intrahepatic	31 (97)	2 (67)
Extrahepatic	1 (3)	1 (33)

CCA, cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EUR, Europe.

Efficacy

- Fusions are a product of chromosomal rearrangement
  - Consistent with Foundation Medicine terminology, rearrangements are classified as fusions if the partner gene is previously described or in-frame
- Among 32 patients in EUR cohort A **(Figure 3)**
  - 26 fusions; 6 rearrangements
  - 23 different partner genes
  - 21 unique to single patients
  - Most common:
    - *BICC1* (25%)
    - No partner identified (3%)

Figure 3. *FGFR2* Fusions/Rearrangements (EUR Cohort A)



- The centrally confirmed ORR in EUR cohort A was 40.6% **(Table 2)**
  - One patient (3.1%) had a confirmed complete response and 12 (37.5%) had confirmed partial responses
- In EUR cohort B, no patients achieved a response
- ORR of the EUR cohorts were generally consistent with the published findings in the FIGHT-202 total study population (Cohort A [N = 107]: 35.5% [95% CI, 26.5–45.4]; Cohort B [N = 20]: 0)[18]

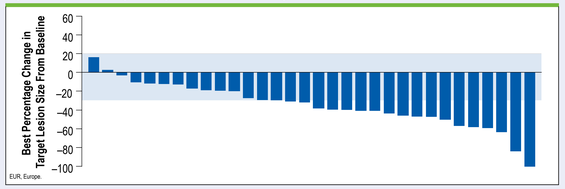
Table 2. Efficacy

Variable	EUR Cohort A (n = 32) *FGFR2* Fusions/Rearrangements	EUR Cohort B (n = 3) Other *FGF/FGFR* Genetic Alterations
ORR (95% CI), %	40.6 (23.7–59.4)	0 (0–70.8)
Best OR,* n (%)		
CR	1 (3.1)	0
PR	12 (37.5)	0
SD	15 (46.9)	2 (66.7)
PD	4 (12.5)	1 (33.3)
Median DOR (95% CI), mo	7.5 (5.5–7.5)	—
DCR (CR + PR + SD) (95% CI), %	87.5 (71.0–96.5)	66.7 (9.4–99.2)

*Assessed and confirmed by independent central review.
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; EUR, Europe; OR, objective response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Most patients in EUR cohort A (30 of 32 patients with postbaseline measurements) had reductions in centrally assessed best percentage change from baseline in target lesion size (sum of diameters) **(Figure 4)**

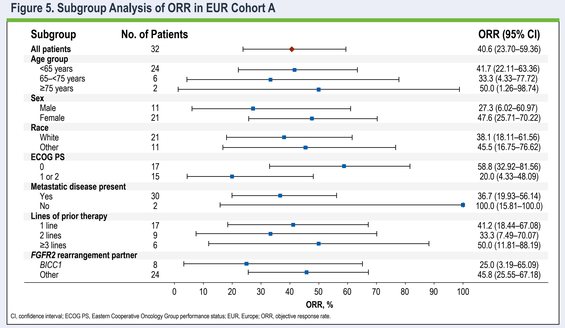
Figure 4. Best Percentage Change From Baseline in Target Lesion Size for Individual Patients in EUR Cohort A



EUR, Europe.

- The ORR in EUR cohort A was similar across demographic and disease subgroups **(Figure 5)**

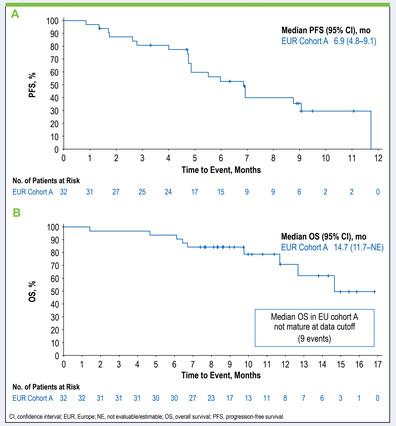
Figure 5. Subgroup Analysis of ORR in EUR Cohort A



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EUR, Europe; ORR, objective response rate.

- Kaplan-Meier estimates of PFS and OS are shown in **Figure 6**
- Median PFS of the EUR population was generally consistent with the published findings in the FIGHT-202 total study population (Cohort A [N = 107]: 6.9 months [95% CI, 6.2–9.6])[18]

Figure 6. Kaplan-Meier estimates of (A) PFS and (B) OS in EUR Cohort A



CI, confidence interval; EUR, Europe; NE, not evaluable/estimable; OS, overall survival; PFS, progression-free survival.

Safety and Tolerability

- Adverse events (AEs) occurring in >20% of patients (across all EUR cohorts) are presented in **Table 3**
- Among the clinically notable AEs, hyperphosphatemia occurred in 60% of patients (all grade 1 or 2), and was managed with a low phosphate diet, phosphate binders, or dose reduction/interruption
- Hypophosphatemia occurred in 14% of patients and was the most common grade ≥3 AE (9%)
  - None of these events were clinically significant/serious and none led to discontinuation or dose reduction
- Serous retinal detachment occurred in 1 patient (grade 1) and did not result in clinical sequelae
- AEs reported in the EUR population were generally consistent with the published findings in the FIGHT-202 total study population[18]

Table 3. Adverse Events Occurring in >20% of Patients

	N = 35	
Adverse Event, n (%)	All Grades	Grade ≥3
Diarrhea	28 (80)	2 (6)
Alopecia	23 (66)	0
Hyperphosphatemia*	21 (60)	0
Nail toxicity*	21 (60)	2 (6)
Nausea	16 (46)	2 (6)
Constipation	15 (43)	0
Dysgeusia	14 (40)	0
Stomatitis	14 (40)	3 (9)
Dry mouth	13 (37)	0
Abdominal pain	12 (34)	1 (3)
Asthenia	12 (34)	0
Decreased appetite	12 (34)	0
Vomiting	12 (34)	2 (6)
Arthralgia	10 (29)	0
Fatigue	10 (29)	2 (6)
PPES	10 (29)	3 (9)
Dry eye	8 (23)	0
Pyrexia	8 (23)	1 (3)

*Combined MedDRA Preferred Terms.
PPES, palmar-plantar erythrodysesthesia syndrome.

Dose Modifications

- **Dose reductions due to AEs: 20.0%**
  - Most frequent: stomatitis (n = 3), palmar-plantar erythrodysesthesia syndrome (n = 3), and asthenia (n = 2)
- **Dose interruption due to AEs: 57.1%**
  - Most frequent: stomatitis (n = 6), palmar-plantar erythrodysesthesia syndrome (n = 4), pyrexia (n = 3), fatigue (n = 2), and asthenia (n = 2)
- **No discontinuations due to AEs**
- Dose reductions and interruptions due to AEs reported in the EUR population were generally consistent with the published findings in the FIGHT-202 total study population; 9% of patients discontinued treatment due to AEs in the FIGHT-202 total study population[18]

Conclusions

- **The efficacy and safety of pemigatinib in the EUR population of patients with locally advanced or metastatic CCA harboring *FGF/FGFR* alterations were consistent with the published FIGHT-202 total study population results[18]**
- **AEs were manageable and consistent with the mechanism of action of pemigatinib**
- **In EUR cohort A, pemigatinib treatment resulted in:**
  - **ORR of 40.6% with durable responses**
  - **Median PFS of 6.9 months**
- **Twenty-three unique *FGFR2* fusion partners were observed, supporting the use of fusion partner–agnostic testing**
- **The study demonstrates the potential therapeutic benefit of pemigatinib for patients with previously treated locally advanced or metastatic CCA and *FGFR2* fusions or rearrangements**
- **A phase 3 study is ongoing in the first-line setting to evaluate pemigatinib versus gemcitabine plus cisplatin in patients with CCA and *FGFR2* fusions or rearrangements (NCT03656536)**
  - **Participating EUR countries include Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and UK**

Disclosures

Hollebecque: Advisory/Consultancy – *Amgen, AstraZeneca, Debiopharm, Eli Lilly and Company, Incyte Corporation, QED Therapeutics.* **Melisi:** Research funding – *Celgene, Evotec, Incyte Corporation, Shire*; consulting role: *Bayhler, Eli Lilly and Company, Evotec, Incyte Corporation, Shire.* **Vogel:** Advisory/consultancy – *AstraZeneca, Bayer, Bristol Myers Squibb, BTG Specialty Pharmaceuticals, Eisai, Eli Lilly and Company, Incyte Corporation, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi, Servier*; honoraria – *AstraZeneca, Bayer, Bristol Myers Squibb, BTG Specialty Pharmaceuticals, Eisai, Eli Lilly and Company, Incyte Corporation, Ipsen, Janssen, Merck, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi, Servier.* **McNamara:** Honoraria – *Ipsen, Mylan, NuCana*; research funding – *Ipsen, NuCana, Servier (previously SHIRE)*; travel assistance – *Bayer, Ipsen, Novartis.* **Macarulla:** Research support – *AstraZeneca, BeiGene, Celgene*; speakers' bureau honoraria – *Celgene, Incyte Corporation, Raffo, Sanofi, Servier*; consultant/advisory board member – *Amgen, AstraZeneca, Celgene, Incyte Corporation, Servier.* **Van Cutsem:** Advisory/consultancy – *Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Incyte Corporation, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, Servier*; research grant/funding – *Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, Ipsen, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, Servier.* **Zhen, Féliz:** Employment and stock ownership – *Incyte Corporation.* **Abou-Alfa:** Research grants – *ActaBiologica, Agios, AstraZeneca, Bayer, BeiGene, Berry Genomics, Bristol Myers Squibb, Casi, Celgene, Exelixis, Genentech/Roche, Halozyme Therapeutics, Incyte Corporation, MabVax Therapeutics, Puma Biotechnology, QED Therapeutics, SillaJen, Yiviva*; consultancy – *Agios, AstraZeneca, Autem Medical, Bayer, BeiGene, Berry Genomics, Celgene, CytomX, Debiopharm, Eisai, Eli Lilly and Company, Exelixis, Flatiron, Genentech/Roche, Gilead, Helio Heath Group, Incyte Corporation, Ipsen, Loxo Oncology, Merck, MHA Therapeutics, Polaris Group, QED Therapeutics, Redhill Biopharma, Silenseed, SillaJen, Sobi, Therabionics, twoXAR, Vector Pharma, Yiviva.*

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