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Pemigatinib for Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma: Update of FIGHT-202

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Background

- Cholangiocarcinoma (CCA) is the most common primary bile duct cancer[1]; worldwide incidence varies regionally (0.3–3.4 per 100,000 patient-years in North America and Europe)[2] and is higher in certain regions of Asia, particularly Thailand (intrahepatic CCA [iCCA], 2.19 per 100,000 patient-years)[3]
- Second-line chemotherapies for patients with advanced/metastatic disease who have progressed following first-line gemcitabine plus cisplatin have shown limited efficacy, with median overall survival (OS) ranging from 6.2 to 7.2 months[4–6]
- Approximately 40% to 50% of patients with CCA harbor at least 1 clinically actionable genetic alteration, which includes fibroblast growth factor (*FGF*) and/or FGF receptor (*FGFR*) gene alterations[7,8]
- *FGFR2* fusions or rearrangements occur almost exclusively in iCCA and are present in 10% to 15% of patients with iCCA in the United States, Europe, Japan, and China[8–15]
- Pemigatinib is a potent, selective, oral FGFR1–3 inhibitor that demonstrated efficacy and safety in patients with locally advanced or metastatic CCA with *FGFR2* fusions or rearrangements in the pivotal phase 2 FIGHT-202 study (NCT02924376)[16]
- Based on this study, pemigatinib is approved in the United States, European Union, and Japan for previously treated, unresectable, locally advanced or metastatic CCA harboring *FGFR2* fusions or rearrangements[17–19]

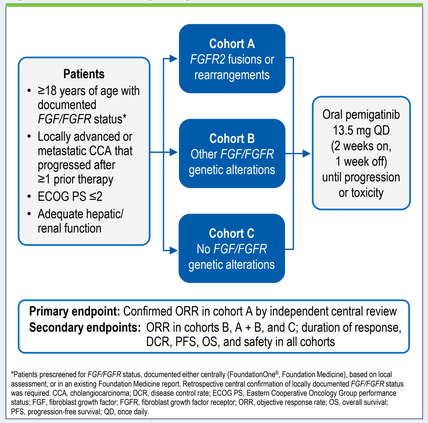
Objective

- To report updated efficacy and safety results for patients enrolled in FIGHT-202 (data cutoff date: April 7, 2020)

Methods

- FIGHT-202 is an ongoing phase 2 single-arm, open-label, multicenter study investigating the efficacy and safety of pemigatinib in patients with locally advanced or metastatic CCA (NCT02924376; **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 in an existing Foundation Medicine report. Retrospective central confirmation of locally documented *FGF/FGFR* status was required. CCA, cholangiocarcinoma; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

Statistical Analysis

- All patients with centrally confirmed *FGF/FGFR* status who received ≥1 dose of study drug were included in the efficacy population
- Survival analyses were conducted using Kaplan-Meier method; 95% confidence interval for objective response rate (ORR) was estimated using the Clopper-Pearson method
- Response assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1
- For the primary endpoint, patients with insufficient baseline or on-study data for adequate assessment of response status were considered nonresponders
- The safety population included all patients who received ≥1 dose of study drug; safety data were summarized using descriptive statistics
- A post hoc analysis compared OS in patients with *FGFR2* fusions or rearrangements achieving complete response (CR) or partial response (PR) ("responders") with those with stable disease (SD) or progressive disease (PD) ("nonresponders")
- The study was not designed to make statistical comparisons between cohorts; no formal hypothesis testing or inferential analyses were conducted

Results

- Full baseline demographics and clinical characteristics, as well as primary efficacy and safety results, have been published previously[16]
  - Briefly, median (range) age was 59 (26–78) years, 58% were female, and most of the patients had iCCA (89%)
  - A majority had metastatic disease (86%), and 39% had received 2 or more prior systemic therapies
- Among 108 patients in cohort A:
  - There were 92 *FGFR2* fusions and 15 rearrangements
  - There were 56 different partner genes (42 partners unique to single patients)
  - Most common fusion partner was *BICC1* (29%)
- At the data cutoff date for this updated analysis, the median duration of follow-up was 30.4 months (**Table 1**)

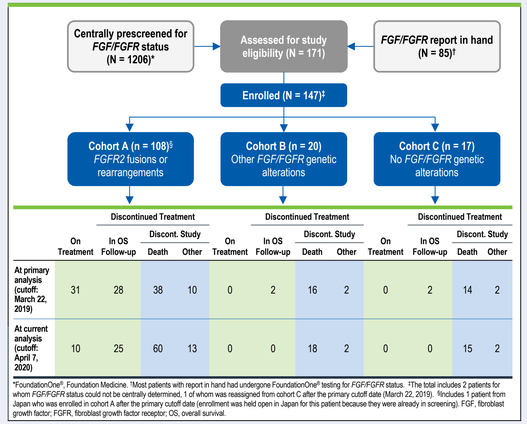
Table 1. Duration of Treatment and Follow-up

Variable	Cohort A (n = 108)* *FGFR2* Fusions or Rearrangements	Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations	Cohort C (n = 17) No *FGF/FGFR* Genetic Alterations	Total (N = 147)†
Duration of treatment, median (range), mo	7.2 (0.2–36.5)	1.4 (0.2–12.9)	1.2 (0.2–4.7)	5.9 (0.2–36.5)
Number of treatment cycles, median (range), n	10.5 (1–52)	2.5 (1–16)	2.0 (1–7)	8.0 (1–52)
Duration of follow-up, median (range), mo	27.9 (4.9–37.2)	32.5 (28.7–36.1)	36.9 (34.5–38.7)	30.4 (4.9–38.7)

*Includes 1 patient from Japan who was enrolled in cohort A after the primary cutoff date (enrollment was held open in Japan for this patient because they were already in screening). †The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined, 1 of whom was reassigned from cohort C after the primary cutoff date (March 22, 2019). FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.

- At the time of the data cutoff for the primary analysis, there were 31 patients in cohort A still on pemigatinib treatment, and an additional 28 patients who had discontinued treatment but were still in the study for survival follow-up[16]
- At the time of the data cutoff for the current analysis, there were 10 patients in cohort A still on pemigatinib treatment and an additional 25 patients still in study (**Figure 2**)
- The ORR for cohort A was 37.0% in this updated analysis with 4 CRs and 36 PRs, and a median duration of response of 8.1 months (**Table 2**)
- The updated median progression-free survival was 7.0 months (**Figure 3, Table 2**), and the updated median OS was 17.5 months (**Figure 4, Table 2**)
- For patients with *FGFR2* fusions or rearrangements, the median OS for patients who responded to pemigatinib with either a CR or PR was 30.1 months; median OS for patients who did not respond to pemigatinib was 13.7 months (**Figure 5, Table 2**)
- No changes in the numbers of patients with CRs or PRs occurred in cohorts B and C in the current vs the primary analysis

Figure 2. Patient Disposition



	Cohort A (n = 108)§				Cohort B (n = 20)				Cohort C (n = 17)			
	On Treatment	In OS Follow-up	Discont. Study Death	Discont. Study Other	On Treatment	In OS Follow-up	Discont. Study Death	Discont. Study Other	On Treatment	In OS Follow-up	Discont. Study Death	Discont. Study Other
At primary analysis (cutoff: March 22, 2019)	31	28	38	10	0	2	16	2	0	2	14	2
At current analysis (cutoff: April 7, 2020)	10	25	60	13	0	0	18	2	0	0	15	2

*FoundationOne®, Foundation Medicine. †Most patients with report in hand had undergone FoundationOne® testing for *FGF/FGFR* status. ‡The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined, 1 of whom was reassigned from cohort C after the primary cutoff date (March 22, 2019). §Includes 1 patient from Japan who was enrolled in cohort A after the primary cutoff date (enrollment was held open in Japan for this patient because they were already in screening). FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; OS, overall survival.

Table 2. Efficacy Outcomes in Patients With *FGFR2* Fusions or Rearrangements (Cohort A)

Variable	Primary Analysis[16] (n = 107)	Current Analysis (n = 108)
ORR (95% CI), %	35.5 (26.5–45.4)	**37.0 (27.9–46.9)**
Best OR,* n (%)		
CR	3 (2.8)	4 (3.7)
PR	35 (32.7)	36 (33.3)
SD	50 (46.7)	49 (45.4)
PD	16 (14.9)	16 (14.8)
Not evaluable†	3 (2.8)	3 (2.8)
DCR (95% CI), %	82.2 (73.7–89.0)	82.4 (73.9–89.1)
mDOR (95% CI), mo	7.5 (5.7–14.5)	8.1 (5.7–13.1)
mPFS (95% CI), mo	6.9 (6.2–9.6)	7.0 (6.1–10.5)
mOS (95% CI), mo	21.1 (14.8–NE)‡	17.5 (14.4–23.0)
Responders	—	30.1 (21.5–NE)
Nonresponders	—	13.7 (9.6–16.2)

*Assessed and confirmed by independent central review. †Postbaseline tumor assessment was not performed owing to study discontinuation (2 participants in cohort A, 4 participants in cohort B, 3 participants in cohort C) or was performed before the minimum interval of 39 days for an assessment of SD (1 participant in cohort A, 1 participant in cohort B). ‡OS not mature at data cutoff used for the primary analysis (March 22, 2019). CI, confidence interval; CR, complete response; DCR, disease control rate; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; OR, objective response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Progression-Free Survival

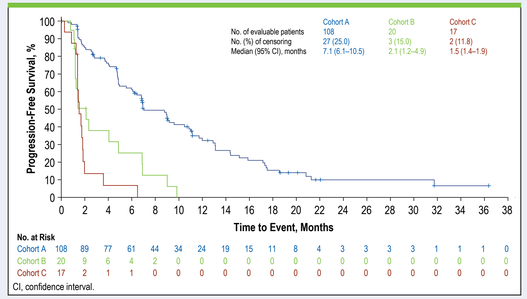


Figure 4. Overall Survival

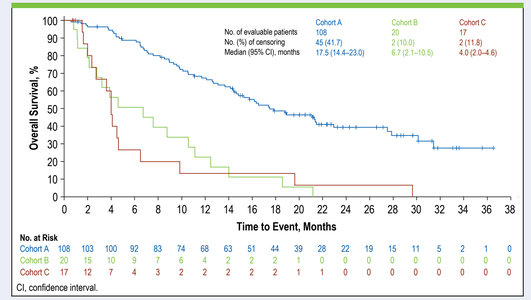
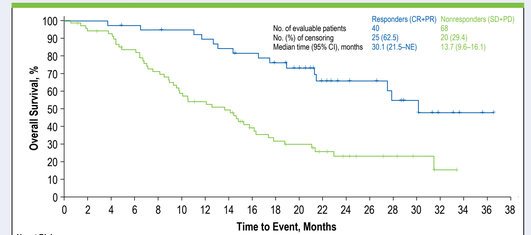


Figure 5. Overall Survival in Responders vs Nonresponders in Patients With *FGFR2* Fusions or Rearrangements (Cohort A)



Safety

- The most common treatment-emergent adverse events of any grade and of grade ≥3 are summarized in **Table 3**
  - Overall, the safety profile observed in the current analysis was consistent with the primary analysis[16] and no new safety signals were observed

Table 3. TEAEs Occurring in ≥25% of Overall Patient Population

Adverse Event, n (%)	Cohort A (n = 108)* *FGFR2* Fusions or Rearrangements		Cohort B (n = 20) Other *FGF/FGFR* Genetic Alterations		Cohort C (n = 17) No *FGF/FGFR* Genetic Alterations		Total (N = 147)†	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hyperphosphatemia	60 (55.6)	0	13 (65.0)	0	12 (70.6)	0	86 (58.5)	0
Alopecia	64 (59.3)	0	4 (20.0)	0	3 (17.6)	0	73 (49.7)	0
Diarrhea	57 (52.8)	4 (3.7)	5 (25.0)	0	6 (35.3)	1 (5.9)	69 (46.9)	5 (3.4)
Fatigue	50 (46.3)	5 (4.6)	5 (25.0)	0	9 (52.9)	3 (17.6)	64 (43.5)	8 (5.4)
Nausea	46 (42.6)	3 (2.8)	7 (35.0)	0	7 (41.2)	0	61 (41.5)	3 (2.0)
Dysgeusia	52 (48.1)	0	3 (15.0)	0	3 (17.6)	0	60 (40.8)	0
Stomatitis	45 (41.7)	9 (8.3)	6 (30.0)	0	3 (17.6)	0	55 (37.4)	9 (6.1)
Constipation	46 (42.6)	1 (0.9)	5 (25.0)	0	2 (11.8)	0	54 (36.7)	1 (0.7)
Decreased appetite	34 (31.5)	1 (0.9)	8 (40.0)	1 (5.0)	7 (41.2)	1 (5.9)	50 (34.0)	3 (2.0)
Dry mouth	42 (38.9)	0	5 (25.0)	0	1 (5.9)	0	50 (34.0)	0
Vomiting	36 (33.3)	2 (1.9)	3 (15.0)	0	4 (23.5)	0	43 (29.3)	2 (1.4)
Dry eye	38 (35.2)	0	1 (5.0)	0	1 (5.9)	0	41 (27.9)	1 (0.7)
Arthralgia	33 (30.6)	7 (6.5)	4 (20.0)	2 (10.0)	1 (5.9)	0	38 (25.9)	9 (6.1)

*Includes 1 patient from Japan who was enrolled in cohort A after the primary cutoff date (enrollment was held open in Japan for this patient because they were already in screening). †The total includes 2 patients for whom *FGF/FGFR* status could not be centrally determined, 1 of whom was reassigned from cohort C after the primary cutoff date (March 22, 2019). TEAE, treatment-emergent adverse event.

Conclusions

- **Overall, 37% of previously treated patients with advanced/metastatic CCA and *FGFR2* fusions or rearrangements achieved a centrally confirmed objective response following treatment with pemigatinib, including 4 patients who had a CR**
- **After a median of 30.4 months of follow-up, the median OS was 17.5 months for patients with *FGFR2* fusions or rearrangements**
  - **Among patients who responded to pemigatinib treatment (CR or PR), median OS was 30.1 months**
  - **Median OS in nonresponders (SD or PD) was 13.7 months, possibly reflecting increased clinical benefit in patients with SD**
- **The adverse event profile remained consistent with data that were previously reported, with no new safety signals emerging with longer-term treatment**
  - **10 patients remained on pemigatinib treatment at the data cutoff date**
- **These results reinforce the primary analysis results,[16] showing durable responses, prolonged OS, and sustained tolerability in patients receiving pemigatinib for advanced/metastatic CCA harboring *FGFR2* fusions or rearrangements**
- **A phase 3 study is ongoing in the first-line setting to evaluate pemigatinib vs gemcitabine plus cisplatin in patients with CCA and *FGFR2* fusions or rearrangements (FIGHT-302; NCT03656536)**

Disclosures

Abou-Alfa: Consulting or advisory role – *Agios, Alnylam Pharmaceuticals, AstraZeneca, Autem Medical, Bayer, BeiGene, Berry Genomics, Celgene, Cytomx, Eisai, Eli Lilly & Company, Exelixis, Flatiron Health, Genentech/Roche, Genoscience Pharma, Helio, Incyte, Ipsen, Legend Biotech, Loxo Oncology, Merck Serono, MINAPHARM, QED Therapeutics, RedHill Biopharma, Rafael Pharmaceuticals, Silenseed, SillaJen, Sobi, Surface Oncology, TheraBionic, twoXAR, Vector Health, Yiviva*; Research funding – *Agios, Arcus, AstraZeneca, Bayer, BioNTech, BMS, Celgene, Flatiron Health, Genentech/Roche, Genoscience Pharma, Incyte, Polaris, Puma Biotechnology, QED Therapeutics, SillaJen, Yiviva*. **Sahai:** Institutional grants – *Incyte* during the conduct of the study; Institutional grants – *Agios, BMS, Celgene, Clovis Oncology, Debiopharm, FibroGen, MedImmune, Merck, National Cancer Institute, Rafael Pharmaceuticals*; Institutional grants and personal fees – *Halozyme Therapeutics, Incyte, Ipsen*; Personal fees – *Klus Pharma, NewLink Genetics, QED Therapeutics*. **Hollebecque:** Grants – *Incyte*, during the conduct of the study; Personal fees – *Amgen, Bayer, Debiopharm, Eisai, Eli Lilly & Company, Incyte, Servier, Spectrum Pharmaceuticals*; Other – *Drug Development Department (DITEP), Gustave Roussy – AstraZeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi*. **Vaccaro:** Personal fees – *Alexion, Amgen, Astellas, Bayer Healthcare, Celgene, Exelixis, Genentech, Incyte, Novartis*; Research funds paid directly to institution – *Astellas, Boston Scientific, Celgene, Eli Lilly & Company, EMD Serono, E.R. Squibb and Sons, Incyte, Merck*. **Melisi:** Grants – *Incyte*, during the conduct of the study; Grants and personal fees – *Celgene, Evotec, Incyte, Ipsen, Servier*; Grants and personal fees – *Baxter, Eli Lilly & Company*. **Al-Rajabi:** Grants – *Incyte*, during the conduct of the study; Grants outside of the institution – *Actinium Pharmaceuticals, Seattle Genetics*; Personal fees – *Sirtex Medical*. **Paulson:** Grants – *Incyte*, during the conduct of the study; Personal fees – *AAA Pharmaceutical, Amgen, Eisai, Incyte, Ipsen*; Grants and personal fees – *BMS, Taiho Pharmaceutical Group, Grants – Exelixis, Incyte*; Other – *Actinium Pharmaceuticals, Alexion, Aptose Biosciences, Immunomedics, Seattle Genetics*. **Borad:** Grants – *Incyte*, during the conduct of the study; Grants – *Adaptimmune, Agios, ARIAD, Basilea, Bioline, Boston BioMed, Celgene, Daiichi Sankyo Pharmaceuticals, EMD Merck Serono, Halozyme Therapeutics, Incyte, Ionis Pharmaceuticals, Medimmune, Mirna Therapeutics, Novartis, Puma Biotherapeutics, QED Therapeutics, Redhill Pharmaceuticals, Senhwa Biosciences, SillaJen, Sun BioPharma, Taiho Pharmaceutical Group, Toray*; Personal fees – *ADC Therapeutics, AstraZeneca, Exelixis, G1 Therapeutics, Immunovative Therapies, Inspyr Therapeutics, Lynx Group, Merck, Western Oncologics*; Other – *AVEO Oncology, Intercept Pharmaceuticals, OncBioMune Pharmaceuticals, Pieris*. **Gallinson:** None. **Murphy:** Grants – *BMS*. **Oh:** Personal fees – *Astan Pharmaceuticals, Bayer, GenentechRoche, Halozyme Therapeutics, Merck Serono, Novartis, Taiho Pharmaceutical Group, Zymeworks*; Grants – *Array, Eli Lilly & Company, Green Cross, Novartis*; Grants and personal fees – *AstraZeneca*. **Dotan:** Grants – *Incyte*, during the conduct of the study; Grants and personal fees – *Boston Medical, Pfizer*; Personal fees – *ARMO Biosciences*; Grants – *AstraZeneca, Incyte, MedImmune, Merck, OncoMed Pharmaceuticals*. **Catenacci:** Grants – *Incyte*, during the conduct of the study; Personal fees – *Astellas, BMS, Eli Lilly & Company, Five Prime, Foundation Medicine, GenentechRoche, Gritstone Oncology, Guardant Health, Merck, Taiho Pharmaceutical Group, Tempus*. **Van Cutsem:** Personal fees – *Incyte*, during the conduct of the study; Personal fees – *Astellas, AstraZeneca, Incyte*; Grants and personal fees – *Bayer, BMS, Celgene, Eli Lilly & Company, Merck KGaA, Merck Sharp & Dohme, Novartis, Roche, Servier*; Grants – *Amgen, Boehringer Ingelheim, Ipsen*. **Lihou, Zhen, Féliz:** Employee and shareholder – *Incyte*. **Vogel:** Personal fees – *Incyte*, during the conduct of the study; Personal fees – *Amgen, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Delcath, Eisai, Eli Lilly & Company, Hengrui, Incyte, Ipsen, Medac Pharma, Merck, Pieris, QED Therapeutics, Roche, Sanofi, Servier, Shire*.

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