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Interim Results of fight-202, A Phase 2, Open-Label, Multicenter Study of INCB054828 in Patients With Previously Treated Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma (CCA) With/Without Fibroblast Growth Factor (*FGF*)/FGF Receptor (*FGFR*) Genetic Alterations

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Presented at the
European Society for Medical Oncology Congress 2018
Munich, Germany
October 19 - October 23, 2018

Background

- Cholangiocarcinoma (CCA) is a rare malignancy. There are no well established second-line regimens after failure of first-line therapy with gemcitabine and cisplatin. The median overall survival (OS) and progression-free survival (PFS) of patients receiving second-line therapy are 7.2 and 3.2 months, respectively[1]
- Dysregulation of FGFR signaling by *FGFR* translocations may be involved in the pathogenesis of CCA[2,3]
- *FGFR2* translocations occur almost exclusively in patients with intrahepatic CCA (iCCA) at an incidence of 13%–17%[4-6]

Table 1. Prevalence of FGFR Aberrations in Select Tumor Types

Gene	Aberration	Tumor Location/Type	Prevalence
FGFR1	Translocation	8p11 myeloproliferative syndrome	100%[7]
FGFR2	Translocation	Cholangiocarcinoma (intrahepatic)	13%–17%[4-6]
FGFR3	Mutation	Bladder (non–muscle invasive)	50%–60%[8]
FGFR3	Mutation	Bladder (muscle invasive)	10%–15%[8]
FGFR3	Translocation	Bladder (muscle invasive)	6%[8]

- Pemigatinib (INCB054828), a selective, potent, oral inhibitor of FGFR1, 2, and 3, has shown efficacy in patients with *FGF/FGFR* genetically altered tumors[9]
- Fibroblast Growth Factor Receptor Inhibitor in Oncology and Hematology Trials (fight)-202 is a phase 2, open-label, multicenter study evaluating the efficacy and safety of pemigatinib in patients with advanced/metastatic or surgically unresectable CCA with *FGFR2* translocation (NCT02924376)

Objective

- To present results of an interim analysis from the fight-202 study based on data from the first 47 patients with *FGFR2* translocations enrolled in cohort A and followed for ≥ 8 months

Methods

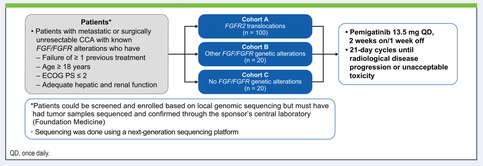
Key Inclusion Criteria

- Patients with histologically or cytologically confirmed CCA who failed ≥ 1 prior treatment
- Documentation of *FGF/FGFR* gene alteration status
- Radiographically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2
- Adequate hepatic function
  - Total bilirubin < 1.5 × upper limit of normal (ULN); < 2.5 × ULN for patients with Gilbert syndrome or metastatic disease involving liver
  - Aminotransferases ≤ 2.5 × ULN; ≤ 5 × ULN for patients with liver metastases
- Adequate renal function
  - Creatinine clearance > 30 mL/min
- Serum phosphate ≤ institutional ULN
- Serum calcium within institutional normal range

Key Exclusion Criteria

- No prior treatment with select FGFR inhibitors
- History of calcium phosphate homeostasis or ectopic mineralization/calcification
- Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination

Figure 1. Phase 2, Open-label Multinational Study



Study Endpoints

Primary endpoint:

- Overall response rate (ORR) in cohort A, assessed by independent review per RECIST v1.1

Secondary endpoints:

- ORR in cohort B, cohort C, and cohorts A + B
- Duration of response (DOR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety and tolerability

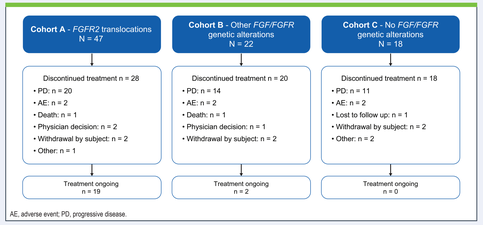
Statistical Methods

- Safety analyses are performed on all patients enrolled in the study who received ≥ 1 dose of study drug; efficacy analyses are performed on all patients enrolled in the study who received ≥ 1 dose of study drug and who have a known *FGF/FGFR* alteration or who have a negative *FGF/FGFR* alteration from the central genomics laboratory
- Primary endpoint, ORR in cohort A: proportion of patients with the best response (complete response [CR], or partial response [PR]) by RECIST v1.1
  - An ORR of 33% is considered clinically meaningful in this setting, and a sample size of 100 patients is estimated to provide >95% probability to have a 95% CI with a lower limit of >15%
  - The 95% CI for ORR is estimated using the Clopper-Pearson method

Disposition

- The data cut (24 Jul 2018) included a total of 91 patients in cohort A; the analysis focuses on the first 47 patients enrolled in cohort A who were followed for ≥ 8 months; 22 and 18 patients in cohorts B and C, respectively, are included **(Figure 2)**
- Median number of treatment cycles in cohort A was 11 (range, 1-23); median duration of treatment was 217 days (range, 14-489)
- Median number of cycles in cohort B was 2.5 (1-14); median duration of treatment was 47.5 days (range, 7-287)
- Median number of cycles in cohort C was 2.0 (1-7); median duration of treatment was 39 days (range, 7-142)

Figure 2. Patient Disposition by Cohort



AE, adverse event; PD, progressive disease.

Results

Baseline Demographics and Disease Characteristics

- Baseline and disease characteristics are presented for all cohorts in **Table 1**
- In cohort A, median age of patients was 55 years (range, 26-76), 53.2% were female, and 98% had iCCA
  - 98% of patients had ECOG PS ≤ 1
  - 49% of patients received ≥ 2 prior therapies
  - 94% of patients were from regions other than Asia
  - 66% of patients had Stage 4 disease at enrollment
  - 1 patient each had a history of chronic hepatitis B or hepatitis C
  - The most common *FGFR2* translocation was *FGFR2-BICC1* (29.8%), followed by *FGFR2-AHCYL1* (4.3%), *FGFR2-MACF1* (4.3%), and *FGFR2* intron 17 rearrangement (4.3%) **(Table 2)**

Table 1. Baseline Demographics and Disease Characteristics

	Cohort A (n = 47)	Cohort B (n = 22)	Cohort C (n = 18)
Age, median (range), years	55 (26-76)	63 (28-78)	65 (31-78)
Sex, n (%)			
Male	22 (46.8)	11 (50.0)	10 (55.6)
Female	25 (53.2)	11 (50.0)	8 (44.4)
Region, n (%)			
Asia	3 (6.4)	11 (50.0)	0 (0.0)
Outside of Asia	44 (93.6)	11 (50.0)	18 (100.0)
ECOG PS, n (%)			
0	15 (31.9)	7 (31.8)	7 (38.9)
1	31 (66.0)	12 (54.5)	8 (44.4)
2	1 (2.1)	3 (13.6)	3 (16.7)
Number of prior systemic therapies, n (%)			
1	24 (51.1)	13 (59.1)	11 (61.1)
2	15 (31.9)	5 (22.7)	3 (16.7)
≥3	8 (17.0)	4 (18.2)	4 (22.2)
Prior surgery, n (%)	16 (34.0)	7 (31.8)	6 (33.3)
Prior radiation, n (%)	9 (19.1)	4 (18.2)	5 (27.8)
Stage at initial diagnosis, n (%)			
1	5 (10.6)	1 (4.5)	1 (5.6)
2	6 (12.8)	1(4.5)	1 (5.6)
3	3 (6.4)	3 (13.6)	1 (5.6)
4	31 (66.0)	17 (77.3)	12 (66.7)
Missing	2 (4.3)	0 (0.0)	3 (16.7)
Tumor location, n (%)			
Intrahepatic	46 (97.9)	15 (68.2)	11 (61.1)
Extrahepatic	0 (0.0)	3 (13.6)	7 (38.9)
Other	0 (0.0)	4 (18.2)	0 (0.0)
Unknown	1 (2.1)	0 (0.0)	0 (0.0)
History of hepatitis, n (%)			
Chronic hepatitis B	1 (2.1)	1 (4.5)	0 (0.0)
Hepatitis C	1 (2.1)	1 (4.5)	0 (0.0)

Table 2. *FGFR2* Translocations in Cohort A

FGFR2 Translocation, n (%)	Cohort A (n = 47)
FGFR2-BICC1	14 (29.8)
FGFR2-AHCYL1	2 (4.3)
FGFR2-MACF1	2 (4.3)
FGFR2 intron 17 rearrangement	2 (4.3)
FGFR-NEDD4L	1 (2.1)
FGFR2-SOGA1	1 (2.1)
FGFR2-POC1B	1 (2.1)
FGFR2-NOL4	1 (2.1)
FGFR2-ACLY	1 (2.1)
FGFR2-SLMAP	1 (2.1)
FGFR2-FILIP1	1 (2.1)
FGFR2-SPICE1	1 (2.1)
FGFR2-KIAA1217/FGFR2 exon 1-17	1 (2.1)
FGFR2-KIAA1217	1 (2.1)
FGFR2-TTC28	1 (2.1)
FGFR2-CCDC158	1 (2.1)
FGFR2-AFR	1 (2.1)
FGFR2-SHROOM	1 (2.1)
FGFR2-NRAP	1 (2.1)
FGFR2-COL16A1	1 (2.1)
FGFR2-GOPC	1 (2.1)
FGFR2-NOL4	1 (2.1)
FGFR2 amp/*FGFR2-RABPGAP1L* and *FGFR2-LAMC1*	1 (2.1)
FGFR2-ARH GAP24	1 (2.1)
FGFR2-PAWR	1 (2.1)
FGFR2-GAB2	1 (2.1)
FGFR2-RASSF4	1 (2.1)
FGFR2-ARHGAP24	1 (2.1)
FGFR2-TACC1	1 (2.1)
FGFR2-STRN4	1 (2.1)
FGFR2-ATF2	1 (2.1)

Efficacy

Primary endpoint:

- ORR in cohort A was 40.4% (95% CI, 26.4%-55.7%) **(Table 3)**
  - 19 patients (40.4%) had a confirmed PR **(Figures 3 and 4)**
  - 21 patients (44.7%) had best response of stable disease (SD)

Secondary endpoints:

- Median DOR in cohort A has not been reached; the probability of maintaining response ≥ 6 months was 86.2% (95% CI, 55.0%-96.4%) **(Table 3)**
- DCR was 85.1% in cohort A **(Table 3)**
  - DCR in cohorts B and C was 45.5% and 22.2%, respectively

Table 3. Primary and Secondary Endpoints by Patient Cohort (Assessed by Independent Reviewer)

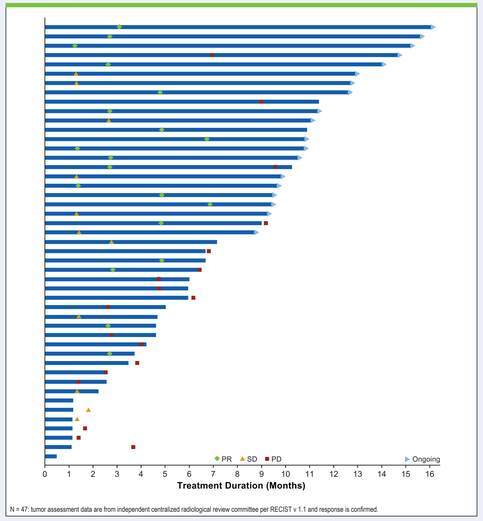
Variable	Cohort A (n = 47)	Cohort B (n = 22)	Cohort C (n = 18)
ORR, % (95% CI)	40.4 (26.4-55.7)	0 (0.0-15.4)	0 (0.0-18.5)
Best OR, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	19 (40.4)	0 (0.0)	0 (0.0)
SD	21 (44.7)	10 (45.5)	4 (22.2)
PD	5 (10.6)	7 (31.8)	10 (55.6)
NE	2 (4.3)	5 (22.7)	4 (22.2)
Median DOR, months (95% CI)	NE (6.93-NE)	NE (NE-NE)	NE (NE-NE)
DCR, % (95% CI)	85.1 (71.7-93.8)	45.5 (24.4-67.8)	22.2 (6.4-47.6)

NE = not evaluable, upper limit was not reached.

Figure 3. Best Percentage Change From Baseline in Target Lesion Size in Patients With CCA and *FGFR2* Translocations as per Independent Reviewer (Cohort A)

N = 44: excludes 3 patients (n = 1 NE, patient died before the first assessment; n = 2 SD, no target lesions).
[a] Patient had a response of SD, and a best percentage change from baseline of 0.0%.

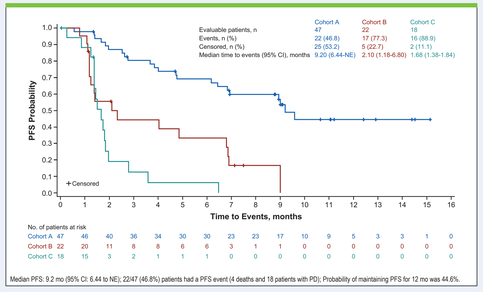
Figure 4. Duration of Treatment and Confirmed Response in Patients With CCA and *FGFR2* Translocations as per Independent Reviewer (Cohort A)



N = 47; tumor assessment data are from independent centralized radiological review committee per RECIST v 1.1 and response is confirmed.

- Median PFS was 9.2 months in cohort A **(Figure 5)**
  - Median PFS in cohorts B and C were 2.1 and 1.7 months, respectively
- Median OS was 15.8 months in cohort A
  - Median OS in cohorts B and C were 6.8 and 4.0 months, respectively

Figure 5. Kaplan-Meier Estimates of PFS (Assessed by Independent Reviewer)



Median PFS: 9.2 mo (95% CI: 6.44 to NE); 22/47 (46.8%) patients had a PFS event (4 deaths and 18 patients with PD); Probability of maintaining PFS for 12 mo was 44.6%.

Safety and Tolerability

- The most common treatment-emergent adverse events (TEAEs) in all patients were hyperphosphatemia (60.7%), alopecia (41.6%), diarrhea (39.3%), decreased appetite (37.1%), fatigue (36.0%), and dysgeusia (36.0%) **(Table 4)**
  - Hyperphosphatemia was managed with diet, phosphate binders, or dose modification
- Grade ≥ 3 TEAEs in > 5% of all patients were hypophosphatemia (13.5%), hyponatremia (7.9%), abdominal pain (6.7%), and arthralgia (6.7%)
- Five patients had TEAEs with a fatal outcome, none were related to study treatment
  - Cohort A: 1 patient died due to failure to thrive
  - Cohort B: 3 patients died due to abdominal distension, sepsis, malignant neoplasm progression, dyspnea, and pleural effusions
  - Cohort C: 1 patient died due to cholangitis

Table 4. Most Common TEAEs and TRAEs Occurring in ≥ 20%[a] of Patients With CCA

	TEAEs - All Cohorts (N = 89)[b]		TRAEs - All Cohorts (N = 89)[b]	
Adverse event, n (%)	All Grades	Grade 3/4	All Grades	Grade 3/4
Hyperphosphatemia	54 (60.7)	0 (0.0)	49 (55.1)	0 (0.0)
Alopecia	37 (41.6)	0 (0.0)	33 (37.1)	0 (0.0)
Diarrhea	35 (39.3)	2 (2.2)	26 (29.2)	2 (2.2)
Decreased appetite	33 (37.1)	2 (2.2)	22 (24.7)	1 (1.1)
Fatigue	32 (36.0)	4 (4.5)	21 (23.6)	1 (1.1)
Dysgeusia	32 (36.0)	0 (0.0)	31 (34.8)	0 (0.0)
Constipation	27 (30.3)	0 (0.0)	10 (11.2)	0 (0.0)
Stomatitis	27 (30.3)	3 (3.4)	24 (27.0)	3 (3.4)
Dry mouth	26 (29.2)	0 (0.0)	21 (23.6)	0 (0.0)
Nausea	26 (29.2)	0 (0.0)	14 (15.7)	0 (0.0)
Hypophosphatemia	23 (25.8)	12 (13.5)	9 (10.1)	5 (5.6)
Arthralgia	21 (23.6)	6 (6.7)	10 (11.2)	4 (4.5)
Edema peripheral	20 (22.5)	1 (1.1)	3 (3.4)	0 (0.0)
Dry eye	18 (20.2)	1 (1.1)	12 (13.5)	1 (1.1)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a] Patients were counted once under each Medical Dictionary for Regulatory Activities (MedDRA) preferred term.
[b] Two patients were classified as "other" due to having no *FGF/FGFR* alteration confirmed by central lab, therefore, no cohort assignment was done.

Conclusions

- **In this interim analysis of patients from cohort A who had at least 8 months follow up, pemigatinib was generally well tolerated and demonstrated preliminary efficacy in previously treated patients with CCA harboring *FGFR2* translocations**
  - **The ORR was 40.4%**
  - **Most common TEAEs included hyperphosphatemia, alopecia, and diarrhea**
- **Overall, these results support continued development of pemigatinib as a promising treatment for patients with CCA harboring *FGFR2* translocations**
- **Patient recruitment is close to completion and presentation of data from the total study population is planned**

Disclosures

Hollebecque: *Servier, Merck Serono, Amgen, Gritstone Oncology*. **Borad:** *Incyte*. **Sahai:** *NewLink Genetics, Halozyme, Celgene, Bristol-Meyers Squibb*. **Catenacci:** *Merck, Bristol-Meyers Squibb, Eli Lilly and Company, Five Prime, Genentech/Roche, Amgen, Taiho, Foundation Medicine, Guardant Health*. **Murphy:** *Bristol-Meyers Squibb*. **Vaccaro:** *Exelixis, Celgene, Merck Sharpe and Dohme, Eli Lilly and Company, Astellas, EMD Serono, Incyte, Bristol-Meyers Squibb, Array BioPharma, NewLink Genetics*. **Paulson:** *Immunomedics, Ipsen, Bristol-Meyers Squibb, Eisai, Taiho, Merrimack*. **Oh:** *AstraZeneca*. **Féliz:** *Incyte* – Employment and Stock Ownership. **Lihou:** *Incyte* – Employment and Stock Ownership. **Zhen:** *Incyte* – Employment and Stock Ownership. **Abou-Alfa:** *Agios, Amgen, Antengene, Aptus, Aslan, Astellas, Array BioPharma, AstraZeneca, Bayer, Bristol-Meyers Squibb, Boston Scientific, Carsgen, Casi, Celgene, CytomX, Daiichi, Debio, Delcath, Eisai, Eli Lilly and Company, Exelixis, Genentech, Gilead, Halozyme, Incyte, Inovio, Ipsen, Mabvax, Medimmune, Momenta, Novartis, OncoMed Pharmaceuticals, Merck, Onxeo, PCI Biotech, Roche, Sanofi, Servier, Silenseed, Sillajen, Sirtex, Vicus, Yakult*.

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study. This study was sponsored by Incyte Corporation (Wilmington, DE). Medical writing assistance was provided by Michael R. Convente, PhD, of Scientific Pathways, Inc (Hamilton, NJ), and funded by Incyte Corporation.

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