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Comprehensive Genomic Profiling and Clinical Outcomes in Patients With Fibroblast Growth Factor Receptor Rearrangement-Positive Cholangiocarcinoma Treated With Pemigatinib in the FIGHT-202 Trial

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Background

- Cholangiocarcinomas (CCA) are heterogeneous tumors classified as intrahepatic and extrahepatic (perihilar and distal), based on biliary tract location; intrahepatic CCA incidence is steadily increasing, as is the associated mortality rate[1]
- First-line treatment for locally advanced or metastatic CCA is gemcitabine/cisplatin[2]
  - Second-line chemotherapies have shown limited efficacy (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%)[3-5]
- Several potentially actionable oncogenic alterations occur in CCA,[6-8] including *FGFR2* fusions/rearrangements, which occur predominantly in intrahepatic CCA (prevalence, 10–16%)[9-11]
- Pemigatinib is a selective, potent oral inhibitor of FGFR1, 2, and 3
- FIGHT-202 is a phase 2 study of pemigatinib (INCB054828) in patients with previously treated locally advanced or metastatic CCA (NCT02924376)
- Efficacy and safety data for 107 *FGFR2*+ CCA patients (*FGFR2*+ = CCA harboring *FGFR2* fusions/rearrangements) enrolled in FIGHT-202 were reported at this meeting (abstract #2550)

Parameter	Value
Median follow-up	15.4 (range, 7.0–24.7) months
Objective response rate	35.5% (95% CI, 26.5–45.4%)
Disease control rate	82% (95% CI, 74–89%)
Median duration of response	7.5 (95% CI, 5.7–14.5) months
Median progression-free survival	6.93 (95% CI, 6.2–9.6) months
Median overall survival (not mature at data cutoff)	21.1 (95% CI, 14.8–not estimable) months

CI, confidence interval.

- In CCA, *FGFR2* rearrangements occur with a large number of partner genes; whether *FGFR2* partner gene has an impact on response/survival associated with FGFR inhibitor treatment remains unresolved. Furthermore, *FGFR2* rearrangements co-occur with other genomic alterations, which may impact response to therapy

Objectives

- We investigated the relationship between these genomic features and clinical outcomes in patients with *FGFR*+ CCA receiving pemigatinib in FIGHT-202

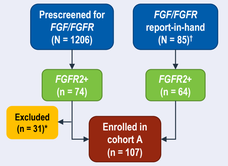
Methods

- Archival, formalin-fixed, paraffin-embedded tumor samples from all patients, prescreened or enrolled, were analyzed for genomic alterations using targeted next-generation DNA sequencing (FoundationOne®, Foundation Medicine Inc., Cambridge, MA, USA). This broad-based genomic panel identifies mutations, rearrangements, and amplifications in 315 cancer genes
- Data visualization and statistical analysis were performed using SAS (Enterprise Guide 7.1) and R (v.3.5.2). Statistical analysis for PFS and OS were performed using a log-likelihood ratio test. Molecular operating environment (Chemical Computing Group Inc., Montreal, QC, Canada) was used for in silico modeling
- Note on nomenclature: *FGFR2* fusions (which are predicted based on FoundationOne® alteration criteria) and rearrangements are collectively referred to as *FGFR2* rearrangements throughout this poster

Prescreening and Enrollment

- *FGFR2*+ rate by country and region

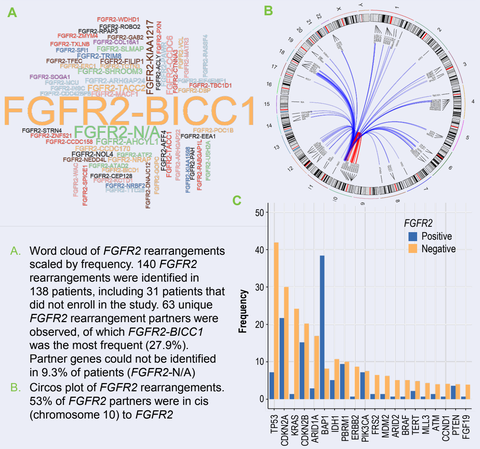
Region	Country	*FGFR2*+, n	N	Frequency	Region
United States	US	21	138	15.2%	15.2%
Europe	France	10	107	9.4%	7.4%
	UK	7	81	8.6%	
	Germany	5	61	8.2%	
	Belgium	4	50	8.0%	
	Italy	13	171	7.6%	
	Spain	3	99	3.0%	
Rest of world	Thailand	2	32	6.2%	2.2%
	Israel	1	25	4.0%	
	Taiwan	1	44	2.3%	
	Korea	5	283	1.8%	
	Japan	2	115	1.7%	



*31 *FGFR2*+ patients not meeting other eligibility criteria were excluded. †Reflects patients with a signed ICF (none were excluded); 21 patients with reports in-hand were enrolled in cohorts B/C or other.

- Prescreening and recruitment cohort diagram (right). 1206 patients were successfully centrally prescreened for FIGHT-202, of whom 74 (6.1%) were *FGFR2*+ and 43 were enrolled in cohort A. An additional 64 patients with *FGFR2*+ reports in-hand and with a signed ICF were enrolled in cohort A. All patients in cohort A were centrally validated

FGFR2 Rearrangements and Co-occurring Alterations



A. Word cloud of *FGFR2* rearrangements scaled by frequency. 140 *FGFR2* rearrangements were identified in 138 patients, including 31 patients that did not enroll in the study. 63 unique *FGFR2* rearrangement partners were observed, of which *FGFR2-BICC1* was the most frequent (27.9%). Partner genes could not be identified in 9.3% of patients (*FGFR2*-N/A)

B. Circos plot of *FGFR2* rearrangements. 53% of *FGFR2* partners were in cis (chromosome 10) to *FGFR2*

C. Frequency of co-alterations in *FGFR2*+ versus *FGFR2*− patients (without *FGFR2* fusions/rearrangements) prescreened in this study. *BAP1* alterations were enriched in *FGFR2*+ patients (38.7% *FGFR2*+ vs 8.2% *FGFR2*−). All other recurrent alterations were less frequent in *FGFR2*+ patients, including *TP53*, *KRAS*, and *ERBB2*. *FGFR2* and *IDH1* alterations were not mutually exclusive (5.1% *FGFR2*+)

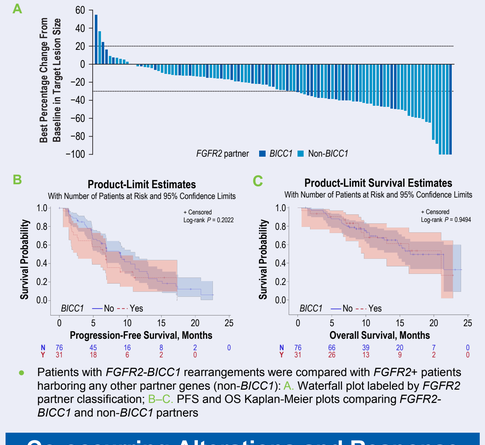
Genomic Correlates of Response to Pemigatinib in *FGFR2*+ CCA

Group (n)		ORR, %	mPFS (95% CI), mo	*P* Value	mOS (95% CI), mo	*P* Value*
FGFR2+ population (107)		35.5	6.9 (6.2–9.6)	—	21.1 (14.8–NE)	—
Alteration classification	Fusion (92)	34.8	7.0 (6.0–10.5)	0.79	21.1 (15.3–NE)	0.41
	Rearrangement (15)	40.0	6.9 (4.7–11.7)		11.7 (7.1–NE)	
FGFR2 partner	Non-BICC1 (76)	36.8	9.0 (6.2–11.1)	0.20	16.5 (14.7–NE)	0.95
	BICC1 (31)	32.3	6.8 (2.6–8.9)		21.1 (9.8–NE)	
BAP1	Unaltered (68)	30.9	9.1 (6.2–11.7)	0.06	21.1 (15.3–NE)	0.35
	Altered (39)	43.6	6.9 (4.7–8.9)		14.8 (10.5–NE)	
CDKN2A/B	Unaltered (86)	38.4	**9.0 (6.4–11.1)**	**0.03**	21.1 (14.6–NE)	0.52
	Altered (21)	23.8	**6.4 (1.7–6.9)**		NE (6.5–NE)	
PBRM1	Unaltered (97)	36.1	**7.0 (6.8–10.5)**	**0.05**	21.5 (15.2–NE)	0.10
	Altered (10)	30.0	**4.7 (1.4–10.8)**		10.5 (2.0–21.1)	
TP53	Unaltered (98)	38.8	**9.0 (6.8–11.1)**	**0.0003**	21.1 (15.2–NE)	0.0014
	Altered (9)	0	**2.8 (1.4–6.8)**		9.8 (1.9–15.77)	
PIK3CA	Unaltered (98)	35.7	8.8 (6.4–10.5)	0.10	21.1 (14.7–NE)	0.81
	Altered (9)	33.3	5.2 (1.5–11.1)		NE (2.0–NE)	
IDH1	Unaltered (102)	36.3	6.9 (6.1–9.6)	0.28	16.5 (14.6–NE)	0.11
	Altered (5)	20.0	NE (1.4–NE)		NE (NE–NE)	

CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate.
*mOS data were not mature as of the data cutoff date.

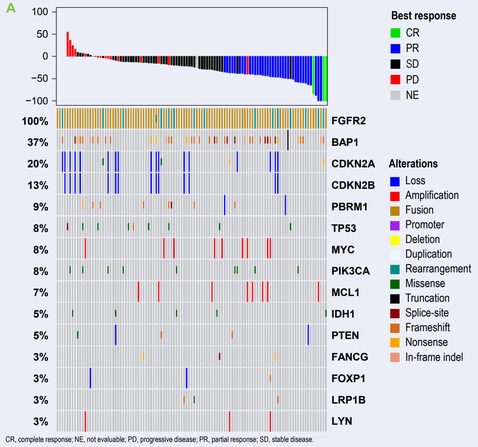
- Relationship between genomic features and ORR, PFS, and OS was assessed for patients in cohort A. 95% confidence intervals (CI) were calculated for median PFS (mPFS) and median OS (mOS). Reported *P* values are derived from the log-likelihood ratio test. Genomic features with significantly different mPFS values are bolded. Alteration classification as fusion or rearrangement was based on FoundationOne criteria

FGFR2-BICC1 Rearrangements and Response to Pemigatinib



- Patients with *FGFR2-BICC1* rearrangements were compared with *FGFR2*+ patients harboring any other partner genes (non-*BICC1*): A. Waterfall plot labeled by *FGFR2* partner classification; B–C. PFS and OS Kaplan-Meier plots comparing *FGFR2-BICC1* and non-*BICC1* partners

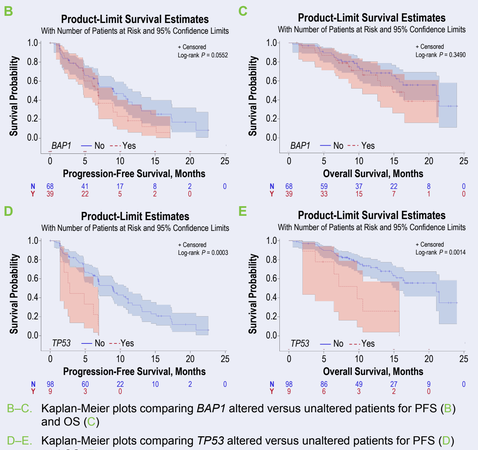
Co-occurring Alterations and Response to Pemigatinib (*FGFR2*+)



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

A. Genomic analysis of frequent co-occurring alterations in *FGFR2*+ patients treated with pemigatinib. Patients were sorted by tumor shrinkage and colored by best response (top panel). One patient had co-occurring *FGFR2* missense mutation (see acquired resistance) due to confirmatory sample being collected at progression

Co-occurring Alterations and Response to Pemigatinib (*FGFR2*+) – Continued



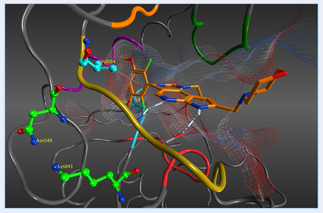
B–C. Kaplan-Meier plots comparing *BAP1* altered versus unaltered patients for PFS (B) and OS (C)

D–E. Kaplan-Meier plots comparing *TP53* altered versus unaltered patients for PFS (D) and OS (E)

Acquired Resistance to Pemigatinib

Patient #	% Change From Baseline	BOR	PFS, Days	*FGFR2* Rearrangement	Acquired *FGFR2* Alterations (Allele Frequency)*
1	−15.7	SD	399	FGFR2-NRBF2	N549K (23.19%)
2	−60.5	PR	483 (censored)	FGFR2-KIAA1217	K659M (6.07%)
3	−58.2	PR	211	FGFR2-CCDC170	K641R (3.50%), N549K (4.03%)

*Acquired resistance mutations were identified in post-progression tumor biopsies using FoundationOne®.



- Acquired resistance mutations in FGFR2 were observed in 3 patients that responded or had prolonged stable disease on pemigatinib followed by progressive disease. FGFR2 p.N549K was the most frequently observed resistance mutation. One patient (#3) developed polyclonal resistance. PFS for patient #2 is censored due to still being on treatment at the time of data cutoff
- In silico structural modeling of pemigatinib (orange sticks) docking into the FGFR2 hinge domain[12] with the identified resistance mutations (green ball and sticks) and the gatekeeper residue (p.V564; cyan ball and sticks). The electrostatic binding pocket surface shown in mesh

Discussion

- Here we report detailed molecular analysis of patients receiving pemigatinib for advanced CCA enrolled in the FIGHT-202 trial. All patients were analyzed using comprehensive genomic profiling allowing for insights into the molecular basis of response. *FGFR2* rearrangements have been reported to be highly promiscuous with respect to partner gene; however, this is the first study with sufficient power to investigate the relationship between partner gene and response to FGFR inhibition. Furthermore, the relationship between co-occurring genomic alterations and response to pemigatinib was investigated. Post-progression tissue biopsies were collected from a small number of patients (n = 3), allowing identification of pemigatinib resistance mutations

Conclusions

- **Of 1206 patients prescreened, 74 were *FGFR2*+ (6.1%), of whom, 43 were enrolled in cohort A (64 *FGFR2*+ patients with reports in-hand and with a signed ICF were also enrolled in cohort A for a total of 107 patients)**
  - **FGFR2+ rates were highest in the United States (15.2%) and lowest in the rest of world (2.2%)**
- **64 unique *FGFR2* rearrangement partner genes were observed in 138 patients**
  - ***FGFR2-BICC1* was the most frequent rearrangement (27.9%) followed by *FGFR2* intron 17 rearrangements (*FGFR2*-N/A) (9.3%)**
  - ***FGFR2* partner genes were found on most chromosomes**
- ***FGFR2* partner gene did not have an on impact on clinical response to pemigatinib**
  - **Classification of *FGFR2* alteration as a fusion or rearrangement did not have an impact on clinical outcomes**
- ***BAP1* was the most frequent and most enriched co-occurring alteration in *FGFR2*+ CCA (38.7% *FGFR2*+ vs 8.2% *FGFR2*−)**
  - **Co-occurring *BAP1* alterations showed different impacts on clinical response to pemigatinib**
    - ***BAP1*+ had higher response rate (43.6% vs 30.9%) but shorter mPFS and mOS (not significant)**
- ***TP53* alterations were depleted in *FGFR2*+ patients (7.2% *FGFR2*+ vs 41.9% *FGFR2*−)**
  - **No responses were observed in patients with *TP53* alterations (0 of 9)**
  - **mPFS was significantly shorter in *TP53*+ patients (*P* = 0.0003)**
- **Patients with *CDKN2A/B* or *PBRM1* alterations had significantly shorter mPFS compared with unaltered patients (*P* < 0.05)**
- ***FGFR2* and *IDH1* are not mutually exclusive but rarely co-occur**
  - **Five patients treated in the study had both an *IDH1* alteration and an *FGFR2* rearrangement, one of which had a complete response**
- **Acquired resistance mutations in kinase domain of FGFR2 were observed in tissue biopsies from 3 patients. One patient had polyclonal resistance**
  - **Acquired resistance mutations were found in the hinge region (p.N549K, p.K641R) and activation loop (p.K659M), consistent with previous reports of acquired resistance to FGFR inhibitors**

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Disclosures

Hollebecque: Grants – *AstraZeneca, BMS, Boehringer Ingelheim, Incyte Corporation, Janssen Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi*; personal fees – *Amgen, Bayer, Debiopharm, Eli Lilly, Eisai, Incyte Corporation, Servier, and Spectrum Pharmaceuticals*; other – *Drug Development Department (institutional financial interests)*. **Melisi**: Grants – *Celgene, Evotec, Incyte Corporation, iOncitura, and Shire*; personal fees – *Baxter, Eli Lilly, Evotec, Incyte Corporation, iOncitura, and Shire*. **Silverman, Owens, Lihou, Feliz, Zhen, Newton, Burn**: Employment and stock ownership – *Incyte Corporation*.

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