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Comprehensive Genomic Profiling in FIGHT-202 Reveals the Landscape of Actionable Alterations in Advanced Cholangiocarcinoma

Ian M. Silverman,[1] Karthikeyan Murugesan,[2] Christine F. Lihou,[3] Luis Féliz,[3] Garrett M. Frampton,[2] Robert C. Newton,[1] Hiroomi Tada,[1] Lee A. Albacker,[2] Timothy C. Burn[1]

[1]Incyte Research Institute, Wilmington, DE; [2]Foundation Medicine, Cambridge, MA; [3]Incyte Corporation, Wilmington, DE

Introduction and Methods

Genomic studies of cholangiocarcinoma (CCA) have identified actionable somatic alterations in multiple genes including *IDH1*, *IDH2*, *FGFR2*, and *BRAF*, but no targeted therapies have been approved for this indication. Pemigatinib (formerly INCB054828) is a selective FGFR1-3 inhibitor currently being evaluated in multiple tumor types, including advanced CCA harboring *FGFR2* rearrangements. Comprehensive genomic profiling (CGP) was used to identify and enroll advanced CCA patients with *FGFR2* rearrangements into FIGHT-202 (NCT02924376), an open-label, phase 2 clinical trial. Here we provide an overview of the genomic landscape of advanced CCA and identify potential actionable alterations based on a next-generation sequencing panel screening approach.

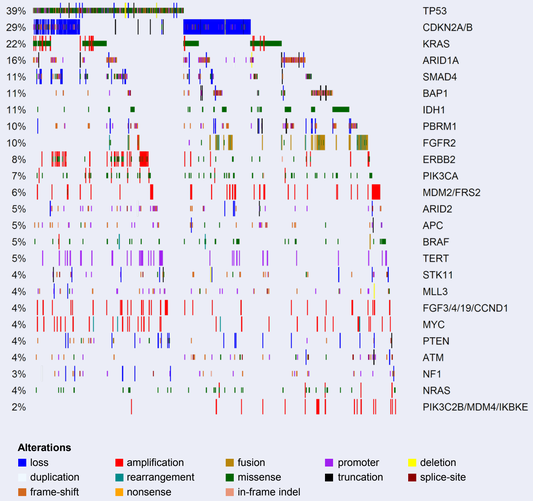
CGP was performed on tumor samples from 1104 patients with advanced CCA using FoundationOne. This broad-based genomic panel identifies mutations, rearrangements, and amplifications in 315 cancer genes. Co-occurrence and mutual exclusivity analysis were performed using Fisher exact test.

Patient Characteristics

Characteristic	Category	Number	Percentage
Country	South Korea	279	25.3
	Italy	169	15.3
	United States	156	14.1
	France	105	9.5
	Spain	89	8.1
	United Kingdom	82	7.4
	Germany	61	5.5
	Belgium	50	4.5
	Taiwan	44	4.0
	Thailand	32	2.9
	Israel	27	2.5
	Japan	10	0.9
Age, y	Median (range)	63 (27–86)	—
Sex	Female	613	55.5
	Male	490	44.4

- Information gathered for prescreening patients was limited to general diagnosis (eg, liver CCA), country of origin, age, and sex. Patients with other biliary tract cancers were prescreened for FIGHT-202; however, only patients with reported primary diagnosis of liver CCA (n = 1104) were included in the analysis. Biopsy samples were from primary or metastatic sites

Genomic Alterations



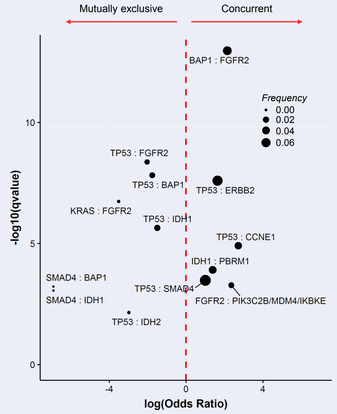
- Amplicons (eg, *CDKN2A/B*, *MDM2/FRS2*) were combined to aid in visualization. The most frequently altered genes in advanced CCA were *TP53* (38.1%), *CDKN2A/B* (28.8%), *KRAS* (21.9%), *ARID1A* (15.7%), *SMAD4* (11.3%), *BAP1* (10.6%), *IDH1* (10.5%), *PBRM1* (10.0%), *FGFR2* (9.4%), *ERBB2* (7.6%), *PIK3CA* (7.0%), *MDM2/FRS2* (5.8%), and *BRAF* (4.7%)

Patient Alterations

Alteration Class	Total	Mean (Max)
All	5042	4.6 (19)
Mutations	3116	2.8 (18)
Copy number	1671	1.5 (15)
Rearrangements	255	0.2 (4)

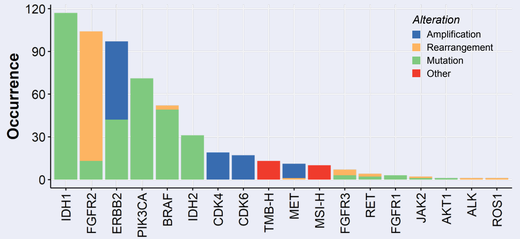
- Only alterations annotated as "known" or "likely" to be cancer associated by Foundation Medicine were included in the analysis. In cases where multiple samples were run for the same patient, alterations were combined

Co-occurrence and Mutual Exclusivity of Genomic Alterations



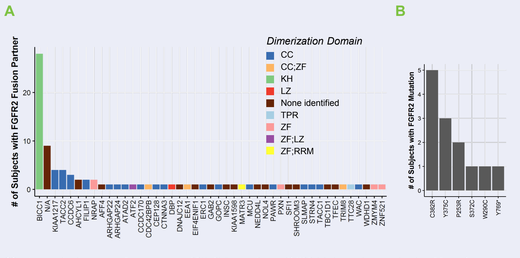
- Genomic alteration co-occurrence and mutual exclusivity were calculated using Fisher exact test and corrected for multiple testing. Only pairs of alterations with a q-value <0.01 and a combined population frequency of >10% were visualized. Odds ratios (OR) of 0 were corrected to 0.001 to allow for visualization. ***FGFR2:BAP1* was the most significantly co-occurring alteration pair (OR 8.5; q-value = 1.0 × 10^{-13})**. *FGFR2:IDH1* and *FGFR2:IDH2* trended toward mutually exclusivity but did not meet statistical significance (not shown)

Actionable Alterations



- The frequency of actionable alterations in advanced CCA was assessed. Genes and alterations were selected based on current use as positive predictive biomarkers for approved or late-stage targeted therapies or immunotherapies in CCA or other indications. **474 (42.9%) patients had at least 1 actionable alteration**. Actionable alterations were most frequent in *IDH1* (n = 117), *FGFR2* (n = 104), *ERBB2* (n = 92), *PIK3CA* (n = 71), *BRAF* (n = 52), and *IDH2* (n = 31)

FGFR2 Rearrangement Partners and Point Mutations

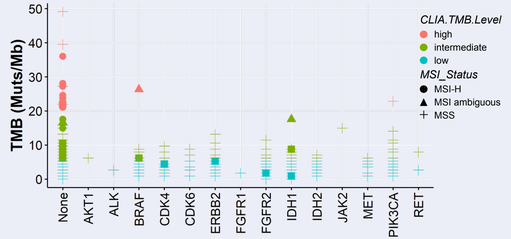


CC, coiled-coil; KH, K homology; LZ, leucine zipper; RRM, RNA recognition motif; TPR, tetratricopeptide repeat protein; ZF, zinc finger.

A. *FGFR2* rearrangement partners and dimerization domains. **91 (8.2%) patients had *FGFR2* rearrangements, accounting for 44 unique rearrangement partners**. The most frequent *FGFR2* rearrangement partner, *BICC1*, accounted for 28 (30.7%) patients with *FGFR2* rearrangements. 37 (84.1%) rearrangement partners were observed only once in the cohort. *FGFR2* rearrangement partner dimerization domains were assessed using UniProt. **Putative dimerization domains were identified in 30 (68.2%) rearrangement partners, accounting for 67 (73.6%) patients**

B. Occurrence of FGFR2 point mutations. **Point mutations in FGFR2 were observed in 13 (1.2%) patients**. C382R was observed in 5 patients. Other recurrent FGFR2 mutations were Y375C (3 patients) and P253R (2 patients)

Driver Alterations and MSI/TMB



- The relationship between actionable driver alterations and microsatellite instability/tumor mutational burden (MSI/TMB) status in advanced CCA was assessed. MSI/TMB information was available for 1091 patients. **10 (0.9%) patients were MSI-H and 13 (1.2%) were TMB-High**. MSI-H status was mutually exclusive with the presence of actionable alterations. TMB-High was observed in a single patient with a BRAF D594N mutation

Conclusions

In this study, we report the use of CGP in 1104 patients prescreened for FIGHT-202, a study of pemigatinib in advanced CCA.

The identity and frequency of genomic alterations are consistent with previous genomic profiling studies in CCA. However, the large number of patients assessed in the current study allowed for a more in-depth analysis that includes co-alteration patterns, analysis of FGFR2 rearrangement partner domains, and relationship between driver alterations. Additionally, MSI-H/TMB status provides further insights into the molecular underpinnings of CCA.

- **43% of advanced CCA patients have actionable alteration**
  - **Underscores the importance of CGP in advanced CCA**
- **91 (8.2%) patients had FGFR2 rearrangements**
  - **44 unique FGFR2 rearrangement partners were observed**
  - **37 (84.1%) rearrangement partners were observed once**
  - **Supports the use of FGFR2 rearrangement-partner agnostic diagnostics in advanced CCA**
- **FGFR2 point mutations, MSI-H and TMB-High, are infrequent (~1%) in advanced CCA**
- ***FGFR2:BAP1* is the most significant co-occurring alteration pair in advanced CCA**
  - **Future studies should assess whether BAP1 alterations modify responses to pemigatinib and/or other FGFR inhibitors**
- **Integration of additional patient clinical characteristics and treatment outcomes are ongoing and will provide genotype-response data that may further elucidate the functional consequences of *FGFR2* rearrangements**
- **CGP will be used for enrollment in FIGHT-302, a phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the efficacy and safety of pemigatinib versus gemcitabine plus cisplatin chemotherapy in first-line treatment of patients with unresectable or metastatic CCA with *FGFR2* rearrangement (NCT03656536)**

Correspondence
Ian Silverman – isilverman@incyte.com
Timothy Burn – TBurn@incyte.com

Disclosures
Silverman, Lihou, Féliz, Newton, Tada, Burn: Employment and stock ownership – *Incyte Corporation*. **Murugesan, Frampton, Albacker:** Employment and stock ownership – *Foundation Medicine*.

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