Encore presentation at NCODA Fall Summit
October 25–27, 2023 | Orlando, FL

This poster was previously presented at the
ESMO World Congress on Gastrointestinal Cancer
June 28–July 1, 2023 | Barcelona, Spain

Futibatinib in Patients With *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma: Responder Analyses of Efficacy and Safety From the Phase 2 FOENIX-CCA2 Study

Antoine Hollebecque, MD,[1] Lipika Goyal, MD,[2] Funda Meric-Bernstam, MD,[3] Junji Furuse, MD,[4] Markus Moehler, MD,[5] Arndt Vogel, MD,[6] Xuan Liu, PhD,[7] Volker Wacheck, MD,[7] John Bridgewater, MBBS[8]

[1]Gustave Roussy, Villejuif, France; [2]Stanford Cancer Center, Palo Alto, CA, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Kanagawa Cancer Center, Yokohama, Japan; [5]Gutenberg University, Mainz, Germany; [6]Hannover Medical School, Hannover, Germany; [7]Taiho Oncology, Inc., Princeton, NJ, USA; [8]UCL Cancer Institute, London, UK

Background

- Fibroblast growth factor receptor 2 (*FGFR2*) fusions or other rearrangements occur in approximately 14% of patients with intrahepatic cholangiocarcinoma (iCCA)[1–4]
- Futibatinib is a novel and highly selective covalent inhibitor of FGFR1–4 that irreversibly inhibits FGF/FGFR signaling[5]
- In a global phase 2 study (FOENIX-CCA2), 42% of patients treated with futibatinib had a confirmed response (median duration of response: 9.7 months), with a median progression-free survival (PFS) and overall survival (OS) of 9.0 months and 21.7 months, respectively[5]
- These findings led to the accelerated approval of futibatinib by the U.S. Food and Drug Administration in September 2022 for adult patients with previously treated, unresectable, locally advanced or metastatic iCCA harboring *FGFR2* gene fusions or other rearrangements[6]
  - In April 2023, the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion recommending the conditional marketing authorization of futibatinib for the second-line treatment of locally advanced or metastatic CCA harboring an *FGFR2* fusion or rearrangement[7]

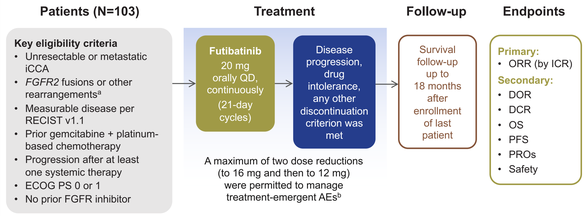
Objective

- To evaluate baseline demographics and measure clinical outcomes in patients with and without a confirmed response to futibatinib in the FOENIX-CCA2 study

Methods

- FOENIX-CCA2 was a multinational, single-arm, phase 2 study (NCT02052778) of futibatinib in patients with unresectable, locally advanced or metastatic, *FGFR2* fusion or rearrangement–positive iCCA and disease progression after at least one previous line of systemic therapy, including gemcitabine plus platinum-based chemotherapy[5]
  - Patients received oral futibatinib at a dose of 20 mg once daily in a continuous regimen over a 21-day cycle (**Figure 1**)
  - The primary endpoint was objective response rate according to Response Evaluation Criteria in Solid Tumors version 1.1, as assessed by independent central review
  - Samples were assessed for genetic coalterations by the TruSight Oncology 500 (Illumina) ctDNA sequencing assay
- In this post hoc analysis of the FOENIX-CCA2 study, baseline demographics, PFS, OS, and dose reductions/interruptions were evaluated descriptively for futibatinib responders (partial or complete response based on independent central review) and nonresponders (stable or progressive disease)
- A post hoc exploratory analysis of the differences in baseline genomic alterations between futibatinib responders and nonresponders was also conducted

Figure 1. FOENIX-CCA2 study design



[a]Identified locally or centrally in tumor tissue by Foundation Medicine or by local laboratory testing of tumor tissue or circulating tumor DNA.
[b]Treatment was discontinued if treatment-emergent AEs did not resolve after two dose reductions or if the next cycle of treatment was delayed by >21 days.
AE, adverse event; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

Patients

- Overall, 103 patients were enrolled in FOENIX-CCA2; of these, 43 (42%) had a confirmed response to futibatinib, and 60 (58%) were nonresponders
  - Baseline characteristics of responders and nonresponders were generally comparable (**Table 1**)

Table 1. Baseline characteristics

Characteristic	Responders[a] (n=43)	Nonresponders (n=60)
Median (range) age, years	60.0 (22–79)	56.0 (28–74)
Sex, n (%)		
Male	17 (39.5)	28 (46.7)
Female	26 (60.5)	32 (53.3)
Race, n (%)		
White	21 (48.8)	30 (50.0)
Asian	13 (30.2)	17 (28.3)
Black	4 (9.3)	4 (6.7)
Native Hawaiian or other Pacific Islander	0	1 (1.7)
Unknown	5 (11.6)	8 (13.3)
Region, n (%)		
North America	19 (44.2)	28 (46.7)
Europe	13 (30.2)	15 (25.0)
Asia Pacific, excluding Japan	7 (16.3)	7 (11.7)
Japan	4 (9.3)	10 (16.7)
ECOG PS, n (%)		
0	22 (51.2)	26 (43.3)
1	21 (48.8)	34 (56.7)
Mean (SD) weight, kg	72.5 (18.2)	74.9 (22.7)

[a]Patients with confirmed partial or complete response based on independent central review.
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

Treatment

- At the data cutoff for this analysis (October 1, 2020), the median duration of treatment among responders and nonresponders was 10.9 months (range: 4.2–24.5) and 6.9 months (range: 0.5–18.9), respectively (**Table 2**)
  - Treatment discontinuation was more frequent in nonresponders, most commonly because of disease progression
  - Median time to first dose reduction/interruption and median duration of interruption due to adverse events (AEs) were both longer in responders

Table 2. Treatment among responders and nonresponders

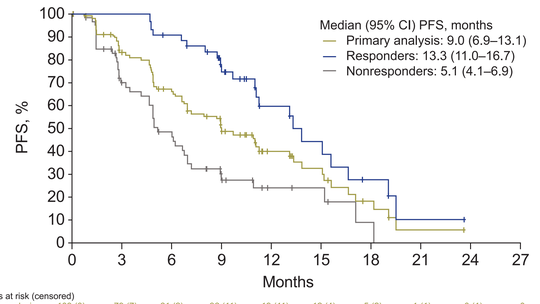
	Responders[a] (n=43)	Nonresponders (n=60)
Median (range) duration of treatment, months	10.9 (4.2–24.5)	6.9 (0.5–18.9)
Treatment discontinuation, n (%)	22 (51.2)	50 (83.3)
Dose reduction/interruption due to AE, n (%)		
Dose reduction	28 (65.1)	31 (51.7)
Dose interruption	30 (69.8)	38 (63.3)
Median (range) time to first dose reduction/interruption due to AEs, days		
Dose reduction	84.5 (5–316)	36.0 (5–332)
Dose interruption	52.0 (4–253)	22.0 (4–325)
Median (range) duration of interruption, days	23.0 (1–140)	14.0 (1–214)

[a]Patients with confirmed partial or complete response based on independent central review.
AE, adverse event.

Progression-free survival

- Median PFS was 13.3 (95% confidence interval [CI]: 11.0–16.7) months in responders and 5.1 (95% CI: 4.1–6.9) months in nonresponders (**Figure 2**)
  - The PFS rates at 6 and 12 months were 90.7% (95% CI: 77.1–96.4) and 59.8% (95% CI: 40.7–74.5), respectively, among responders and 46.4% (95% CI: 32.7–59.1) and 24.1% (95% CI: 12.8–37.3), respectively, among nonresponders

Figure 2. Progression-free survival

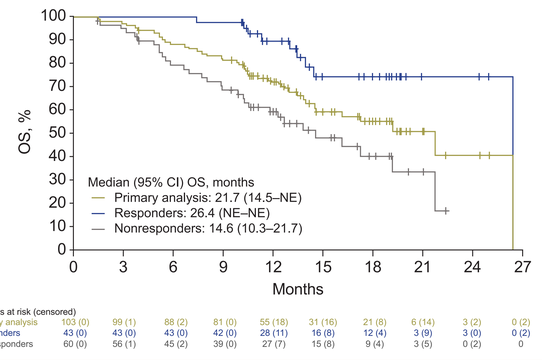


CI, confidence interval; PFS, progression-free survival.

Overall survival

- Median OS was 26.4 (95% CI: not evaluable–not evaluable) months in responders and 14.6 (95% CI: 10.3–21.7) months in nonresponders (**Figure 3**)
  - The OS rates at 6 and 12 months were 100% (95% CI: 100–100) and 89.6% (95% CI: 74.5–96.0), respectively, among responders and 79.3% (95% CI: 66.4–87.7) and 59.2% (95% CI: 45.1–70.8), respectively, among nonresponders
  - The impact of differences in poststudy therapies, including chemotherapy, resection in oligometastatic disease, and other local therapies, was not assessed

Figure 3. Overall survival



CI, confidence interval; NE, not evaluable; OS, overall survival.

Genomic alterations

- While genomic subsets were small, an exploratory analysis showed that differences in co-occurring baseline genomic alterations between responders and nonresponders were varied and did not suggest a clear association with response (**Table 3**)

Table 3. Co-occurring baseline genomic alterations with >5% difference between responders and nonresponders

Patients with genomic alteration, n (%)	All treated patients (N=103)	Responders[a] (n=43)	Nonresponders (n=60)
BAP1	40 (38.8)	14 (32.6)	26 (43.3)
MLL2	11 (10.7)	7 (16.3)	4 (6.7)
PIK3C2B	11 (10.7)	7 (16.3)	4 (6.7)
IKBKE	10 (9.7)	6 (14.0)	4 (6.7)
MDM4	10 (9.7)	6 (14.0)	4 (6.7)
AKT3	9 (8.7)	8 (18.6)	1 (1.7)
CDC73	9 (8.7)	8 (18.6)	1 (1.7)
DDR2	9 (8.7)	7 (16.3)	2 (3.3)
PBRM1	9 (8.7)	2 (4.7)	7 (11.7)
BTG2	8 (7.8)	6 (14.0)	2 (3.3)
FH	8 (7.8)	7 (16.3)	1 (1.7)
RAD21	8 (7.8)	5 (11.6)	3 (5.0)
SDHC	8 (7.8)	5 (11.6)	3 (5.0)
H3F3A	7 (6.8)	5 (11.6)	2 (3.3)
CREBBP	6 (5.8)	4 (9.3)	2 (3.3)
NOTCH2	6 (5.8)	4 (9.3)	2 (3.3)
TET2	6 (5.8)	1 (2.3)	5 (8.3)
CALR	5 (4.9)	0 (0)	5 (8.3)
PARP1	5 (4.9)	4 (9.3)	1 (1.7)
JAK1	4 (3.9)	0 (0)	4 (6.7)
BCORL1	3 (2.9)	3 (7.0)	0 (0)
ERBB4	3 (2.9)	3 (7.0)	0 (0)
FANCC	3 (2.9)	3 (7.0)	0 (0)

[a]Patients with confirmed partial or complete response based on independent central review.

CONCLUSIONS

- **This post hoc analysis of the FOENIX-CCA2 study found that patients with a confirmed response to futibatinib had numerically longer PFS and OS versus nonresponders**
- **Although dose reductions and dose interruptions due to AEs were numerically more frequent in responders than nonresponders, they occurred later during treatment, suggesting a potential benefit of maintaining the starting dose for longer**
- **Further investigation of co-occurring genomic alterations as potential predictors of response to FGFR inhibitors is warranted**

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Acknowledgments

This study was sponsored by Taiho Oncology, Inc. Medical writing assistance was provided by Harlene Ghuman, PhD, of Envision Pharma Group, funded by Taiho Oncology, Inc.