ARQ 087, an Oral Pan-Fibroblast Growth Factor Receptor (FGFR) Inhibitor, in Patients with Advanced Intrahepatic Cholangiocarcinoma (iCCA) with FGFR2 Genetic Aberrations

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BACKGROUND

ARQ 087 is a multi-kinase inhibitor with a potent pan-FGFR activity that is currently being evaluated for its potential use in the clinic.[1,2] FGFR genetic aberrations have been implicated in the development and progression of a number of solid tumor types, including iCCA. Patients with advanced iCCA who relapse after first-line multi-agent chemotherapy have limited treatment options with poor prognosis. In recent years, FGFR2 fusions, observed approximately in up to 20% of patients, have been recognized as a potential iCCA-specific therapeutic target.[3]

METHODS

119 cancer patients were enrolled in the phase 1/2, open-label study of ARQ 087 (NCT01752920). Study design and results of the Dose Escalation portion of the study were reported previously.[4,5]. Assessments included response by RECIST v1.1 every 8 weeks, safety (physical examination, vital signs, Eastern Cooperative Oncology Group Performance Status [ECOG PS], laboratory tests), plasma concentrations of phosphate and FGF19, 21 and 23 (potential biomarkers).[5]

The objectives of this study were evaluation of safety, tolerability and anti-cancer activity of ARQ 087 in patients with unselected advanced solid tumors (part 1) and in patients with FGFR genetic alterations, including patients with iCCA with FGFR2 genetic aberrations (part 2).

Patients with histologically or cytologically confirmed advanced, inoperable, or metastatic solid tumors who failed to respond to standard therapy or for whom standard curative therapy does not exist (part 1) and who received ≤2 prior lines of prior systemic therapy with confirmed disease progression (part 2); age ≥ 18 years; radiologically evaluable or measurable disease; ECOG PS ≤2; and adequate bone marrow, liver, renal and cardiovascular function were eligible. Patients who received treatment with chemotherapy, radiotherapy within 28 days of study commencement, previous anticancer therapy with FGFR inhibitors, or who had unstable CNS metastases, history of or current clinically significant disorders (e.g., myocardial infarction less than 6 months prior to enrollment, active HIV infection) were excluded.

RESULTS

As of 28 April 2017, 35 patients with iCCA with FGFR2 genetic aberrations were treated with oral ARQ 087 at 300 or 400 mg daily (n=33 or n=2, respectively). FGFR2 genetic alteration status was identified by fluorescent in situ hybridization (FISH, n=18) or next-generation sequencing (NGS, n=17). Twenty nine patients were FGFR2 fusion positive (FISH, n=15; NGS, n=14) and 6 patients had FGFR2 gene amplification or mutation (FISH amp, n=3; NGS mut, n=3). All patients had advanced, inoperable, metastatic disease, intrahepatic metastases were reported in 33/35 (94%) patients and distant metastases in 27/35 (77%) patients, including to lung 16 patients, abdominal/peritoneal and retroperitoneal spread in 13 patients, bone in 4 patients. Thirty four patients had at least one post-treatment radiographic assessment and 1 patient was not evaluable. The best response was partial response (PR) in 6 patients, stable disease (SD) in 22 patients, and progressive disease (PD) in 6 patients.

RESULTS

Table 1. Patient Baseline Characteristics

Parameter	iCCA n=35 (%)	FGFR2 fusion n=29 (%)	FGFR2 amp/mut n=6 (%)
Age years, median (min, max)	58 (31, 82)	59 (38, 82)	57 (31, 76)
Female	21 (60)	18 (62)	3 (50)
White	35 (100)	29 (100)	6 (100)
ECOG PS: ≤1	34 (97)	28 (97)	6 (100)
Extrahepatic spread	34 (97)	28 (97)	6 (100)
Median sum of target lesions (mm)/(min, max)	96 (11, 273)	99 (11, 273)	79 (48, 237)
Median size of largest target lesion (mm)/(min, max)	53 (11, 158)	53 (11, 158)	42 (21, 152)
Prior surgery	14 (40)	13 (45)	1 (17)
Prior radiation therapy	4 (11)	3 (10)	1 (17)
Prior systemic therapy:			
# of regimens: 0	3 (9)	2 (7)	1 (17)
# of regimens: 1	13 (37)	12 (41)	1 (17)
# of regimens: ≥2	19 (54)	15 (52)	4 (67)

Table 2. Patient Disposition

Parameter	Total n=35 (%)	FGFR2 fusion n=29 (%)	FGFR2 amp/mut n=6 (%)
Treatment status			
Ongoing	12 (34)	9 (31)	3 (50)
Reasons for treatment discontinuation, n=23 (%)			
Radiological disease progression	12 (52)	11 (55)	1 (33)
Clinical disease progression	4 (17)	3 (15)	1 (33)
Adverse Event	4 (17)	4 (20)	0
Death	1 (4)	0	1 (33)
Other	2 (9)	2 (10)	0

Date of data extract: 28 April 2017

Table 3. Adverse Events Summary

Parameter	iCCA n=35 (%)	FGFR2 fusion n=29 (%)	FGFR2 amp/mut n=6 (%)
Patients with any adverse event* (AE), n (%)	35 (100)	29 (100)	6 (100)
Patients with serious AE (SAE), n (%)	7 (20)	6 (21)	1 (17)
Patients with ARQ 087-related AE, n (%)	33 (94)	27 (93)	6 (100)
Patients with ARQ 087-related severe (≥Grade 3) AE, n (%)	9 (26)	8 (28)	1 (17)
Patients with ARQ 087-related SAE, n (%)	2 (6)	1 (3)	1 (17)
Patients with treatment interruption due to ARQ 087-related AE, n (%)	8 (23)	7 (24)	1 (17)
Patients discontinued due to ARQ 087-related AE**	3 (9)	3 (10)	0
Patients with ARQ 087-related hyperphosphatemia***	23 (66)	21 (72)	2 (33)
Patients with ARQ 087-related ocular toxicity	13 (37)	11 (38)	2 (33)

*AE were graded according to the NCI CTCAE version 4.03
**Two patients were discontinued due to grade 2 eye toxicities, and one patient due to upper GI bleeding
***Due to lack of CTCAE defined criteria, hyperphosphatemia was reported per AE report and/or Sponsor definition based on lab results. Sponsor defined hyperphosphatemia: Grade 1: > ULN to ≤ 1.2 x ULN, Grade 2: Non-invasive intervention required or > 1.2 x ULN to ≤ 1.4 x ULN; Grade 3: Severe or medically significant, but not immediately life threatening or > 1.4 x ULN to ≤ 1.6 x ULN; Grade 4: Life-threatening consequences, urgent intervention indicated (e.g., dialysis or > 1.6 x ULN)

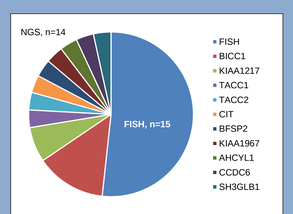
Table 4. Most Common ARQ 087-related Adverse Events: All Grades in ≥20% of Patients and Grade ≥3 in 2 or More Patients

Preferred Term	iCCA n=35 (%)		FGFR2 fusion n=29 (%)		FGFR2 amp/mut n=6 (%)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hyperphosphatemia	23 (66)	2 (6)	21 (72)	2 (7)	2 (33)	0
Nausea	15 (43)	0	13 (45)	0	2 (33)	0
Dry Mouth	14 (40)	0	13 (45)	0	1 (17)	0
Asthenia	11 (31)	2 (6)	8 (28)	2 (7)	3 (50)	0
Fatigue	11 (31)	1 (3)	10 (34)	1 (3)	1 (17)	0
Dysgeusia	10 (29)	0	9 (31)	0	1 (17)	0
Vomiting	10 (29)	1 (3)	8 (28)	1 (3)	2 (33)	0
Abnormal LFTs	8 (23)	2 (6)	7 (24)	1 (3)	1 (17)	1 (17)
Alopecia	8 (23)	0	7 (24)	0	1 (17)	0
Mucosal Inflammation	2 (6)	0	0	0	2 (33)	0
Ocular Toxicity	13 (37)	2 (6)	11 (38)	2 (7)	2 (33)	0
Vision Blurred	6 (17)	1 (3)	6 (21)	1 (3)	0	0
Conjunctivitis	4 (11)	0	4 (14)	0	0	0
Dry Eye	3 (9)	1 (3)	3 (10)	1 (3)	0	0

Table 5. Best Overall Response in Evaluable Population

	iCCA n=35 (%)	FGFR2 fusion n=29 (%)	FGFR2 amp/mut n=6 (%)
Partial Response (PR)	6 (17)	6 (21)	0
Stable Disease (SD)	22 (63)	18 (62)	4 (67)
Progressive Disease (PD)	6 (17)	5 (17)	1 (17)
No assessment available	1 (3)	0	1 (17)
Disease control rate (PR+SD)	28 (80)	24 (83)	4 (67)
Clinical benefit (PR+SD; SD≥ 16 wks)	**25 (71)**	**21 (72)**	**4 (67)**

Figure 1. FGFR2 Fusion Positive Patients and Best Response



FGFR2 Fusion status and best response	Number of patients
FISH (PR+SD+PD)	15 (3 + 10 + 2)
NGS (PR+SD+PD)	14 (3 + 8 + 3)
• FGFR2-BICC1	4 (1 + 2 + 1)
• FGFR2-KIAA1217	2 (1 + 1+ 0)
• FGFR2-SH3GLB	1 (PR)
• FGFR2-KIAA1967	1 (SD)
• FGFR2-AHCYL1	1 (SD)
• FGFR2-BFSP2	1 (SD)
• FGFR2-CCDC6	1 (SD)
• FGFR2-TACC2	1 (SD)
• FGFR2-CIT	1 (PD)
• FGFR2-TACC1	1 (PD)

Figure 2. Best Percent Change from Baseline in Target Lesions and Best Overall Response

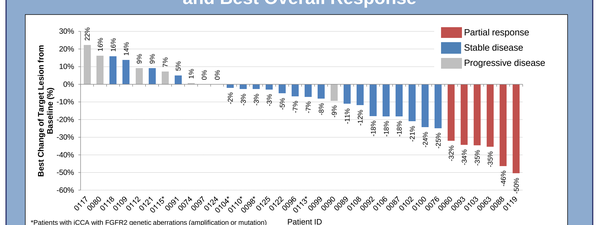


Figure 3. Duration on Treatment and Best Overall Response

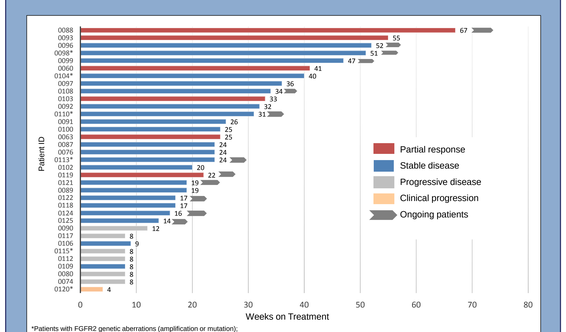
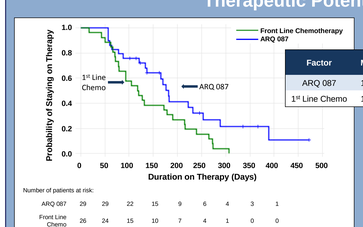


Figure 4. Intra-patient Front-Line Chemotherapy vs 2nd Line ARQ 087 in iCCA FGFR2 Fusion Positive Points to 1st Line Therapeutic Potential*

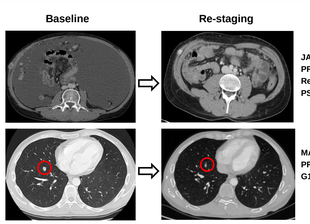


Factor	Mean	SE	95% CI for Mean	Median	95% CI for Median
ARQ 087	178.4	20.2	137.1–219.6	182.0	137.0–263.0
1st Line Chemo	140.5	16.3	106.9–174.1	119.0	79.0–178.0

ARQ 087 intra-patient 1st line chemotherapy vs 2nd line ARQ 087: duration of therapy in iCCA FGFR2 fusion positive patients (* as data reported in the CRF; 2 patients were treatment-naive)

Figure 5. Efficacy

A 37-year-old male, with stage II moderately differentiated iCCA with FGFR2 gene translocation in 70% of tumor cells, has been on ARQ 087 therapy since Nov-2016. Patient had right hepatectomy with 6 cycles of adjuvant gemcitabine in 2016; after disease progression he received 2 cycles of gemcitabine + cisplatin and treatment was discontinued due to PD in Oct-2016. Patient demonstrated 47% and 50% decrease in tumor burden compared to baseline at the first and second re-staging, respectively. Treatment is ongoing.



JAN 2017 (C3D1):
PR (target lesions -47%)
Resolution of ascites
PS 0

MAR 2017 (C5D1):
PR (target lesions -50%)
G1 drug-related AEs

CONCLUSIONS

- **Patients with advanced or inoperable iCCA have a poor prognosis and limited treatment options. A number of selective and multi-kinase FGFR inhibitors are currently under development for FGFR-driven tumors, including intrahepatic cholangiocarcinoma.**
- **ARQ 087 has a potent biochemical activity against the FGFR2 kinase and has demonstrated *in vitro* efficacy in models with FGFR2 fusion.[1]**
- **In the 29 evaluable patients with iCCA with FGFR2 gene fusion:**
  - **The objective response rate was 21% (6 PR) and disease control rate was 83% (PR+SD).**
    - **Significant reduction in tumor burden (10-29%) was observed in 26% (8 patients).**
    - **Clinical benefit (PR+SD; SD ≥16 wks) was observed in 72% (21 patients).**
    - **9 patients are still on-going.**
  - **PD was the best response in 17% (5 patients).**
- **In the 5 evaluable patients with iCCA with FGFR2 gene amplification or mutation, durable disease control (≥16 weeks) was observed in 67% (4 patients).**
- **ARQ 087 showed a manageable safety profile with mostly Grade 1-2 adverse events, including class-related AEs of hyperphosphatemia and ocular toxicity.**
- **Both FISH and NGS proved to be equally useful methods for detection of FGFR2 genetic aberrations.**
- **Further development of ARQ 087 as monotherapy for second- or first-line therapy for patients with iCCA with FGFR2 fusion is deemed feasible considering its favorable safety profile and preliminary evidence of anti-cancer activity.**
- **A registration study of ARQ 087 in iCCA patients with FGFR2 fusion who received at least one line of prior systemic therapy and then experienced documented radiographic PD or were not able to tolerate prior systemic therapy is being planned.**

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