ARQ 087, an Oral Pan- Fibroblast Growth Factor Receptor (FGFR) Inhibitor, in Patients with Advanced and/or Metastatic Intrahepatic Cholangiocarcinoma (iCCA)

V. Mazzaferro[1], W. Shaib[2], L. Rimassa[3], W.P. Harris[4], N. Personeni[3,5], B. El-Rayes[2], A.W. Tolcher[6], T. Hall[7], Y. Wang[7], B. Schwartz[7], J. Kazakin[7], M. Droz Dit Busset[1], C. Cotsoglou[1], K.P. Papadopoulos[6]

[1]Istituto Nazionale Tumori, Milan, Italy; [2]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [3]Humanitas Cancer Center, Humanitas Clinical and Research Center, Rozzano (Milano), Italy; [4]Seattle Cancer Care Alliance, Seattle, WA, USA; [5]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; [6]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; [7]ArQule, Inc., Burlington, MA, USA

Abstract # 340

PD #19

BACKGROUND

- ARQ 087 is a multi-kinase inhibitor designed to preferentially inhibit the fibroblast growth factor receptor (FGFR) family
- ARQ 087, an orally bioavailable, ATP-competitive compound, is a dual kinase inhibitor that binds to the inactive form of FGFR1 and FGFR2 and potently inhibits the active forms of FGFR1 and FGFR2
- Intrahepatic cholangiocarcinoma (iCCA) is associated with very poor prognosis, high mortality rate and limited treatment options
- Molecular characterization of iCCA by next generation sequencing (NGS) or fluorescence in situ hybridization (FISH) has enabled identification of actionable genetic alterations[1]
- FGFR2 fusion, a novel genetic translocation, has been recently implicated in the development and progression of iCCA, and recognized as a potential therapeutic target

METHODS

Study Design and Assessments

Study Design

This is an open-label multi-center Phase 1/2 dose-escalation (Part 1) and signal-finding (Part 2) study of ARQ 087. Part 1 results were reported previously[2]. Part 2 of the study is ongoing (NCT01752920).

- Dose Escalation/Part 1: December 2012 – November 2015 – completed
  - Cohorts 1-4: dose was doubled
  - Cohort 5 and in all subsequent cohorts: modified Fibonacci scheme was implemented
  - 3+3 patients per cohort (if Dose Limited Toxicity (DLT), standard DLT criteria)
  - Maximum Tolerated Dose (MTD) if ≤ 1 DLT out of 6 treated patients
- Expanded cohort/Part 2: December 2015 – ongoing

Assessments

Assessments included response by RECIST v1.1 (investigative sites' and independent readers) at baseline and every 8 weeks (wks), safety (physical examination, vital signs, Eastern Cooperative Oncology Group Performance Status (ECOG PS), laboratory tests), plasma concentrations of phosphate and FGF19, 21, 23 (potential biomarkers). Treatment-emergent adverse events (TEAE) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Study Endpoints

Primary Endpoints

Safety and tolerability in patients with advanced solid tumors (Part 1) and with FGFR genetic alterations, including iCCA with FGFR2 fusion (Part 2)

Secondary Endpoints

- Pharmacokinetic profile, incl. food effect (Part 1)
- MTD and/or Recommended Phase 2 Dose (RP2D) (Part 1)
- Pharmacodynamic activity
- Preliminary evidence of anti-tumor activity and biomarker evidence of target inhibition
- Target patient-population, e.g., iCCA w/FGFR2 fusion or other tumors w/FGFR genetic alterations

Exploratory Endpoints

- Association between markers of the FGFR (specifically FGFR2) signaling pathway, toxicity and clinical activity
- Evaluation of markers of the FGF signaling pathway

Key Eligibility Criteria

- Male/Female ≥ 18 years of age; ECOG PS ≤ 2
- Life expectancy ≥ 12 weeks
- Known (documented) and/or confirmed FGFR genetic alterations, incl. iCCA with FGFR2 gene fusion
- Availability of archival tissue and/or agreement to undergo paired tumor biopsy (optional), if feasible
- Evaluable or measurable disease
- Adequate bone marrow, cardiovascular, hepatic and renal function
- Failure to respond to standard therapy or patients for whom standard therapy does not exist
  - ≤ 2 prior systemic regimens with confirmed disease progression
  - iCCA treatment-naïve pts w/FGFR2 fusion who may benefit from treatment with ARQ 087
- No concurrent serious co-morbidities that could limit patients' full participation and compliance
- No previous treatment with FGFR inhibitors
- No prior anti-cancer treatment within 4 wks prior to dosing or 5 times the half-life (which ever is longer)

RESULTS

As of 6-June-2016, 21 patients with iCCA were treated with ARQ 087 at 400 or 300 mg qd dose levels. Mutation status by NGS or FISH was reported in 20 patients, including 14 patients with FGFR2 fusion. Radiographic response was assessed in 18 patients

Table 1. Patient Characteristics

Parameters	iCCA n=21 (%)
Age yrs/median (min, max)	64 (39, 81)
Sex: Male/Female	8 (38%) / 13 (62%)
Race: White/Black	20 (95%) / 1 (5%)
ECOG PS: 0/1	12 (57%) / 9 (43%)
Prior surgery	11 (52%)
Prior radiation therapy	3 (14%)
Prior systemic therapy	19 (90%)
Prior systemic therapy (≥2)	11 (52%)
Number of regimens: 0	2 (10%)
Number of regimens: 1	8 (38%)
Number of regimens: 2	6 (29%)
Number of regimens: 3	3 (14%)
Number of regimens: ≥ 4	2 (10%)

Table 2. Patient Disposition

Disposition	iCCA n=21 (%)
Time on treatment	
Mean (SD)	93.1 (66.9)
Median time on study treatment, days (Min, Max)	57 (19, 289)
Treatment status	
Ongoing	7 (33%)
Reasons for treatment discontinuation	
Progressive Disease (PD)	11 (52%)
Physician's decision	2 (10%)
Withdrawal consent	1 (5%)

Table 4. Adverse Events Summary

	iCCA n=21 (%)*
Number of patients with any adverse event (AE)	21 (100%)
Number of patients with ARQ 087-related AE	19 (90%)
Number of patients with ARQ 087-related Severe (≥Grade 3) AE	5 (24%)
Number of patients with treatment interruption due to ARQ 087-related AE	6 (29%)

- None of the patients were discontinued from the treatment due to ARQ 087-related AE
- No ARQ 087-related SAE or death were reported as of data cutoff date

Table 5. Most Common (≥10%) ARQ 087-related Adverse Events

Preferred Terms	All Grades (n=21)(%)	Grade ≥3 (n=21)(%)
Dry Mouth	8 (38%)	–
Fatigue	8 (38%)	1 (5%)
Nausea	7 (3%)	–
Alanine Aminotransferase Increased	5 (24%)	1 (5%)
Dysgeusia	5 (24%)	–
Aspartate Aminotransferase Increased	3 (14%)	2 (10%)
Decreased Appetite	3 (14%)	–
Vision Blurred	3 (14%)	1 (5%)
Vomiting	3 (14%)	1 (5%)
Diarrhoea	3 (14%)	–
Stomatitis	3 (14%)	1 (5%)
Alopecia	2 (10%)	–
Anemia	2 (10%)	1 (5%)
Asthenia	2 (10%)	–
Dermatitis	2 (10%)	–
Dizziness	2 (10%)	–
Headache	2 (10%)	–
Neuropathy Peripheral	2 (10%)	–

Table 3. FGFR2 Fusion and the Best Tumor Response

FGFR2 Genetic Aberration (N=14)

ID #	FGFR status	Mutational status	Best Response
0060	FGFR2-KIAA1217	*KRAS/LYN/MYC* amp *MLL2*	PR (32%↓)
0063	FGFR2-BICC1	*FBXW7; BAP1*	PR (35%↓)
0088	FGFR2 fusion*	unknown	PR (44%↓)
0076	FGFR2-CCDC6	*IDH2; BAP1*	SD (25%↓)
0093	FGFR2 fusion*	unknown	SD (26%↓)
0087	FGFR2 fusion*	unknown	SD (18%↓)
0089	FGFR2-BFSP2 & trunc.intron 17	*BRCA2*	SD (11%↓)
0092	FGFR2-BICC1	*BAP1; AKT3* amp	SD (7%↓)
0091	FGFR2 fusion*	unknown	SD (5%↑)
0090	FGFR2 fusion*	unknown	PD (9%↓)**
0074	FGFR2-TACC1	*STK11; TSC1; ATM*	PD (0%)**
0080	FGFR2-BICC1	*CDKN2; TP53 EPHA3* amp *MUTYHY*	PD (16%↑)**
0096	FGFR2 fusion*	unknown	pending
0097	FGFR2-TACC2	not identified	Pending

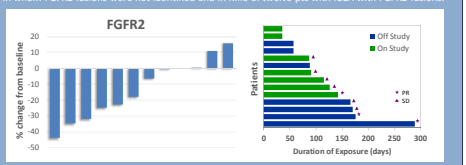
No FGFR2 Genetic Aberration Detected (N=7)

ID #	FGFR status	Mutational status	Best Response
0059	no tissue	no tissue	SD (17%↑)
0065	not identified	*BAP1* H169Q	PD (62%↑)
0075	not identified	*ERBB3* amp; *PBRM1*	PD (13%↑)
0070	not identified	*IDH1; ARID1A; PBRM1*	n/a (DOD)
0078	not identified	BCR-ABL1 fusion; *PTEN FBXW7; NOTCH2; TP53*	PD (69%↑)
0082	not identified	*IDH2*	PD (27%↑)
0083	not identified	*BRAF; ARID1; CHD4*	PD(14%↑)

*FGFR2 status tested by FISH
** new lesion
00XX bold/underline numbers mean the pts are still ongoing
SD - stable disease
PR - partial response

Figure 1. Best % Change from Baseline in Size of Target Lesions and Duration of Exposure

Tumor control (complete or partial response or stable disease) was achieved in one of seven iCCA pts in whom FGFR2 fusions were not identified and in nine of twelve pts with iCCA with FGFR2 fusions.



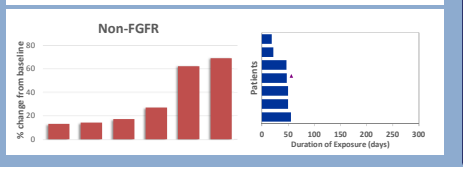
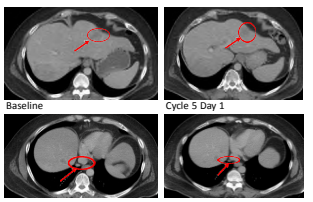


Figure 2. Decreases in Tumor Burden

Patient 0060 with iCCA (FGFR2 KIAA1217 fusion) whose disease progressed after four prior regimens of systemic therapy had a partial response: 32% decrease in tumor burden, completed 10 cycles.



Patient 0088 with iCCA (FGFR2 fusion) whose disease progressed after one prior regimen of systemic therapy had a partial response: 44% decrease in tumor burden, completed 4 cycles (ongoing).

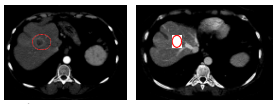
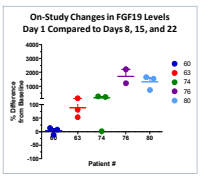


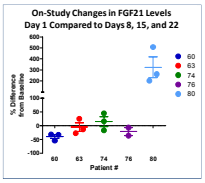
Figure 3. Pharmacodynamic Evaluation[3]

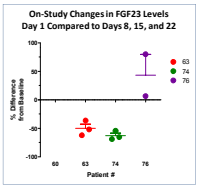
FGF19 levels were dramatically increased in the majority of iCCA patients with FGFR2 fusion.

FGF21 levels were significantly changed only in one patient with iCCA with FGFR2 fusion.

FGF23 levels were generally lower than other FGFs monitored; there is no clear trend in observed changes.







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 such as iCCA. ARQ 087 has a potent biochemical activity against the FGFR2 kinase and has demonstrated *in vitro* efficacy in models with FGFR2 fusion[4]**
- **In the 12 evaluable patients with iCCA with FGFR2 fusion:**
  - **The objective response rate was 25% (3 PR) and disease control rate was 75% (PR+SD)**
    - **Significant reduction in tumor burden (15-29%) was observed in 25% (3 patients)**
    - **Durable disease control (≥16 weeks) was observed in 50% (6 patients)**
    - **Five patients are still on-going**
  - **PD was the best response in 25% (3 patients)**
- **In seven patients in whom FGFR2 fusion was not identified, PD was the best response**
- **ARQ 087 showed a manageable safety profile with mostly Grade 1-2 adverse events**
- **Increased FGF19 levels may be a potential surrogate marker for FGFR receptor engagement**
- **Further development of ARQ 087 as monotherapy or in combination with other anti-cancer agents as 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[5]**

REFERENCES and ACKNOWLEDGMENTS

1. Moeini, et al. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. Clin Cancer Res. 2016 Jan 15;22(2):291-300.
2. Papadopoulos, et al. Phase 1, dose-escalation, first-in-human study of ARQ 087, an oral pan- FGFR Inhibitor, in adult subjects with advanced solid tumor. 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 18-21 November 2014, Barcelona, Spain. Abstract #389
3. Hall, et al. Determination of FGF-19, 21, and 23 protein levels in a phase 1 clinical trial of ARQ 087, an oral pan-FGFR inhibitor. AACR Annual Meeting 2015, 18-22 April 2015, Philadelphia, PA USA. Abstract #CT319
4. Hall, et al. In FGFR2 driven tumors, preclinical pharmacokinetics (PK), pharmacodynamics (PD) and efficacy translate into clinical activity of ARQ 087. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 5-9 November, 2015; Boston, MA USA. Abstract #333
5. Chila, et al. Combinations of ARQ087 with chemotherapeutic agents are safe and show a striking antitumor activity in different xenograft models. AACR Annual Meeting 2015, 18-22 April 2015, Philadelphia, PA USA. Abstract #3500

The authors express their sincere appreciation and gratitude to patients, their families and investigators who participated in this trial.

18th ESMO World Congress on Gastrointestinal Cancer. 29 June – 2 July, 2016, Barcelona, Spain.