Derazantinib (ARQ 087) Pharmacodynamics: Alterations in FGF19/21/23 and Phosphate in Patients with Cholangiocarcinoma

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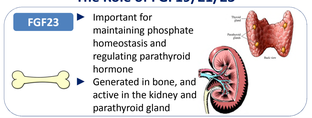
LB-232
AACR Annual Meeting
April 14-18, 2018, Chicago, IL

BACKGROUND

Fibroblast growth factors (FGFs) and their receptors (FGFRs) play important roles in cells including; proliferation, differentiation, migration, survival, protein synthesis, and angiogenesis. The FGFR family consist of four genes encoding tyrosine kinase receptors (FGFR1, FGFR2, FGFR3, and FGFR4). Dysregulation of FGFR signaling has been implicated in a number of developmental syndromes as well as cancers, e.g., intrahepatic cholangiocarcinoma (iCCA), squamous non-small cell lung cancer, small cell lung cancer, gastric, liver, breast, ovarian, endometrial, and bladder carcinomas, fueling significant interest in FGFRs as targets for therapeutic intervention. In human cancers, FGFRs have been found to be dysregulated by multiple mechanisms, including aberrant expression, mutations, chromosomal rearrangements, and amplifications.

Unlike the majority of FGFs that act locally, the FGF19 subfamily (FGF19/21/23) circulate throughout the body, and can act as endocrine hormones at organs distant from their site of synthesis. FGFs 19, 21 and 23 are involved in the regulation of bile acid synthesis, energy and metabolism, and phosphate homeostasis, respectively. The wide circulation of FGFs 19, 21, 23 makes them excellent potential biomarkers for FGFR inhibition.

The Role of FGF19/21/23



Clinical Trial ARQ 087-101 (NCT01752920)

Baseline Demographic and Clinical Characteristics

Characteristics	Patients (N=29) n (%)
Median age, years (range)	58.7 (37.9 - 82.0)
Sex, n (%) Female	18 (62.1)
Male	11 (37.9)
Race, White	29 (100.0)
ECOG Performance Status	
0	19 (65.5)
1	9 (31.0)
2	1 (3.4)
Median time since initial diagnosis, months (range)	14.1 (1.1 - 76.5)
Tumor Stage at Study Entry (AJCC Cancer Staging Manual, 7th ed.)	
I	1 (3.4)
II	6 (20.7)
III	4 (13.8)
IV	17 (58.6)
IVB	1 (3.4)
Histology	
Well Differentiated	3 (10.3)
Moderately Differentiated	12 (41.4)
Poorly Differentiated/Undifferentiated	5 (17.2)
Unspecified	9 (31.0)
Prior systemic regimens	
0	2 (6.9)
1	13 (44.8)
2	10 (34.5)
3	2 (6.9)
4	2 (6.9)
Best response to prior systemic therapy	
PR	4 (13.8)
SD	9 (31.0)
PD	11 (37.9)
Unknown/not applicable	3 (10.3)
No prior systemic therapy	2 (6.9)
Prior surgery No	15 (51.7)
Yes	14 (48.3)
Prior radiation therapy No	26 (89.7)
Yes	3 (10.3)

Response to Treatment* with Derazantinib (ARQ 087) in 29 advanced or inoperable FGFR2 gene fusion-positive iCCA

Response	(N=29) n (%)
Best response	
Complete response (CR)	0
Partial response (PR)	6 (20.7)
Stable disease (SD)	18 (62.1)
Progressive disease	5 (17.2)
Overall response rate (PR)	6 (20.7);
Median duration of overall response, months	4.6 (95% CI, 2.3 – 8.9)
Disease control rate (PR+SD)	24 (82.8);
Median duration of disease control, months	5.8 (95% CI, 5.3 – 8.4)
PFS events	
Progression	22
Death	2
Censored	5
Median PFS, months	5.7 (95%; CI, 4.0 – 9.2)
Median duration of exposure**, months (range)	
Partial response (N=6)	5.6 (1.5 – 18.2)
Stable disease (N=18)	7.9 (5.5 -18.2)
Progressive disease (N=5)	5.6 (1.5 – 18.0)
	1.8 (1.8 – 2.5)

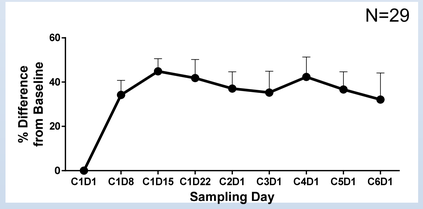
*Assessed by investigators as per Response Evaluation Criteria in Solid Tumors v1.1.
** Duration of exposure in days = last dosing date – first dosing date + 1

MATERIALS AND METHODS

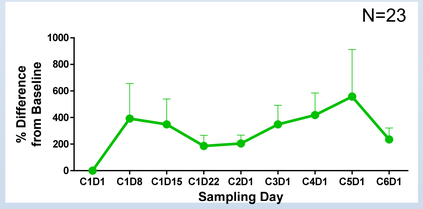
During clinical trial ARQ 087-101 (NCT01752920) patients' plasma samples were collected (on Day 1, 8, 15, 22 of Cycle 1 and Day 1 of Cycles 2-6) and analyzed for levels of FGF & phosphate (patients enrolled in the expanded cohort were not evaluated on day 1, 8, or 22 of Cycle 1). FGF levels were quantified using commercially available ELISA kits for FGF-19 and 21 (R&D Systems, Minneapolis, MN), and FGF-23 (EMD-Millipore, Billerica, MA). Phosphate levels were collected as a part of clinical chemistry monitoring during the clinical trial.

RESULTS

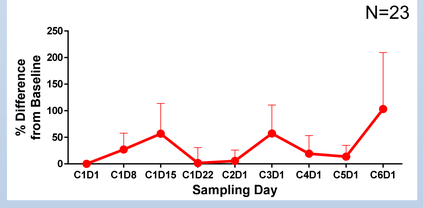
Mean (SEM) % Change in Phosphate



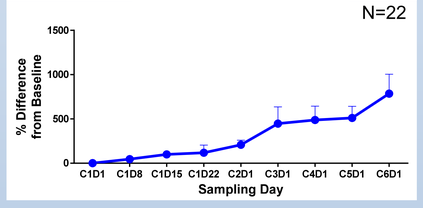
Mean (SEM) % Change in FGF19



Mean (SEM) % Change in FGF21

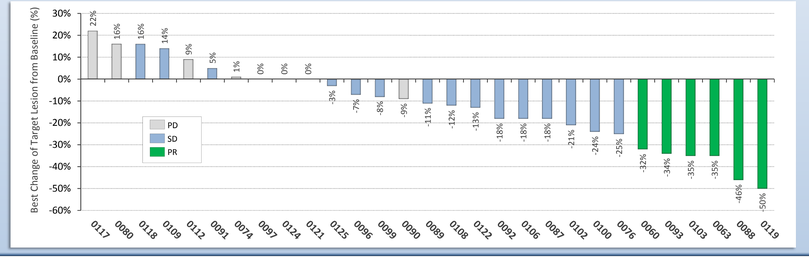


Mean (SEM) % Change in FGF23



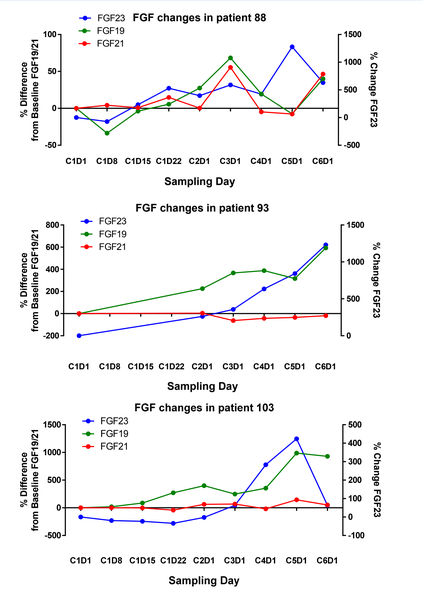
Preliminary analysis of results from cholangiocarcinoma patients treated with derazantinib showed clear increases in mean FGF19, 23, and phosphate levels while receiving ARQ 087. On Cycle 2 Day 1, phosphate levels increased on average by 37% over baseline. FGF19 and FGF23 increased by 203% and 208% respectively. Phosphate levels along with FGF19 and FGF23 remained elevated for the duration of treatment.

Efficacy in Patients Treated with Derazantinib



Representative Individual FGF Trends

The trends in all patients were also observed in patients responding to derazantinib treatment.



CONCLUSIONS

- **The changes in FGF19, FGF23, and phosphate observed during treatment suggest that, at the recommended Phase 2 dose of derazantinib (300 mg QD), clinical signs of target engagement are detectable. FGF21 failed to show consistent changes.**
- **Increases in phosphate and all three FGFs were observed in patients treated with derazantinib.**
- **DeLiver-FGFR, a pivotal study of derazantinib in patients with FGFR2 gene fusion positive iCCA is ongoing (NCT03230318).**