MOLECULAR SCREENING OF PATIENTS WITH FGFR ALTERATIONS FOR A PHASE 1 (PH1) STUDY WITH THE SELECTIVE FGFR INHIBITOR (FGFRi) DEBIO 1347

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ABSTRACT #3019

INTRODUCTION

Oncogenic alterations in fibroblast growth factor receptors (FGFR) are seen across multiple solid tumors. Debio 1347 is an oral, highly selective FGFR1/2/3 inhibitor undergoing phase I clinical trial evaluation in patients harboring an FGFR genetic abnormality. The availability of tumor tissue for genotyping, diversity of genetic alterations, and concordance with central laboratory (CL) testing were evaluated.

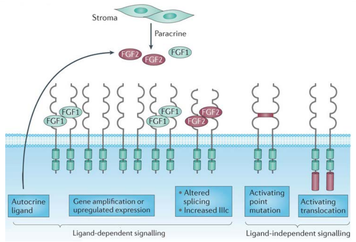

Figure 1. Figure 1. (A) Mechanisms of FGFR activation (adapted from Knowles et al., 2015[1]).

METHODS

Patients harboring an FGFR1/2/3 gene amplification, mutation, or fusion were identified by local laboratories using different technologies, including DNA or RNA-based high-throughput sequencing, FISH or Nanostring. Patients were enrolled into the study based on local identification of one of the FGFR alterations as specified in the study protocol. Enrolled patients received escalating doses of Debio 1347 from 10 to 150 mg/daily. Diagnostic tumor tissue was secured for post hoc analysis at a CL to confirm alterations reported on enrollment. Whenever possible, fresh biopsies were collected at screening for comparison.

RESULTS

Central Laboratory Genotype Confirmation (Diagnostic FFPE +/- Screening Biopsy)

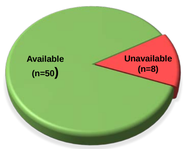

Figure 2. 86% of patients had either a diagnostic FFPE or on-study biopsy that could be used in Central Lab genotype confirmation

On-Study Screening Biopsy Versus Diagnostic FFPE For Testing Availability/Sufficiency

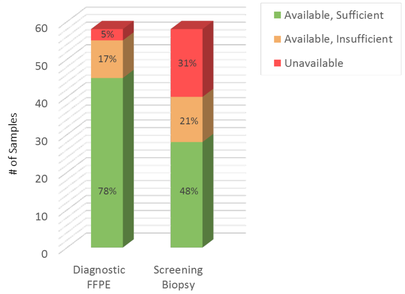

Figure 3. Overall, diagnostic tissue was more readily secured than on-study biopsies.

REFERENCES

(1) Knowles M.A. et al. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nature Reviews Cancer. (2015) 15, pages 25–41

RESULTS

On-Study Screening Biopsy Versus Diagnostic FFPE For Testing Availability/Sufficiency

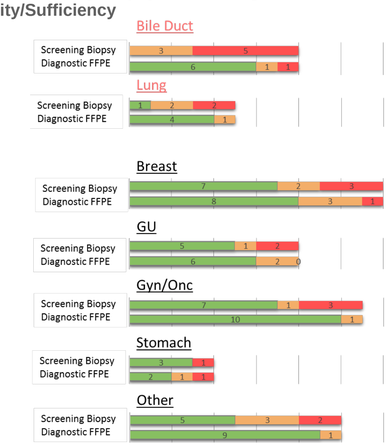

Figure 4. By disease site. There was largely no ability to obtain screening biopsies from bile duct and lung but a reasonable ability to obtain screening biopsies for breast, GU, Gyn/Onc, and stomach tumors.

Concordance of Central Lab Test Results Derived from Diagnostic or Screening Biopsy Tissue Relative to Original Testing Performed by Site

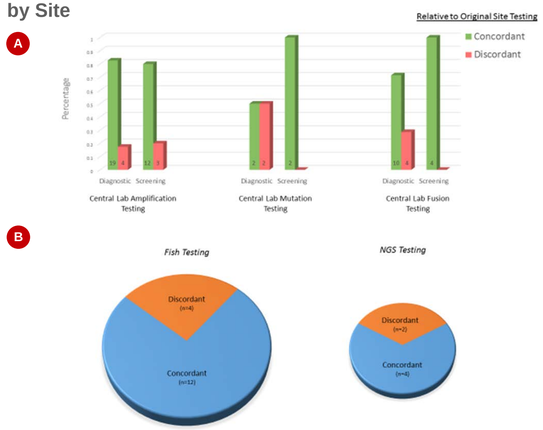

Figure 5. (A) Concordance of Central Lab test results derived from diagnostic or screening biopsy tissue relative to original testing performed by sites, (A) depending on type of genetic alteration detected, (B) depending on technology used. The cofounding factors are however that the screening and diagnostic samples were tested at different sites and on different platforms. Central lab detected mutations and fusions by NGS, and amplification by FISH.

Therapeutic Response Relative to Tissue Genotype in Diagnostic Tissue

		Central Laboratory Diagnostic Tumor Testing				On-Study Response				
Tumor type	Site Diagnostic Tumor Testing	Condordant?	Amplification	Mutation (AF)	Fusion (reads)	BOR (non-confirmed response)	BOR (RECIST 1.1 confirmed response)	Dose [mg]	Safety	Best target lesion change
ESOPHAGEAL CANCER	FGFR1 amplif	N	FGFR1 (1.0)	-	-	PD	PD	80 mg	Yes	28.26
HIGH GRADE ENDOMETRIOID ADENOCARCINOMA, CERVICAL CANCER	FGFR2 amplif + FGFR2 mut	Y	FGFR2 (25)	Two FGFR2 mut (95 and 88%)	-	PR	PR	80 mg	Yes	-50
BREAST CANCER	FGFR1 amplif	Y	FGFR1 (4.2)	-	-	PD	PD	80 mg	Yes	22
SIGNET RING ADENOCARCINOMA PRIMARY SITE UNKNOWN	FGFR1 amplif + FGFR2::INA fusion	N	FGFR1 (1.0)	-	FGFR2:INA fusion (191r)	PR	NA	110 mg	Yes	-39.64
BREAST CANCER	FGFR1 amplif	Y	FGFR1 (2.6)	-	-	PD	PD	80 mg	Yes	13.79
UROTHELIAL CARCINOMA	FGFR3:TACC3 fusion	Y	-	-	FGFR3 :TACC3 fusion (363r)	PR	SD	80 mg	Yes	-40
HIGH GRADE SARCOMATOID MALIGNANT NEOPLASM	FGFR1 mut	N	-	No mutation detected		PD	PD	80 mg	Yes	35.91
GALLBLADDER CANCER	FGFR3 amplif (1.7) + FGFR3:TACC3 fusion	Y	nt	-	FGFR3: TACC3 fusion (991r)	SD	SD	110 mg	Yes	-14.29
INTRAHEPATIC CHOLANGIOCARCINOMA	FGFR2::DDX21, FGFR2:CTNNA3, FGFR2::SH2C fusion	Y/N	-	-	FGFR2:DDX21 fusion (708r)	SD	SD	110 mg	Yes	-13.04
ENDOMETRIAL CANCER	FGFR2 mut	Y	-	FGFR2 mut (25%)	-	SD	SD	80 mg	Yes	0
GALLBLADDER CANCER	FGFR2 mut	Y	-	FGFR2 mut (33%)	-	PD	PD	110 mg	Yes	#N/A
CHOLANGIOCARCINOMA	FGFR2::KIAA1217 fusion	Y	-	-	FGFR2:KIAA1217 fusion (196r)	SD	SD	110 mg	Yes	-7.27
UROTHELIAL CARCINOMA	FGFR3:TACC3 fusion		-	-	FGFR3:TACC3 fusion (469r)	SD	SD	150 mg	Yes	-25.84

Figure 6. Therapeutic response relative to tissue genotype in diagnostic tissue, FGFR alterations of patients who responded partially in green, those with stable disease in yellow and progressive disease in red. A correlation of lack of concordance between site diagnostic and central laboratory confirmatory testing was observed in some cases and correlated with progressive disease outcome.

Central Laboratory Genotype Concordance Between Diagnostic and Screening Samples

A

			Diagnostic					Screening		
				FGFR:CEP Ratio					FGFR:CEP Ratio	
Tumor type	Alteration reported on inclusion	Avg	Condordant?	Avg	>3	1.8-3	~1	Polysomic	Condordant?	Avg	Polysomic
UTERINE (ENDOMETRIUM)	FGFR1 amplif		Y	3.1	20%	10%	70%	28%	N	1.4	n
ENDOMETRIAL ADENOCARCINOMA	FGFR1 amplif		Y	5.2	94%	4%	2%	4%	Y	2.2	y
SEROUS CARCINOMA TO THE PERITONEUM	FGFR3 amplif	4.6	Y	2.3	18%	58%	24%	56%	Y	6.1	n
UTERINE CARCINOSARCOMA	FGFR2 amplif	2.1	Y	2.1	22%	40%	38%	24%	Y	2.6	n
PROSTATE	FGFR1 amplif	2.9	Y	2.3	28%	42%	32%	22%	N	1.4	y
ESOPHAGEAL CANCER	FGFR1 amplif		N	1	2%	12%	86%	66%	N	1.5	n
HIGH GRADE ENDOMETRIOID ADENOCARCINOMA, CERVICAL CANCER	FGFR2 mut (FGFR2 amplif)	32	Y	25	100%	0%	0%	0%	Y	15	n
BREAST CANCER	FGFR1 amplif	2.8	Y	4.2	70%	30%	0%	22%	Y	2.8	n
SIGNET RING ADENOCARCINOMA PRIMARY SITE UNKNOWN	FGFR1 amplif (+INA:FGFR2 fusion)	2	N	1.1	2%	18%	80%	44%	Y	no amplif	n
SQUAMOUS NSCLC	FGFR1 amplif	2.9	N	1.1	0%	16%	84%	18%	N	3.5	n
BREAST CANCER	FGFR1 amplif	15.9	Y	3	50%	48%	2%	84%	Y	40	y
GASTRIC CANCER	FGFR1 amplif	5.3	Y	5.2	100%	0%	0%	0%	N	1.8	
	FGFR2 amplif	4.0	Y	2.3	16%	46%	38%	20%	Y	3.5	n
GASTRIC CANCER	FGFR2 amplif	33	Y	25	100%	0%	0%	0%	Y	40	n
BREAST CANCER	FGFR1 amplif	17	Y	2.9	36%	60%	4%	82%	Y	3.2	y
BREAST CANCER	FGFR2 amplif	6	Y	2.6	30%	42%	28%	14%	Y	13.7	n
BREAST CANCER	FGFR1 amplif	27	Y	2.6	34%	30%	36%	20%	Y	6.3	n

B

		Diagnostic		Screening	
Tumor type	Alteration reported on inclusion	Condordant?	Genotype	Condordant?	Genotype
SIGNET RING ADENOCARCINOMA PRIMARY SITE UNKNOWN	INA:FGFR2 fusion (+FGFR1 amplif)	Y	FGFR2:INA fusion	nd	Technology not allowing this fusion detection
ANAL SQUAMOUS CELL CARCINOMA	FGFR3 mut	N	(PIK3CA)	Y	FGFR3 mut
CANCER OF UNKNOWN PRIMARY	FGFR2::BICC1	Y	FGFR2::BICC1 fusion	nd	Technology not allowing this fusion detection
UROTHELIAL CARCINOMA	FGFR3-TACC3 fusion	Y	FGFR3::TACC3 fusion	Y	FGFR3::TACC3 fusion
ADENOID CYSTIC CARCINOMA	G561A FGFR3 mut	N	-	Y	FGFR3 mut
HIGH GRADE ENDOMETRIOID ADENOCARCINOMA, CERVICAL CANCER	FGFR2 mut (FGFR2 amplif)	Y	FGFR2 Missense	nd	No biopsy material

Figure 6. Central Laboratory Genotype Concordance Between Diagnostic and Screening Samples, FISH testing (A), NGS testing (B).

CONCLUSIONS

- The clinical diagnostic landscape proves to be complex.
- The use of various technologies with different sensitivities and analysis pipelines constitute one of many diagnostic hurdles.
- Biopsy availability across different cancer types and tumor heterogeneity add to its complexity, as well as tumor evolution over time from initial diagnosis to treatment.

CLINICAL TRIAL

Debio 1347 (CH5183284) is currently under phase II clinical investigation in selected patients harboring FGFR fusions (NCT03834220).

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