SAFETY AND EFFICACY OF THE SELECTIVE FGFR INHIBITOR DEBIO 1347 IN PHASE 1 STUDY PATIENTS WITH FGFR GENOMICALLY ACTIVATED ADVANCED BILIARY TRACT CANCER

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ABSTRACT #447

SUMMARY

- Biliary tract cancers (BTC) are aggressive tumors with limited treatment options and poor overall survival.
- Aberrant Fibroblast Growth Factor Receptor (FGFR) signaling has been implicated in BTC carcinogenesis.
- Debio 1347 is an orally available selective FGFR inhibitor with potent antitumor effect in preclinical model bearing FGFR alterations.[1,2]
- Debio 1347 showed encouraging preliminary clinical activity and manageable treatment-emergent adverse events (TEAEs) in its first-in-human (FIH) Phase 1 study dose-escalating part (NCT1948297).[2]
- Here we report preliminary results from the BTC patients of the dose-escalation portion of this study.

METHODS

- This FIH study enrolled patients with advanced solid malignancies harboring defined activating alterations of FGFR1, 2, or 3: amplifications, mutations and translocations.
- Pharmacokinetics and pharmacodynamics were serially evaluated in blood, skin and/or tumor tissue.
- A confirmatory post-hoc analysis was performed centrally for all available biopsies.

RESULTS

- Eight patients, six with intrahepatic cholangiocarcinoma (iCCA) and two with gallbladder cancer (GBC), were treated with Debio 1347 at doses between 60 and 150 mg orally daily in 28-day cycles (Table 1).
- All patients had been heavily pretreated, with 1-5 prior systemic lines of treatment (mostly 2 or 3 lines).
- The most common TEAEs were hyperphosphatemia (8/8), nail changes (5/8), nausea (5/8), dry mouth (4/8) and stomatitis (3/8).
- No Grade ≥ 3 related TEAEs were reported except Grade 3 hyperphosphatemia (4/8).
- A partial response was observed in an iCCA patient, whose tumor habored a FGFR2 mutation (deletion exon 5). The duration of treatment was 57 weeks.
- The Independent Radiological Review updated this response to confirmed complete response (CR) (Fig. 2, Fig. 3).
- Three additional iCCA patients (FGFR2 translocations: ROCK1; KIAA1217; DDX21) and one GBC patient (FGFR3-TACC3 translocation) had target lesions regression < 30% and stayed on treatment between 24 – 37 weeks (Fig. 1, Fig. 4).
- Overall disease control rate was 62.5%.
- Increase in phosphate levels , used as an indicator of target engagement, was observed in all patients (Fig. 5).
- Pharmacokinetics in BTC patients was comparable to that in patients with other solid malignancies (Fig. 6).

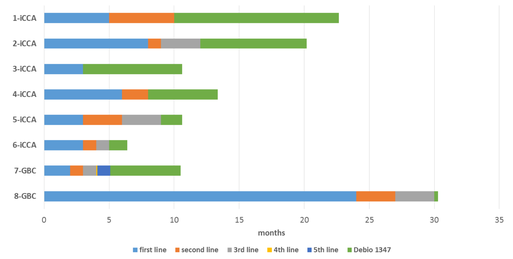

Figure 1 Duration of treatment to Debio 1347 versus prior chemotherapies

ID #	Age	Genetic alteration	Previous lines of treatment	Previous treatments	Treatment duration (months)	BOR	Debio 1347 Dose (mg)	Best relative change in tumour size	BOR (RECIST)	Treatment duration (weeks)
1 iCCA	55	FGFR2 Mutation (del ex 5)	2	Hepatectomy	Palliative surgery		110 reduced to 80	-51.23%	PR	Up to 57
				1st line - Gemcitabine	5 mo	PD				
				Liver tumor resection	Palliative surgery					
				2nd line - Cisplatin	5 mo	PD				
2 iCCA	55	FGFR2 Fusion (ROCK1)	3	Hepatectomy resection liver partial lobectomy, cholecystectomy, laparoscopy diagnostic	Curative surgery		60	-21.43%	SD	Up to 36.9
				1st line - Rituximab	8 mo	PR				
				2nd line - Rituximab + cyclophosphamide + vincristine + doxorubicin	1 mo	PR				
				3rd line - Gemcitabine + cisplatin	3 mo	SD				
3 iCCA	45	FGFR2 Fusion (KIAA1217)	1	Gemcitabine + oxaliplatin	3 mo	PD	110	-14.02%	SD	Up to 34.3
				Surgery related to recurrence of liver lesions	Palliative surgery					
4 iCCA	54	FGFR2 Fusion (DDX21)	2	1st line - Gemcitabine + cisplatin	6 mo	PR	110 reduced to 80	-13.04%	SD	Up to 24.1
				Cholecystectomy, laparoscopy diagnostic, exploratory laparoscopy, exploratory celiotomy	Curative surgery					
				2nd line – Gemcitabine + cisplatin	2 mo	PD				
5 iCCA	63	FGFR2 Mutation (Y805FS11)*	3	Radiotherapy			80	+63.16%	PD	Up to 7.3
				1st line - Docetaxel	3 mo	Unknown				
				2nd line - Gemcitabine + cisplatin	3 mo	Unknown				
				3rd line - Xeloda (capecitabine)	3 mo	PD				
6 iCCA	70	FGFR3 Mutation (D758N)*	3	1st line - Gemcitabine + cisplatin + abraxane	3 mo	PD	150	+21.78%	PD	Up to 6.3
				2nd line - IDH 305 (IDH1 inhibitor)	1 cycle	PD				
				3rd line - Folic acid + 5-FU + irinotecan	1 cycle	PD				
7 GBC	65	FGFR3 Fusion (TACC3)	5	Diagnostic laparoscopy, cystic duct lymph node biopsy, tru-cut liver biopsy, cholecystectomy			110 Reduced to 60mg	-14.29%	SD	Up to 24.3
				1st line - Folfox	2 mo	CR				
				Radiotherapy						
				2nd line - Gemcitabine	1 mo	Unknown				
				3rd line - modified Folfox	1 mo	Unknown				
				4th line - modified Folfox	1 d	CR				
				5th line - Gemcitabine + cisplatin	1 mo	SD				
8 GBC	67	FGFR2 Mutation (S529C)	3	Cholecystectomy			110	Unknown	PD	Up to 1.3
				1st line - Gemcitabine + cisplatin	2 years	PD				
				2nd line - Oxaliplatin + 5FU + irinotecan	3 mo	PD				
				3rd line - Bevacizumab	3 mo	PD				

* Alteration outside of tyrosine kinase domain

Table 1 Characteristics of the BTC patients enrolled in the Phase I Study (dose-escalation part) and preliminary efficacy results obtained with Debio 1347

(1) Nakanishi et al. The fibroblast growth factor receptor genetic status as a potential predictor of the sensitivity to CH5183284/Debio 1347, a novel selective FGFR inhibitor. Mol Cancer Ther 2014;13:2547-2558.
(2) A. Vaslin Chessex et al. Preclinical activity of Debio 1347, an oral selective FGFR1, 2, 3 inhibitor, in models harboring FGFR alterations. European Journal of Cancer 50(6):177-178, 2014
(3) M.H. Voss et al. Debio 1347, an oral FGFR inhibitor: Results from a first-in-human, phase I dose-escalation study in patients with FGFR genomically activated advanced solid tumors. Journal of Clinical Oncology 35, no. 15_suppl (May): Abstract 2500, 2017

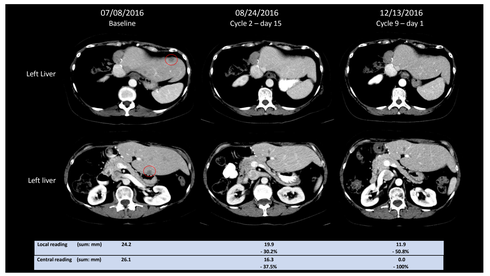

Figure 2 Response at 110 mg in iCCA patient with FGFR2 mutation (del ex 5)

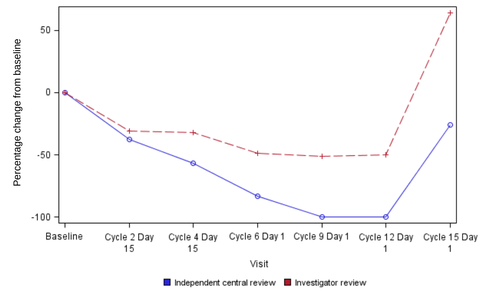

Figure 3 Response at 110 mg in iCCA patient with FGFR2 mutation (del ex 5). Comparison between Investigator and Independent Radiological Review.

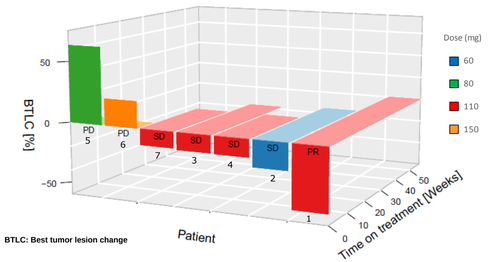

Figure 4 Best percent tumor lesion change from baseline in target lesion size and duration of treatment in patients with BTC and FGFR gene alterations.

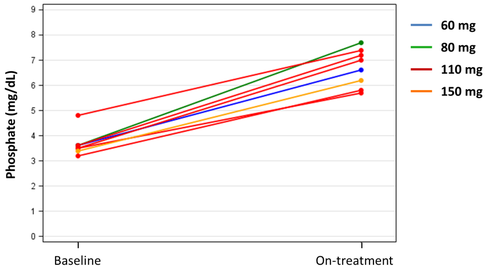

Figure 5 Phosphate modulation observed in BTC patient subset

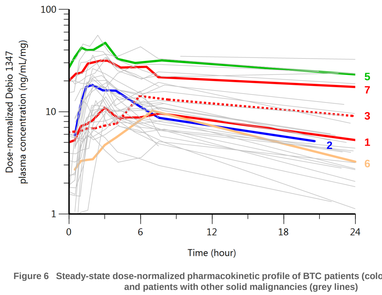

Figure 6 Steady-state dose-normalized pharmacokinetic profile of BTC patients (colored lines) and patients with other solid malignancies (grey lines)

CONCLUSIONS

- All explored doses demonstrated sustained plasma exposure to Debio 1347 and target engagement.
- These results suggest that BTC patients with genomic events, translocations and mutations leading to activation of FGFR2/3, may benefit from treatment with Debio 1347.
- Further recruitment is ongoing in the expansion cohort of this trial focused on translocations only.

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