DEBIO 1347 IN PATIENTS WITH GASTROINTESTINAL CANCERS HARBORING AN FGFR GENE FUSION: PRELIMINARY RESULTS

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BACKGROUND

Aberrant FGFR signaling has been implicated in GI cancer carcinogenesis especially in biliary tract, gastro-esophageal and colon cancers.

Debio 1347 is a selective oral inhibitor of FGFR 1-3 tyrosine kinases. It exhibited high antitumor activity in *in vitro* and *in vivo* tumor models with FGFR1-3 gene alterations.[1,2] Debio 1347 showed encouraging preliminary clinical activity and manageable treatment-emergent adverse events (TEAE) in its first-in-human (FIH) phase 1 study (NCT1948297). Here we report results from the patients with GI cancers harboring an FGFR fusion.

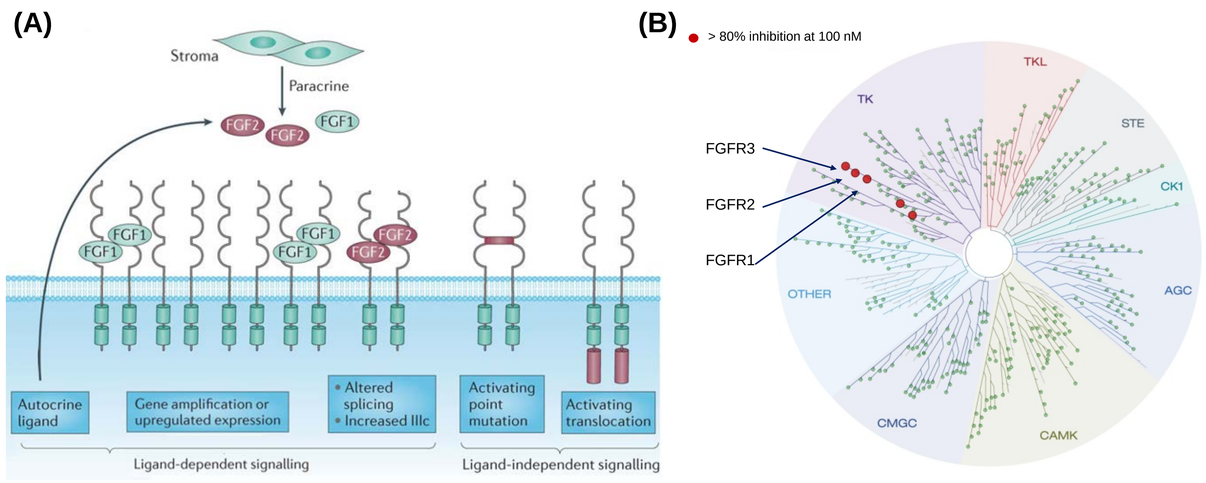

Figure 1. (A) Mechanisms of FGFR activation (adapted from Knowles et al., 2015).[4]
(B) Kinome Scan panel (442 kinases). Image generated using TREEspot™ Software Tool and reprinted with permission from KINOMEscan®, a division of DiscoveRx Corporation©.

METHODS

This FIH study enrolled patients with advanced solid malignancies harboring activating alterations of FGFR 1, 2, or 3. A confirmatory post-hoc genetic analysis was performed centrally for all available biopsies.

Patients received Debio 1347 at doses between 60 and 150 mg orally daily in 28-day cycles. Pharmacokinetics and pharmacodynamic were serially evaluated in blood, skin and/or tumor tissue.

The primary endpoints were to investigate the safety and to determine the MTD in the dose-escalation part of the study. Objective response rate (ORR) assessed per RECIST 1.1 and safety were the primary endpoints in expansion part.

EFFICACY

Eight-teen patients harboring FGFR1-3 fusions were enrolled as of March 11, 2019. Among 13 patients with GI cancers, 8 had intrahepatic cholangiocarcinoma (7 FGFR2 and one FGFR1 fusion), 1 had a gallbladder cancer (FGFR3 fusion), 2 had a colon cancer (FGFR2 fusion), and 2 had a gastric cancer (FGFR2 and FGFR3 fusion).

All had prior systemic therapy (mostly 2 or 3 lines; range 1-5). Partial responses were observed in 3 over 10 of the evaluable patients, 2 with a colon cancer and one with a cholangiocarcinoma; additional 6 patients had target lesions regression < 30% (SD).

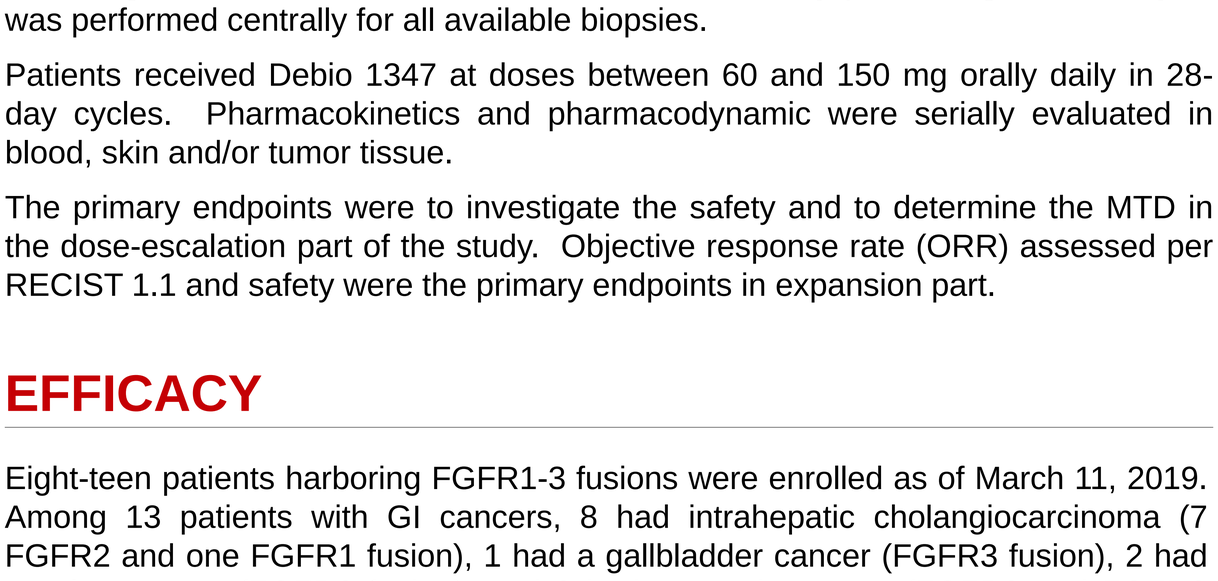

Figure 2. Time on treatment and time on previous therapies

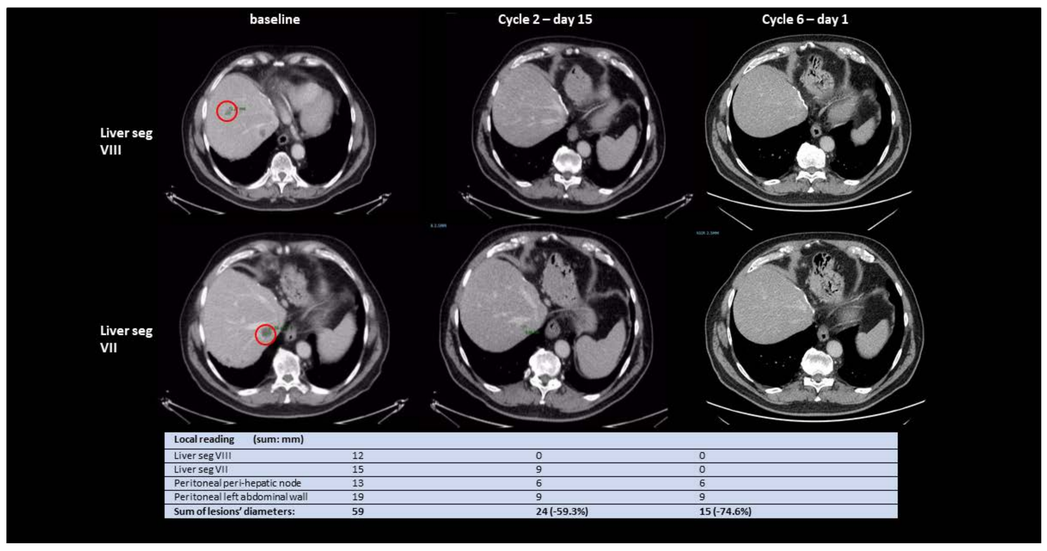

Figure 3. Response at 80 mg in a 68 years old male with an iCCA patient with FGFR2 fusion

SAFETY

Debio 1347 - All doses (N=13)		
TEAEs (MedDRA Preferred Term)	**All Grades (%)**	**Grade 3-4 (%)**
Hyperphosphataemia	69	31
Nausea	61	
Constipation	54	
Fatigue	54	
Alopecia	46	
Nail changes	46	
Blood bilirubin increased	31	
Decreased appetite	31	
Diarrhoea	31	
Dry skin	31	
Palmar-plantar erythrodysaesthesia syndrome	31	
Stomatitis	31	
Vomiting	31	
Cough	23	
Dry eye	23	
Dry mouth	23	
Dysgeusia	23	
Oedema peripheral	23	

The median time on treatment was 24 weeks (range 4-47). The most common TEAEs were hyperphosphatemia, nausea, constipation, fatigue, alopecia and nail changes.

Only Grade 3 TEAE was hyperphosphatemia in 4 patients (31%).

CONCLUSION

DEBIO 1347 demonstrated promising antitumor activity in patients with GI cancers harboring an FGFR1-3 fusion with an acceptable initial safety profile.

The FUZE clinical trial of Debio 1347 for patients with advanced solid tumors harboring FGFR1-3 fusions includes patients with GI cancers (NCT03834220).

REFERENCES

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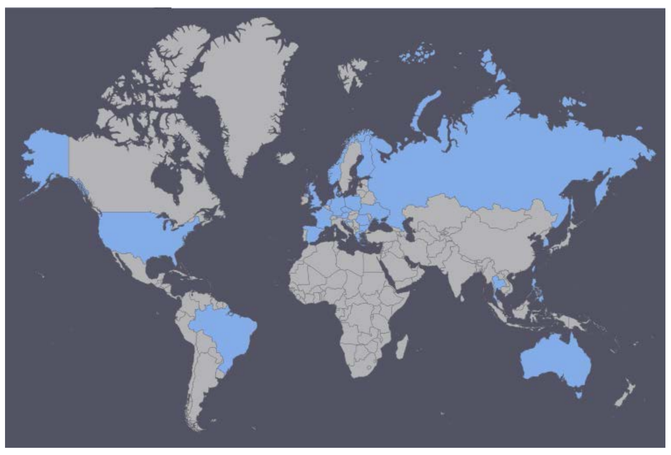

FUZE is a worldwide clinical trial with participating countries in blue Recruitment started in February 2019

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