FUZE Clinical Trial: a Phase 2 study of Debio 1347 in FGFR fusion-positive advanced solid tumors irrespectively of the tumor histology

#TPS3157

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BACKGROUND

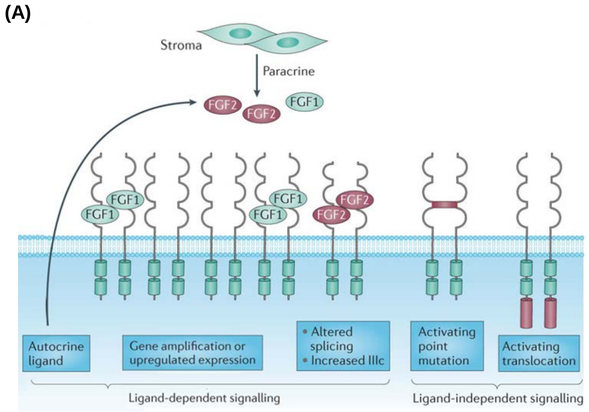
Dysregulation of fibroblast growth factor receptor (FGFR) signaling by FGFR fusions is implicated in many cancers.

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 fusions. [1,2]

Results from dose-escalation part of ongoing Phase 1 (NCT01948297) show efficacy and tolerability in patients harboring FGFR 1-3 fusion irrespectively of tumor type. [3]

Here we present the design for a multicenter, basket, 2-stage, adaptive single arm Phase 2 trial investigating Debio 1347 in patients with solid tumors harboring FGFR1-3 fusion/rearrangement.

(A)



(B)

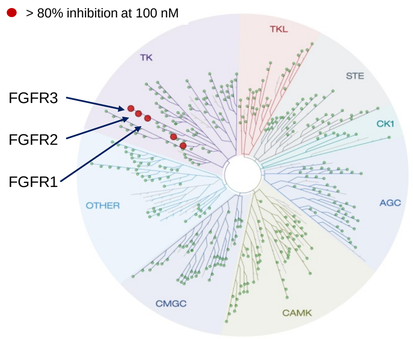


Figure 1. (A) Mechanisms of FGFR activation (adapted from Knowles et al., 2015). [4] **(B) Kinome Scan panel (442 kinases). Image generated using TREEspot™ Software Tool and reprinted with permission from KINOMEscan®, a division of DiscoveRx Corporation©.**

FGFR FUSION TESTING

The FGFR fusion testing is performed by Caris Life Sciences and the turnaround time is within 14 days from sample receipt.

The FGFR fusion pre-screening is done using Whole Transcriptome Sequencing (WTS) test.

FDA has granted Breakthrough Device designation for the WTS CDx assay.

Patients can be enrolled based on a local testing result, but in that case, a post-hoc confirmatory test by Caris is required.

References

(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: A Phase I, Open-Label, Multicenter, Dose-escalation Study of the Oral Selective FGFR Inhibitor Debio 1347 in Patients with Advanced Solid Tumors Harboring FGFR Gene Alterations. Clin Cancer Res. 2019 May 1;25(9):2699-2707.
(4) Knowles MA et al. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer. 2015 Jan;15(1):25-41.

ELIGIBILITY

Main Inclusion Criteria

- Cytologically or histologically confirmed advanced solid tumor
- Age ≥18 years
- Locally-advanced (unresectable) or metastatic disease harboring an FGFR1-3 gene fusion/rearrangement
- The subject must have received at least one prior line of standard therapy appropriate for tumor type and stage of disease (if available)
- Measurable disease according to RECIST criteria version 1.1
- Eastern Cooperative Oncology Group performance status 0 to 1
- Laboratory values:
  - Total bilirubin ≤ 2 x UNL
  - Creatinine clearance ≥ 30 mL/min
  - AST and ALT ≤ 2.5 x UNL (5 x UNL in the presence of liver metastases)
  - Serum Phosphate < 1.5 x UNL

Main Exclusion Criteria

- Chemotherapy, radiotherapy or small molecule anti-cancer agents within 2 weeks prior to initial dosing with Debio 1347 Prior treatment with a FGFR1-3 selective inhibitor
- Known evidence of clinically significant corneal/retinal disorder confirmed by ophthalmologic examination
- History and/or current evidence of ectopic mineralization/calcification
- Symptomatic or unstable brain metastases < 1 month

STUDY OBJECTIVES

Primary

- Efficacy of Debio 1347 in terms of objective response rate (ORR)

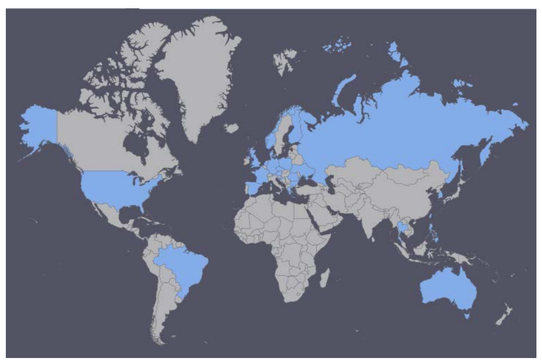
Secondary

- Efficacy of Debio 1347 in terms of duration of response (DoR), DCR, PFS and OS
- To assess the safety of Debio 1347
- To assess exposure-response relationships vs efficacy & safety (notably QTcF)

Exploratory

- To assess the effects of intrinsic factors and extrinsic factors on the PK of Debio 1347
- Impact of biomarkers on Debio 1347 efficacy
- To assess patient-reported outcome - QOL questionnaire

STATUS



FUZE is a worldwide clinical trial with participating countries in blue

Recruitment started in February 2019

NCT03834220

STUDY DESIGN

Adaptive Phase-2, non-controlled, open-label, multicenter study (NCT03834220).

Subjects with solid tumors harboring FGFR1-3 gene fusion/rearrangement:

I. Cohort 1: biliary tract cancer
II. Cohort 2: urothelial cancer
III. Cohort 3: all other solid tumor histologies (Non-Small Cell Lung Cancer (NSCLC), head and neck cancer, thyroid cancer, oral cancer, breast cancer, prostate cancer, and other malignancies but excluding primary brain tumors)

Debio 1347 will be administered at 80 mg once daily (in the morning), with each cycle consisting of 28 days of dosing administered on a continuous basis in 28-day cycles until progression of disease or unacceptable toxicity.

Subjects will be treated with Debio 1347 daily in 28-day cycles until the occurrence of disease progression or unacceptable toxicity.

An interim analysis for futility and homogeneity will be performed after 27 evaluable patients.

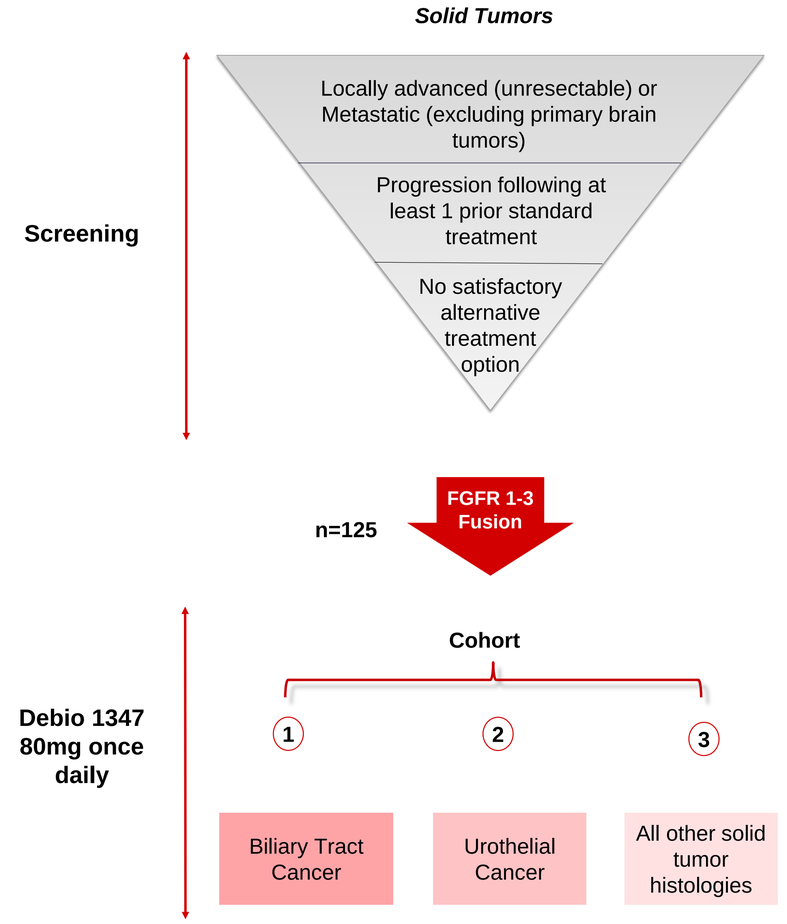


Figure 2. FUZE Trial Study Scheme

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