First-in-human Phase I "Basket" Study of Debio 1347 (CH5183284), a Novel FGFR Inhibitor in Patients with FGFR Genomically Activated Advanced Solid Tumors

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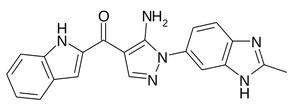
Background

Debio 1347 is a novel FGFR inhibitor for cancer therapy

The fibroblast growth factor receptors (FGFRs) are tyrosine kinases that regulate multiple biological processes, such as cell proliferation, migration, apoptosis, and differentiation. Various genetic alterations, such as gene amplifications, point mutations, or chromosomal translocations/rearrangements, can enhance kinase activity of the receptors and the pathway signaling, which is associated with tumor growth and survival. Therefore, the FGFR family represents an attractive therapeutic target for treating cancer.

Debio 1347/CH5183284, an orally available and selective inhibitor of FGFR1, 2, and 3 displayed preferential antitumor activity against cancer cells with various FGFR genetic alterations in a panel of 327 cancer cell lines and in xenograft models. In addition, the unique ability of Debio 1347/ CH5183284 to inhibit a relevant FGFR2 gatekeeper mutant (V564F) was documented in cellular phosphorylation assays, both *in vitro* and *in vivo*.

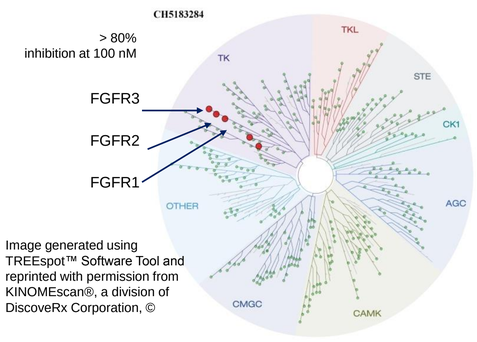
Chemical structure



Molecular weight: 356 Da
ATP competitive
Kinase activity IC_{50} (nM)

FGFR1	9
FGFR2	8
FGFR3	22
FGFR4	290
KDR	2100

KinomeScan panel (442 kinases)



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Methods

Objectives

Primary

Dose escalation part

- To identify dose limiting toxicities (DLT) and estimate the maximally tolerated dose (MTD) of Debio1347/CH5183284 in patients with advanced solid malignancies, whose tumors have an alteration of the FGFR 1, 2 or 3 genes.

Expansion part

- To evaluate the safety profile at the recommended dose, in a larger cohort of patients.

Secondary

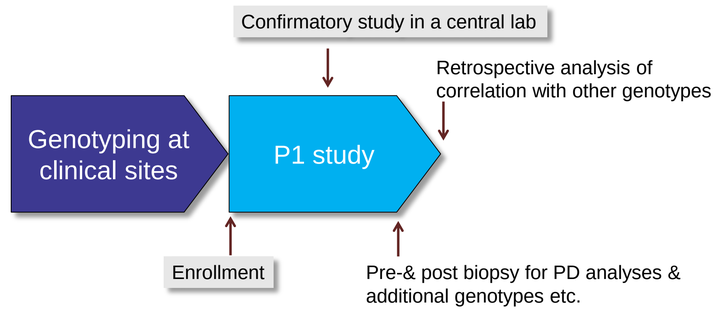
- To determine the recommended dose for the expansion phase of Debio1347/CH5183284
- To explore the anti-tumor activity of Debio1347/CH5183284 in patients with advanced solid malignancies, whose tumors have an alteration of the FGFR 1, 2 or 3 genes.
- To make a preliminary assessment of biologic markers that might act as predictors of Debio1347/CH5183284 anti tumor activity in patients with advanced solid malignancies, whose tumors have an alteration of the FGFR 1, 2 or 3 genes.
- To determine the PK parameters of Debio1347/CH5183284 after single and repeated administration.

Eligibility Criteria include:

- Patients with advanced solid malignancies, whose tumours have an alteration of the FGFR 1, 2 or 3 genes, confirmed by genetic tests
- Age ≥ 18 years.
- ECOG PS ≤ 2.
- Adequate organ function
- Phosphate ≤ 1.1 x ULN;
- No history and/or current evidence of endocrine alteration of Ca^{++}/P^{+++} homeostasis.
- No brain tumors and/or brain metastases
- No corneal disease, such as bullous or band keratopathy, corneal desquamation, keratitis, corneal ulcer, or keratoconjunctivitis.

	Dose escalation part	Expansion part "selected tumors-genotypes" + "Basket trial"
DE Design	3+3 design Extra slots up to 3 allowed	
Tumor types	Solid tumors with FGFR1, 2 or 3 genetic alteration, such as bladder, sq NSCLC, gastric, breast and H&N cancer patients	• Bladder cancer with FGFR3 fusion (n=10) • Sq NSCLC with FGFR 1 amplification (n=10) • Gastric cancer with FGFR2 amplification (n=10) • Breast cancer with FGFR 1, 2 and 3 amplification (n=10) • Other different histological tumor types with FGFR1, 2 or 3 alterations (Basket trial cohort, n=20)
Patient #	Approx. 40	Approx. 60

Genetic screening



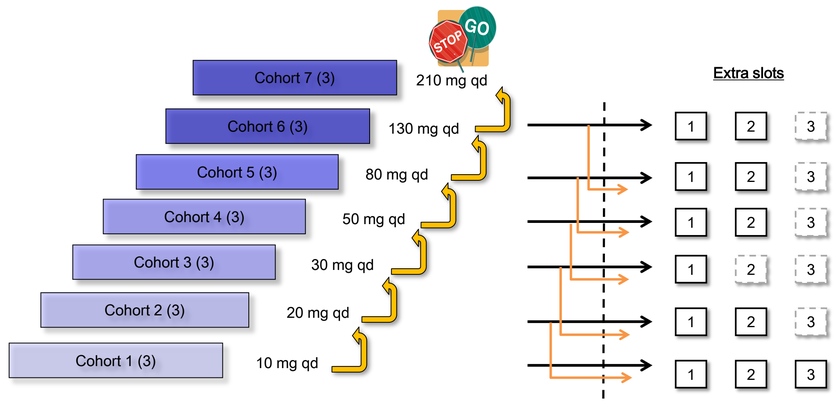
Dose Escalation Study design

3 + 3 Design with extra slots

- Additional patients can be enrolled separately at the dose level below (up to 3 patients).

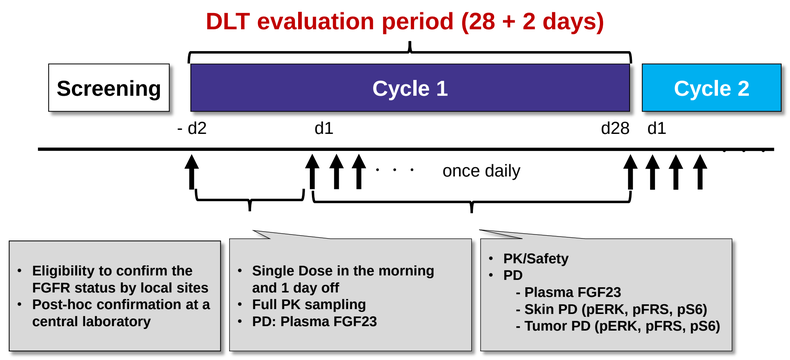
In case of no ≥ Grade 2 toxicity occurred

- 100% increment after the first dose, then a Fibonacci sequence up to 210 mg
- Further dose escalation to be discussed



In case ≥ Grade 2 toxicity occurred

- Stop enrolment to extra slots after Grade 2 toxicity
- Further dose levels will be escalated by 50% and then 40%



Definition of DLT

Non Hematologic:

Grade 3 diarrhea, constipation, nausea, vomiting or skin toxicity that lasts longer than 72 h despite optimal symptomatic therapy,

Grade 4 diarrhea, constipation, nausea, vomiting or skin toxicity

Any ≥ Grade 3 non-hematologic toxicity excluding

- Grade 3 electrolyte abnormalities lasting < 48 h
- Grade 3 hepatotoxicty that resolves to Grade 1 within 7 days or ≤ Grade 2 within 7 days in patients with liver metastases
- ≥ Grade 3 of ALP clearly related to bone metastases evolution

Hyperphosphatemia:

- Serum Pi > 7,0 mg/dL for > 7 consecutive days despite phosphorus lowering therapy for at least 14 days
- Serum Pi > 9,0 mg/dL despite phosphorus lowering therapy for at least 14 days
- Serum Pi > 10,0 mg/dL

Any toxicity which in the judgment of the investigator and Medical Monitor is considered a DLT

Hematologic:

Febrile neutropenia

≥ Grade 3 neutropenia persisting > 7 days

Grade 4 thrombocytopenia persisting > 7 days or Grade 3 thrombocytopenia requiring platelet transfusion

General:

Any treatment delay > 7 days because of treatment-related AEs or laboratory abnormalities occurring during the DLT period

Any other life threatening toxicity

Status

Recruitment started in September 2013.
Cohort 1 and 2 have been completed without DLT.
Cohort 3 began in May 2014.

ClinicalTrials.gov identifier: NCT01948297

Contacts

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