MATWIN
MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

ET-D5

First-in-class PP1 inhibitor - anti-cancer drug candidate

CONTEXT & BACKGROUND

The company is developing an innovative small molecule ET-D5, which is a new targeted therapy with an original molecular target involved in cancer progression. ET-D5 shows an anti-proliferative and anti-vascular activity. Contrary to many anti-vascular compounds, ET-D5 does not target tubulin or protein kinases but the Protein Phosphatase 1 (PP1). Overexpression of PP1 in certain cancers is correlated with poor prognosis, suggesting that a PP1 inhibitor may improve the survival of these patients. The inhibition of PP1 by ET-D5 leads to the destruction of tumor blood vessels and therefore effectively shuts down the supply of O2 and nutrients to cancer cells, provoking massive intratumoral necrosis.

Another mechanism by which ET-D5 targets (certain) cancer cells is by arresting their proliferation, followed by cell death. The team have identified a putative biomarker, associated with the sensitivity of responder cells and the validation of the biomarker is under way. Most importantly, ET-D5 presents interesting pharmacological properties and is active when administered orally. The company carried out the regulatory toxicology studies (ADMET) and defined the toxicology profile of ET-D5, allowing the first-in-human clinical trial. Contrary to many "traditional" chemotherapies, ET-D5 does not show haematological or gastrointestinal toxicity, suggesting that sensitive cancer cells (over) harbour mutations rendering them sensitive to ET-D5 action.

The proposed study is an open-label first-in-human (FIH) Phase I trial with an expansion cohort (Phase IIa), conducted in adult patients with advanced solid tumors. The primary objective of the proposed study is to define the Dose-Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and the recommended dose for the Phase II trial (RP2D) of ET-D5 as a single agent in patients with advanced solid cancers. Secondary objectives will be (i) to determine the safety profile of ET-D5; (ii) to evaluate its pharmacokinetics parameters in human; (iii) to obtain preliminary evidence of antitumor activity in patients with evaluable disease. Summing up, the successful realization of the project will open the way to the clinical development of the promising first-in-class compound ET-D5 in the field of oncology.
This trial will take up 40 months and should result in the clinical proof of concept of ET-D5. At the end of the trial we expect to have identified individual cancer types responding to ET-D5. The trial will pave the way to the randomized blinded trial of Phase IIb/III.

SCOPE

Preclinical and clinical development of the first-in-class cancer drug candidate

KEYWORDS

Protein phosphatase 1; PP1; cancer; first-in-class

The project is innovative and challenges the current state-of-the-art in several ways. We contest the common notion that ser/thr phosphatase inhibitors must be excessively toxic in vivo and show in terms of the actual toxicology results that the selective PP1 inhibitor ET-D5 is much better tolerated than the non-selective PP2A/PP1 inhibitor cantharidine.
Finally, a canine Phase I/IIa clinical trial on patients suffering from spontaneous sarcomas is under way. This clinical trial allows us to quickly test the hypothesis that ET-D5 would be particularly active in sarcoma patients. The preliminary evidence of activity was already observed in this trial, validating this approach.

INNOVATIVE COMPONENT & TECHNOLOGY

First-in-class selective protein phosphatase 1 inhibitor with an original mechanism of action.

OBJECTIVES

Realizing the proof-of-concept in the clinical trial of Phase I/IIa in monotherapy;
In parallel, realizing the preclinical proof-of-concept of the combination therapy in order to maximize the OS in cancer patients.

DEVELOPMENT & MATURATION STAGE

–Preclinical regulatory toxicology realized
–GMP CMC part realized
–IND application under way

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

Patent WO2011/107709/A1 - 2010
Grenoble University/Institut Curie/CNRS
Granted: EU, USA, Japan
National phase : Canada, EAPO

World-wide exclusive license

TARGET POPULATION

Patients suffering from aggressive, highly vascularized tumours, expressing relevant biomarker(s).

TARGET PROFILE

MOA	• Binds to the catalytic site of PP1, blocking its activity
Clinical pharmacology and PK	• Oral administration • Safety and PK profiles compatible with the daily dosing
Indication(s) and usage	• Aggressive, highly vascularized tumors (over) expressing the relevant biomarker
Primary efficacy endpoints	1. Tumor regression in monotherapy 2. Tumor regression in combination therapy; improved OS
Secondary efficacy endpoints	• Progression free survival • Objective response rate
Expected safety and tolerability outcomes	1. Rare hypersensitivity reactions; no CV AEs
Dosage and regimen	Oral nanosuspension or oral solid form; QD or BID

STRENGHTS & COMPETITIVE ADVANTAGES

- An original selective PPI inhibitor with robust IP and FTO.
- Robust and straightforward CMC
- Extremely potent in vitro effects across a panel of cell lines tested at nM concentrations
- Moderate effects on normal cells (fibroblasts) only observed at µM concentrations
- Orally active product
- Excellent safety and toxicology profile
- At least two in vivo activity biomarkers identified

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

- Product ready for the FIH clinical trial testing in cancer patients
- The company is open for partnerships and investment opportunities

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