

An open-label, multicentre, dose-escalation, first-in-human phase I study to evaluate safety, tolerability and antineoplastic activity of OATD-02 (dual arginase 1 and arginase 2 inhibitor) in patients with selected advanced and/or metastatic solid tumors

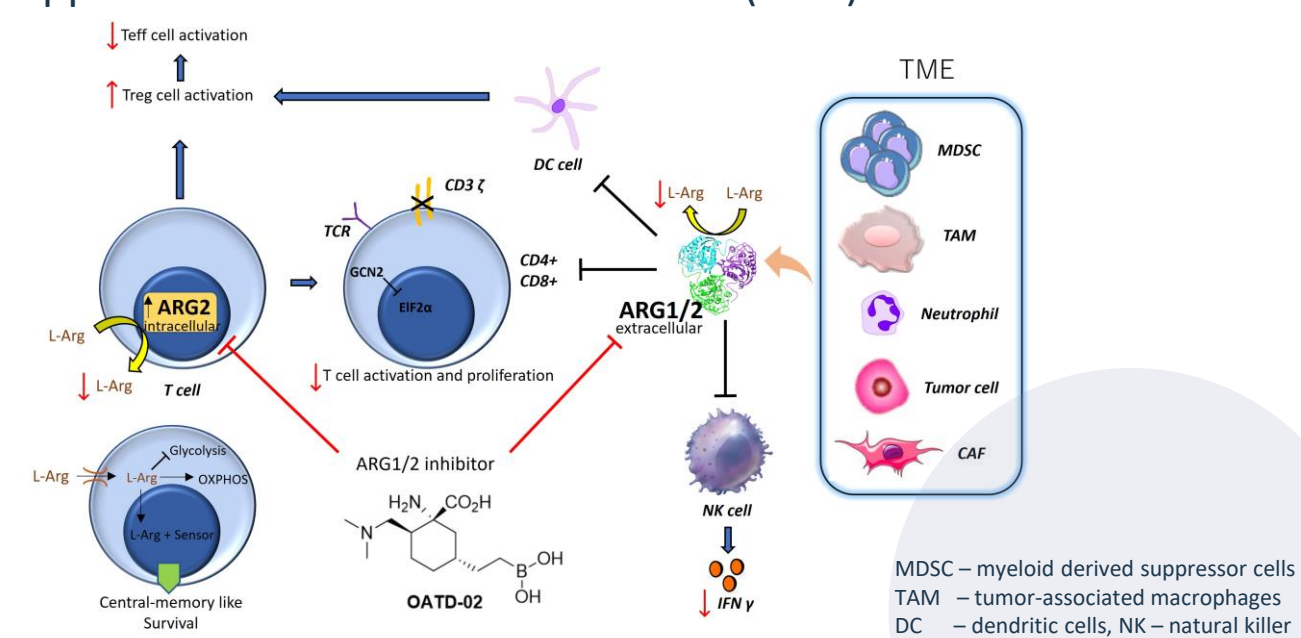
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OATD-02-C-01 study
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Therapeutic target

The **arginine** metabolism pathway is hyperreactive in several cancers and overexpression of arginases, **arginase 1 (ARG1)** and **arginase 2 (ARG2)**, is considered as a poor prognostic factor and major contributor to the immunosuppressive tumor microenvironment (TME).



The OATD-02 mechanism of action includes activation of NK cells and effector T-cells as well as central memory-like T cells.

OATD-02: ARG1 and ARG2 inhibitor

OATD-02 is the only small molecule with **dual activity** against intracellular **ARG1** and **ARG2** under clinical development. Through the direct inhibition of arginase activity, OATD-02 acts to increase and balance plasma and tumor arginine levels, which in turn **modulates the suppressive TME** leading to activation of NK and effector T cells. Data from non-clinical studies showed dose-dependent tumor growth inhibition with an associated increase in arginine levels in monotherapy setting. Prediction of human pharmacokinetics of OATD-02 resulted in moderate oral **bioavailability of 35%** and the **half-life of ~33 h**.

Despite the constant expansion of the therapeutic armamentarium, patients with advanced/metastatic **Colorectal Cancer (CRC)**, **Ovarian Cancer (OC)**, **Pancreatic Ductal Adenocarcinoma (PDAC)**, or **Renal Cell Carcinoma (RCC)** have limited options after standard of care therapies and high **unmet medical needs** once they relapse or progress. Low plasma arginine levels and high activity of ARG1 and ARG2 have been observed in patients with aggressive tumors including CRC, OC, PDAC, and RCC.

First-In-Human study OATD-02-C-01

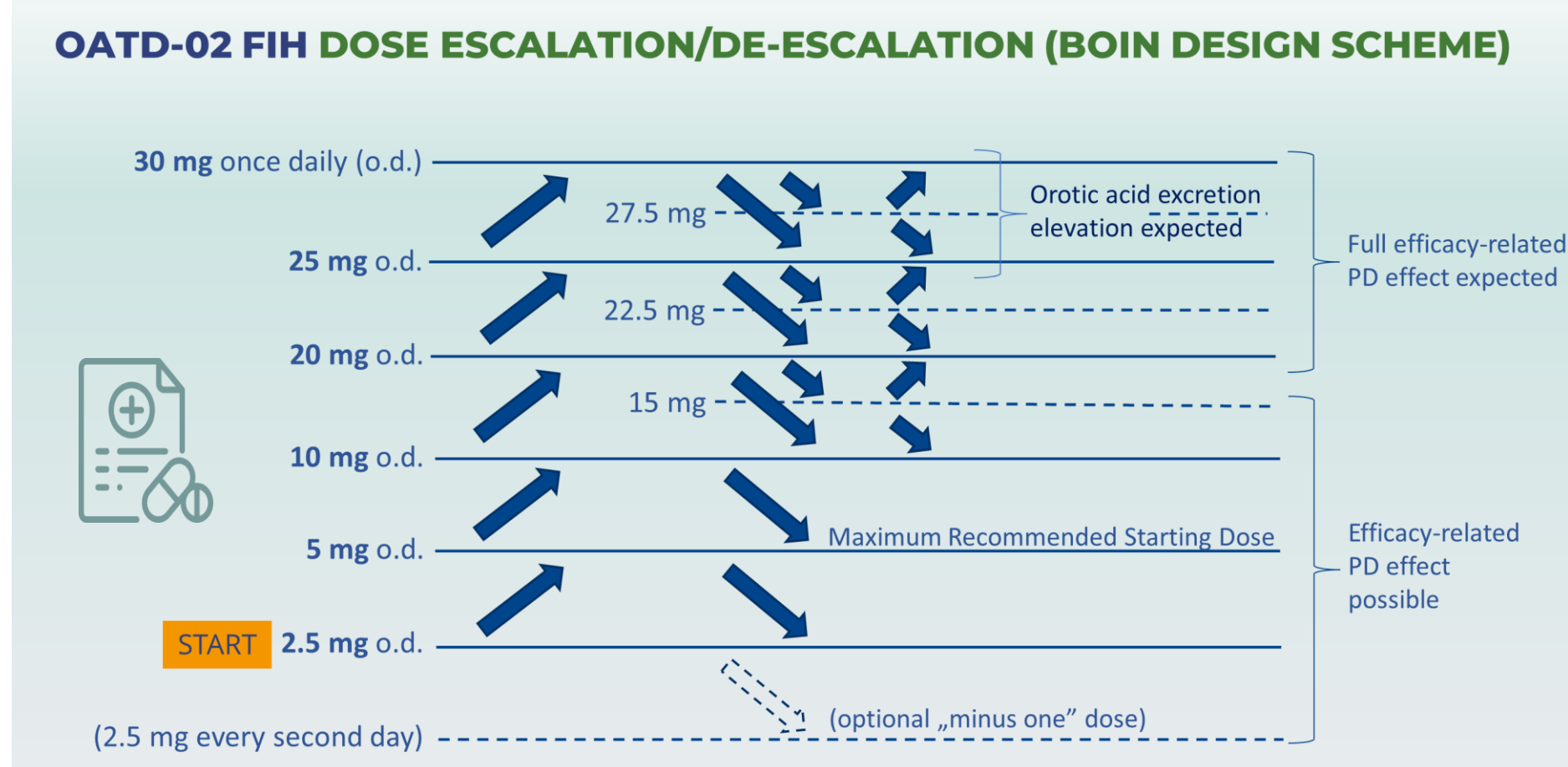
Key study information

The primary objective of this Phase I, open-label First-In-Human (FIH) clinical study is to investigate the **safety** and **tolerability of OATD-02** and determine the **MTD** and **RP2D** for OATD-02 administered as monotherapy.

Oral OATD-02 is administered in patients with advanced and/or metastatic colorectal, ovarian, pancreatic cancer, or renal cell carcinoma. Up to **40** female and male patients will be enrolled to receive OATD-02 once daily until disease progression. One study treatment cycle is **4 weeks**.

The study follows **Bayesian Optimal Interval (BOIN)** dose escalation/de-escalation design with overdose control based on **dose-limiting toxicities (DLTs)** during the evaluation period (first cycle).

Bayesian Optimal Interval Design



Study overview

Planned country / sites	Poland 3 sites in Warsaw, Otwock, Bydgoszcz
Study treatment	Six pre-defined dose levels of OATD-02 planned to be explored ranging from 2.5 mg to 30 mg (monotherapy)
Study population	30-40 male and female subjects with advanced cancers previously treated with standard of care therapies
Recruitment	Expected duration 18 months Drop-outs will not be replaced Re-screening is not allowed

Study endpoints

Primary Endpoints	<ul style="list-style-type: none"> Nature, frequency and severity of Adverse Events (AEs) Occurrence of DLTs
Secondary Endpoints	<ul style="list-style-type: none"> PK parameters for OATD-02 and major metabolite(s) (i.e. C_{max}, t_{max}, C_{min}, AUC_{0-24}) PD parameters (Arginine in plasma/serum) Anti-tumour activity parameters: <ul style="list-style-type: none"> Objective Response Rate (ORR) Duration of Response (DoR) Progression Free Survival (PFS)
Exploratory Endpoints	<ul style="list-style-type: none"> Concentrations of PD biomarkers in plasma at baseline and on treatment with OATD-02: <ul style="list-style-type: none"> Ornithine at pre-defined timepoints Other circulating biomarkers (e.g., microRNA, circulating tumour DNA [ctDNA], cell-free DNA [cfDNA]) Excretion of orotic acid in urine Liquid Chromatography coupled with tandem Mass Spectrometry characterisation of metabolites of OATD-02 in plasma and urine

Key study criteria

INCLUSION	<ul style="list-style-type: none"> Histologically or cytologically confirmed advanced and/or metastatic CRC, RCC, or PDAC, or recurrent serous OC (platinum-resistant/ineligible to receive platinum-based chemotherapy), that either progressed or relapsed after all relevant standard of care cancer therapies (at least 1 line of systemic cancer therapy) Imaging proof of measurable disease per RECIST 1.1 at Screening ECOG performance status of 0-1 Serum ammonia below ULN
EXCLUSION	<ul style="list-style-type: none"> Clinically active central nervous system metastases and/or carcinomatous meningitis; however, patients with treated brain or meningeal metastases may participate if lesions are radiologically stable Symptomatic ascites (except if due to OC) or pleural effusion Treatment with valproic acid/valproate-containing therapies, allopurinol and other xanthine oxidase inhibitors Liver failure and/or cirrhosis (Child-Pugh >A) Known deficiencies of urea cycle including deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase

Study progress

The first patient has been enrolled in the FIH study in March 2023.

As of September 2023, four patients have been enrolled.

The study is ongoing. ClinicalTrials.gov: NCT05759923.

All patients to complete the FIH study without major safety issues and with clinical benefit (no progression per RECIST 1.1) will be given an opportunity to enter a **rollover study** (no. OATD-02-C-02).

The first patient, at the OATD-02 daily dose of 2.5 mg, completed the 6 cycles of FIH study treatment and entered the rollover study in August 2023.

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