EVT801, a novel selective VEGFR-3 inhibitor targeting tumour angiogenesis, is pursuing dose escalation stage of Phase I first-in-human study

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For researchers:

Abstract #CT088

EVT801: A differentiating anti-tumour approach

Targeting tumour angiogenesis with the selective VEGFR-3 inhibitor EVT801 in combination with cancer immunotherapy

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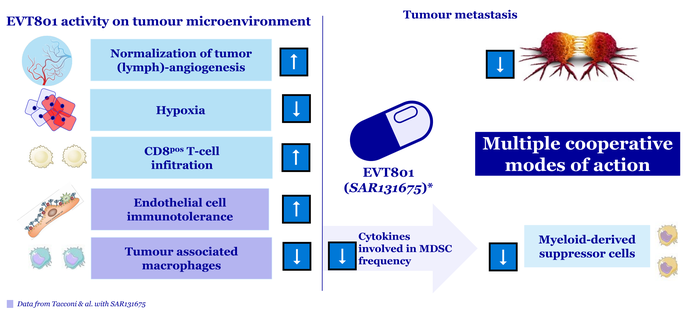


EVT801 MoA hypothesis: by destructing VEGFR3pos tumour blood vessels, EVT801 would induce tumour blood vessels normalization, reducing hypoxia and improving CD8 T-cells infiltration

NCT05114668
EVT801 in Phase I clinical trial KZA-0801-101

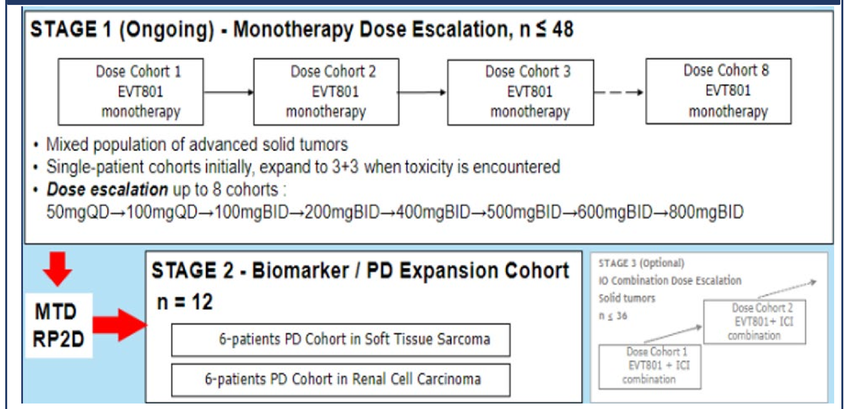
Approvals from regulatory bodies obtained in September 2021

- First-Patient-In in Oct 2021
- 2 clinical sites in France :
  - Toulouse (IUCT): PI = Dr Gomez-Roca
  - Lyon (CLB): PI = Dr Philippe Cassier

To date 32 patients enrolled in stage I

- 6 screening failure
- 26 patients treated
- 6 cohorts at different doses
  - 50mg QD to 500mg BID
- 11 patients with ovarian carcinoma

Clinical trial design



Clinical trial main objectives

Primary Objective:

- To evaluate the safety and tolerability of EVT801 in subjects with advanced or metastatic solid tumours.
- To determine the maximum tolerated dose (MTD) and / or a recommended Phase 2 dose (RP2D) of EVT801 when administered daily to subjects with advanced or metastatic solid tumours.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of EVT801 following administration in an oral capsule formulation.
- To identify active metabolites of EVT801 in plasma.
- To determine preliminary anti-tumour activity of EVT801 via assessment of overall response rate (ORR).

Exploratory Objectives:

- To calculate progression-free survival (PFS) and overall survival (OS) for patients treated with EVT801.
- To identify biomarkers for EVT801 patient characterization in blood and/or in tissue
- To investigate potential mode of action and pharmacodynamics biomarkers of EVT801
- To correlate PD response and ORR to VEGFR3 expression in tumour samples.

Based on protocol v5.0 dated 25 Nov 2023

Patients main selection criteria for stage 1

INCLUSION CRITERIA

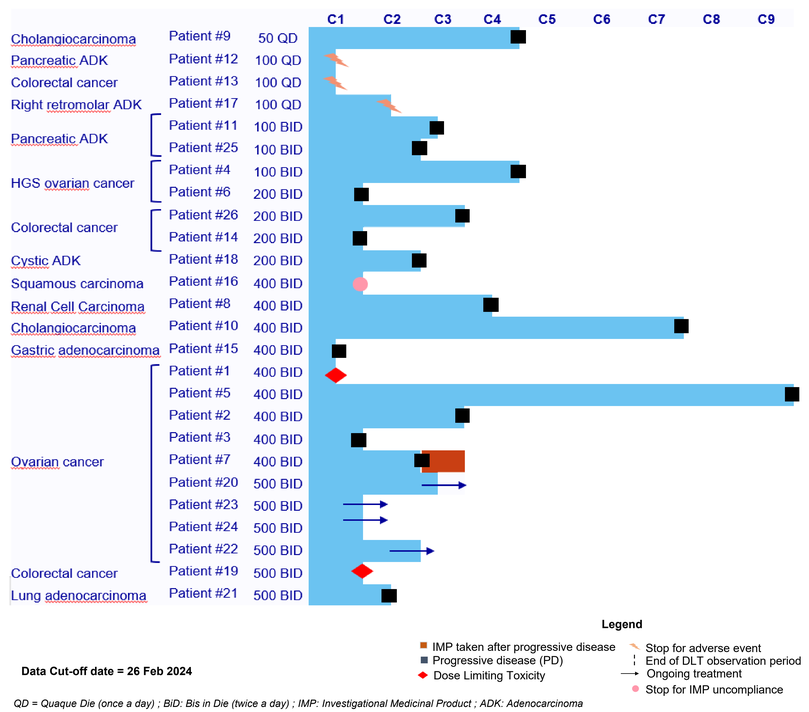
1. Subjects of any gender who are ≥18 years of age at the time of study entry;
2. Histologically-confirmed advanced or metastatic solid tumours, unresponsive to standard treatment, or for whom no standard treatment is available;
3. Measurable or evaluable disease per RECIST 1.1 criteria;
4. ECOG performance status <2;
5. Life expectancy of greater than 3 months, in the opinion of the investigator;
6. Able and willing to provide archived tumour samples, or to undergo pre-treatment tumour biopsy if feasible;
7. Written, signed, and dated informed consent to participate in this study in a format approved by the ethics committee;
8. Adequate organ and bone marrow function at the time of screening including haematology, renal function, liver function and coagulation;
9. a)Women of child-bearing potential must have a negative serum pregnancy test at screening and must agree to use adequate contraception prior to and during study participation and for a period of 6 months after the last dose of EVT801;
   b) Fertile men must agree to use adequate contraception up to 90 days after the last dose of EVT801;
10. Able and willing, in the judgment of the investigator, to meet all protocol-required treatments, investigations and visits.

EXCLUSION CRITERIA

1. Recent history of antitumor therapy administered with the intent of treating cancer prior to study entry, including pharmacological agents, surgical procedures, or radiotherapy; exclusion period will be adapted to the previous line of therapy;
2. Any unresolved toxicity from prior treatment of Grade ≥2, according to NCI CTCAE version 5.0;
3. CNS tumours: symptomatic or steroid-dependent lesions. Cured lesions are acceptable;
4. History of another primary malignancy, unless treated with curative intent and with no known active disease for ≥2 years prior to study entry;
5. Current participation in another interventional or noninterventional clinical trial, or participation within 28 days prior to study entry;
6. Clinically significant cardiac disease or impaired cardiac function;
7. Any disease of the GI tract which renders the subject unable to take oral medications, or which might affect the absorption of oral medicines;
8. Active hemorrhagic syndrome, or presence of tumour in contact with large vessels (e.g. neck, mediastinum, retroperitoneum);
9. Patients with known history of thrombosis of less than 6 months and or currently taking antithrombotic therapies;
10. Acute uncontrolled infection within 1 week prior to starting study treatment;
11. Diagnosis of SARSCoV2, confirmed by PCR within 3 months prior to starting study treatment, unless fully resolved;
12. Known active infection including hepatitis B (HbsAg positive), hepatitis C, or HIV are not eligible;
13. Any preexisting or intercurrent illness or pathology which, in the judgment of the investigator, has the potential to increase the safety risk associated with EVT801 administration, or to confound the results of the study;
14. History of severe allergic reactions to any unknown allergens or to any components of the study drug or to any other VEGFR3 inhibitor;
15. Subjects receiving any medications or substances that are CYP3A4 inhibitors and which may affect the metabolism of EVT801;
16. Subjects not covered by a healthcare insurance system;
17. Subjects deprived of liberty by a judicial or administrative decision.

Based on protocol v5.0 dated 25 Nov 2023

Overview of patients follow-up



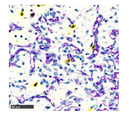
Data Cut-off date = 26 Feb 2024

QD = Quaque Die (once a day) ; BID: Bis in Die (twice a day) ; IMP: Investigational Medicinal Product ; ADK: Adenocarcinoma

EVT801 Biomarkers strategy

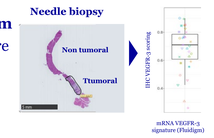
Patients characterization based on VEGFR-3 expression in archival tissues and/or biopsies

- VEGFR-3 signature by IHC: VEGFR-3/CA9/CD8/CD31/ PD-L1



VEGFR-3 & response to immune checkpoint therapies mRNA signatures by Fluidigm

- VEGFR-3 gene signature
- PD-1 response gene signature on archival tissues and/or biopsies



Circulating pharmacodynamic biomarkers

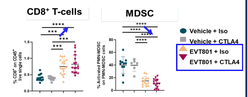
- Bulk RNA sequencing on blood cells at C1D1 vs C2D1 (Paxgene tube)

Safety biomarkers to control hypertension

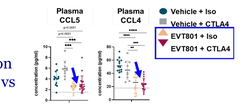
- Blood pressure measurement to control that EVT801 does not induce hypertension (as demonstrated in preclinical model)

Circulating endpoint biomarkers

- **Immunomonitoring** based on CD8+ T-cells /MDSC ratio at C1D1 vs C2D1



- **Proteins signature** based on chemokines involved in inflammation & angiogenesis at C1D1 vs C2D1



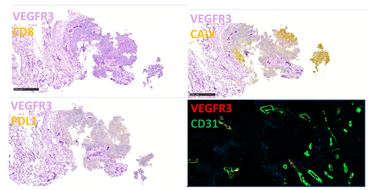
Resting samples will include

- Frozen whole blood & plasma
- Frozen PBMCs
- FFPE biopsies

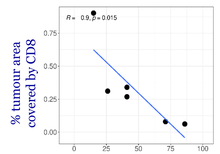
Interest in ovarian cancer patients

- 11 patients with ovarian cancer (10 with high grade serous ovarian cancer (HGS-OC) and 1 with low grade serous ovarian cancer) were included and treated among the 32 patients enrolled.
- This represents a consequent subpopulation with the same disease that allows to perform statistical analysis on clinical and biomarkers data. To date, samples of 6 of these patients have been analyzed for biomarkers

Staining on patients with High Grade Serous Ovarian Cancer (HGS-OC)



Anti-correlation between VEGFR-3 expression and immune infiltration



	VEGFR3 H-score	CD8 quantification	CAIX quantification
Score	71	0,07	35,2
Status	High	Immune desert	High

Working hypothesis

Patients with high VEGFR3 expression poorly infiltrated with CD8pos T-cells could benefit from combination of EVT801 treatment with immune checkpoint inhibitors

Conclusion and next steps

- **By end of February 2024, 26 patients have been treated in six different cohorts for EVT801 doses ranging from 50mg QD to 500mg BID**
- **To date, collection of safety data on enrolled patients in stage 1 showed no safety alert which:**
  - Allows dose escalation until cohort 6 to date
  - Reinforces the strong safety profile of EVT801 observed during the preclinical toxicology studies
- **Ovarian cancer, a poorly immune infiltrated (cold) tumour type expressing VEGFR3, could be an indication of interest for EVT801**
- **Stage 2 will be pivotal to :**
  - Consolidate safety data at RP2D
  - Consolidate our hypotheses on EVT801 mode of action