# Phase I study of EVT801, a VEGFR-3 inhibitor, shows promising clinical activity in HGS ovarian cancer

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## Abstract #P110

## 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 activity on tumour microenvironment**

- Normalization of tumor (lymph)-angiogenesis ↑
- Hypoxia ↓
- CD8$^{pos}$ T-cell infiltration ↑
- Endothelial cell immunotolerance ↑
- Tumour associated macrophages ↓

*Data from Tacconi & al. with SAR131675*

**Tumour metastasis** ↓

**Multiple cooperative modes of action**

**EVT801 (*SAR131675*)***

↓ Cytokines involved in MDSC frequency

↓ Myeloid-derived suppressor cells

** SAR131675, a close analogue of EVT801*

**EVT801 MoA hypothesis: by inhibiting VEGFR3$^{pos}$ tumour blood vessels formation, 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**

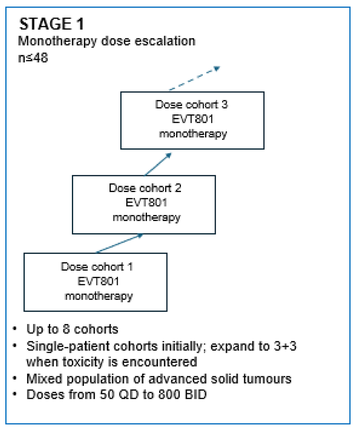
- First-Patient-In in Oct 2021
- 2 clinical sites in France :
  - Toulouse (IUCT): PI = Dr Gomez-Roca
  - Lyon (CLB): PI = Dr Philippe Cassier

**32 patients enrolled in stage 1**

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

## Clinical trial design

**A Phase 1, First-in-Human, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of EVT801 in Patients with Advanced Solid Tumours**




- Up to 8 cohorts
- Single-patient cohorts initially; expand to 3+3 when toxicity is encountered
- Mixed population of advanced solid tumours
- Doses from 50 QD to 800 BID

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## 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:**

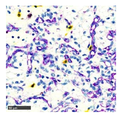
- To calculate progression-free survival (PFS) and overall survival (OS) for patients treated with EVT801.
- To identify biomarkers for EVT801 patient characterization in blood and/or in tissue
- To investigate potential mode of action and pharmacodynamics biomarkers of EVT801
- To correlate progressive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

**Based on protocol v5.0 dated 25 Nov 2023**

## EVT801 Biomarkers strategy

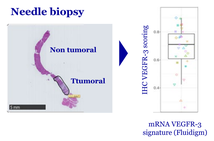
**Patients characterization based on VEGFR-3 expression in archival tissues and/or biopsies**

- 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**

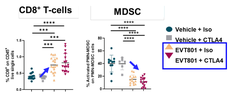
- Bulk RNA sequencing on blood cells at C1D1 vs C2D1 (Paxgene tube)

**Safety biomarkers to control hypertension**

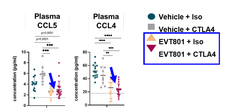
- Blood pressure measurement to control that EVT801 does not induce hypertension (as demonstrated in preclinical model)

**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




Data were obtained on orthotopic 4T1 tumor mouse model

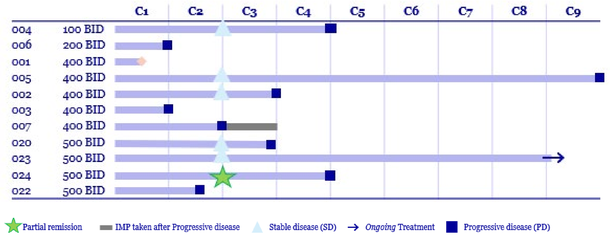
**Resting samples will include**

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

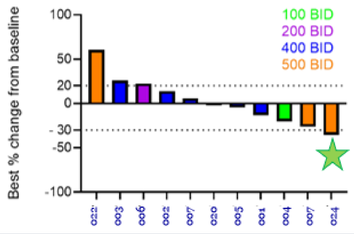
## Overview of patient's follow-up Focus on Ovarian cancer patients

- 11 patients with ovarian cancer (10 with high grade serous ovarian cancer (HGS-OC) and 1 with low grade serous ovarian cancer) that have received multiple lines of previous treatments were included 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

**Number of cycles of treatment**
Status on 11th of September 2024



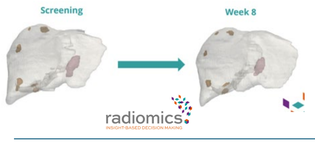

**Tumor best responses plot**




- **These 11 patients with ovarian cancer had an average age of 67 years (range: 56-76) and a median time from diagnosis of nine years.**
- **Forty-six percent (46%) of the ovarian cancer patients had stable disease or better for at least three cycles of EVT801 therapy.**
- **Patient 024 had a partial response (-39% decrease) at the end of cycle 2**

## Case study: Analysis of patient 024 – 3D renderings by Radiomics.org

**The 3D renderings** show the evolution of the lesions from screening to week 8 with a significant reduction of volume




**The volumetric analysis shows a partial response** from screening to week 8

| Lesion | Screening | Week 8 (Week 8-to/to) | |
|---|---|---|---|
| Liver lesions | 4,83 cm3 | 3,16 cm3 | -34,5 % |
| Abdominal lymph node | 7,22 cm3 | 4,47 cm3 | -38,2 % |
| Total | 12,06 cm3 | 7,63 cm3 | -36,7% |

**Potential disease response= -39%**

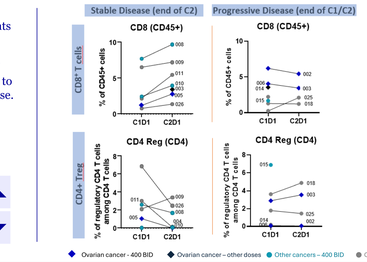
- Some of the quantified radiomics features are **clearly impacted by the treatment**
- Following EVT801 treatment:
  - The lesions became more homogenous & less dense intensity-wise
  - The lesions became more compact

## Immunomonitoring: analysis on patients with Stable Disease vs Progressive disease

**Working hypothesis:** patients with stable disease have an increase of circulating CD8$^+$ T-cells and a decrease of CD4$^+$ Treg-cells in comparison to patients with progressive disease.

**Circulating CD8$^{pos}$ T-cell** ▲

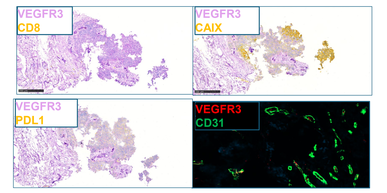
**Circulating CD4$^{pos}$ Treg-cell** ▼




- **Patients with stable disease in comparison to patients with progressive disease :**
  - **Tendency of an increase of circulating CD8$^+$ T-cells**
  - **Tendency of a decrease of circulating CD4$^+$ Treg-cells.**
- **Blood immunomonitoring should be performed at different cycles of treatment(not only after one cycle) during the phase 2 clinical trial to confirm these trends**

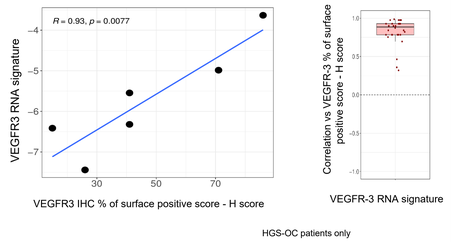
## VGFR3 expression in patients with High Grade Serous Ovarian Cancer enrolled in EVT801 clinical trial phase 1

**Immunohistochemistry: a case study**




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

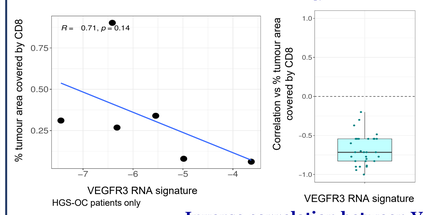
**Aggregated VEGFR3 gene signature correlation with VEGFR3 histology**



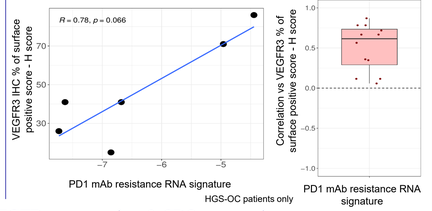

**High correlation between VEGFR3 staining by histology and VEGFR3 gene signature allowing to compare RNA signatures with other histology readouts**

## Correlation between VEGFR3 and immune profile in patients with High Grade Serous Ovarian Cancer enrolled in EVT801 clinical trial phase 1

**Individual and aggregated VEGFR3 gene signature Anti-correlation with CD8 histology**




**Individual and aggregated PD1 mAb resistance gene signature correlation with VEGFR3 histology**




**Inverse correlation between VEGFR3 expression & CD8 expression**
**Positive correlation between VEGFR3 expression & PD1 mAb response signature**

## Conclusion and next steps

- **Stage 1 is complete - primary and secondary endpoints achieved:**
  - 32 patients included in the study with 26 patients treated
  - 6 dosing cohorts completed ranging from 50mg QD to 500mg BID
  - MTD identified as 500mg BID with 400mg BID being RP2D as monotherapy
  - Patients with eleven different cancer types (ex. colon, renal cell, pancreatic) were enrolled in the study, with advanced ovarian cancer being the most prevalent indication (11 patients).
  - Number of patients have remained on treatment for two or more cycles with 9 reaching cycle 3 or greater (two reached cycle 9)
- **EVT801 was well tolerated across all doses with majority of toxicities being mild to moderate and transient in nature:**
  - Reinforces the safety profile of EVT801 observed during the preclinical toxicology studies
- **Biomarkers have shown strong VEGFR3 expression in some indications, and we have observed encouraging clinical activity in High Grade Serous ovarian cancer**
- **Next clinical trial will be pivotal to:**
  - Consolidate safety data at RP2D and our hypotheses on EVT801 mode of action
  - Validate High Grade Serous Ovarian Cancer as indication of choice for clinical trial phase 2 for standalone therapy or in combination with standard-of-care