VEGFR-3 expression profiling by histology and biomarkers strategy to classify patient population for the selective VEGFR-3 inhibitor EVT801

Carlos Gomez-Roca[1], Philippe Cassier[2], Philippe Rochaix[1], Jean-Pierre Delord[1], Lise Davenne[3], Pierre-Benoit Ancey[3], Oona Delpuech[3], Vincent Piras[3], Michael Paillasse[3], John Friend[4], Michael Fitzgerald[4] & Pierre Fons[3]*

1) Oncopole IUCT, Toulouse, France, 2) Centre Léon Bérard, Lyon, France, 3) Evotec, Toulouse, France, 4) Kazia Therapeutics, Sydney, Australia

**Corresponding author : pierre.fons@evotec.com*

FPN: 137P

EVT801: A differentiating anti-tumour approach

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

Cancer Research Communications (2022) 2 (11): 1504–1519.

EVT801 activity on tumour microenvironment

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

Data from Tacconi & al. with SAR131675

EVT801 (*SAR131675*)*

Cytokines

Tumour metastasis ↓

- Multiple cooperative modes of action

Blood

↓ Myeloid-derived suppressor cells

EVT801 MoA hypothesis: EVT801 would induce VEGFR3^{pos} tumour blood vessels normalization, reducing hypoxia and improving CD8^{pos} T-cells infiltration

EVT801 in Phase I clinical trial KZA-0801-101

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Clinical trial design

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

Sponsor: Kazia Therapeutics Ltd
Product : EVT801
EudraCT: 2021-002483-47 / NCT: NCT05114668

Clinical sites (France):
IUCT-Oncopole, Toulouse - PI : Dr Gomez-Roca
Centre Léon Bérard, Lyon – PI : Dr Philippe Cassier

STAGE 1 (Ongoing) - Monotherapy Dose Escalation, n ≤ 48

Dose Cohort 1 EVT801 monotherapy → Dose Cohort 2 EVT801 monotherapy → Dose Cohort 3 EVT801 monotherapy → … → Dose Cohort 8 EVT801 monotherapy

- Mixed population of advanced solid tumors
- Single-patient cohorts initially, expand to 3+3 when toxicity is encountered
- ***Dose escalation*** up to 8 cohorts :
  50mgQD→100mgQD→100mgBID→200mgBID→400mgBID→500mgBID→600mgBID→800mgBID

MTD RP2D

STAGE 2 - Biomarker / PD Expansion Cohort n = 12

- 6-patients PD Cohort in Soft Tissue Sarcoma
- 6-patients PD Cohort in Renal Cell Carcinoma

STAGE 3 (Optional): IO combination Dose Escalation, solid tumors, n ≤ 36 — Dose Cohort 1 EVT801 + SCI combination → Dose Cohort 2 EVT801 + SCI combination

Approvals from regulatory bodies obtained in September 2021

- First-Patient-In in Oct 2021
- 2 clinical sites in France (Toulouse IUCT and Lyon CLB)

To date 26 patients included in stage I

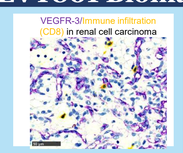
- 20 patients treated
- 5 cohorts (doses) reached up to 400 BID

NCT05114668

EVT801 Biomarkers strategy

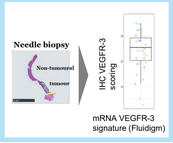
Patient characterization based on VEGFR-3/CAIX/CD8 expression on archival tissues and/or biopsies

- VEGFR-3 protein signature by histology
- VEGFR-3/CAIX/CD8/CD31/PD-L1



VEGFR-3 & Resistance to PD-1 mAb mRNA signatures on archival tissues and/or biopsies:

- VEGFR-3 mRNA signature by Fluigdim
- PD-1 mAb resistance mRNA signature



Unbiased biomarker:

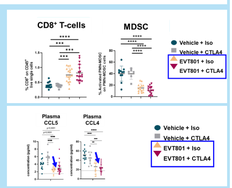
- Total RNA sequencing on blood cells at C1D1 vs C2D1

Safety biomarkers to control hypertension:

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

Circulating endpoint biomarkers:

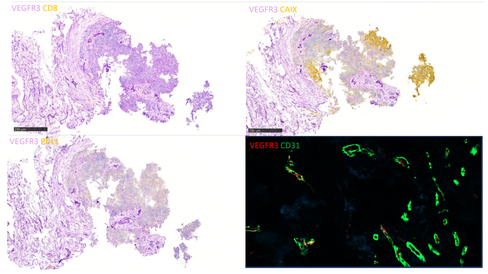
- **Immunomonitoring** based on CD8^{pos} T-cells /MDSC ratio
- **Proteins signature** based on chemokines involved in inflammation & angiogenesis



Resting samples will include:

- Frozen plasma
- Frozen whole blood
- Frozen PBMCs

Example of histology labelling on HGS-OC patient

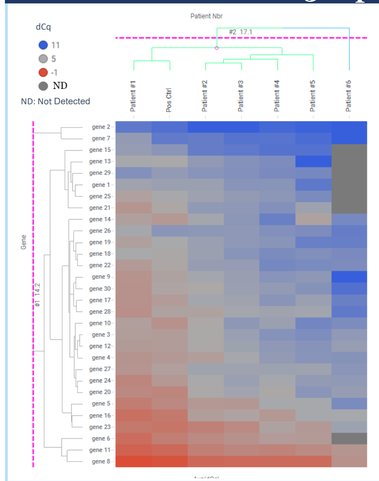


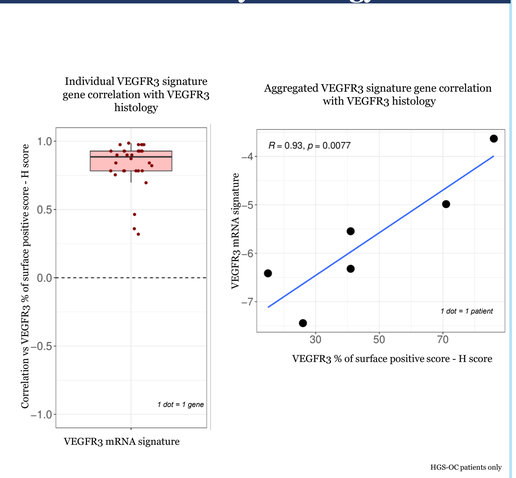
	VEGFR3 H-score (% of positive surface H-score)	CD8 quantification (% of tumour surface)	CAIX quantification (% of tumour surface)
Score	71	0,07	35,2
Status	High	Immune desert	High

Correlation analysis in ovarian cancer patients

- **Data analysis was performed on 6 patients with high grade serous ovarian cancer (HGS-OC) included into the clinical trial**
- **Hypotheses need to be confirmed with inclusion of new patients in different indications**
- **Bioinformatics team has designed signatures based on VEGFR3 associated genes and genes regulated differentially in resistant versus sensitive patients to PD1 mAb therapy**
- **Stage 2 will be pivotal to consolidate our hypotheses**

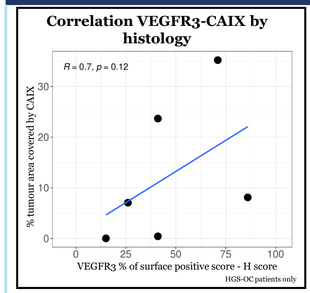
Correlation of VEGFR3 expression detected by histology & mRNA

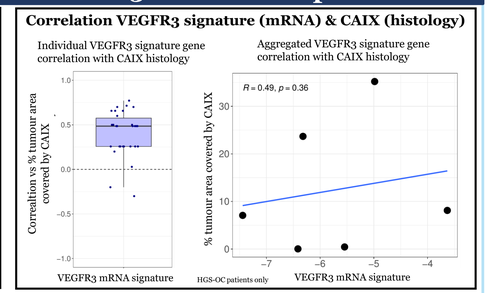




Very strong correlation between VEGFR3 by histology and VEGFR3 mRNA signature allowing to compare mRNA signatures with other histology readouts

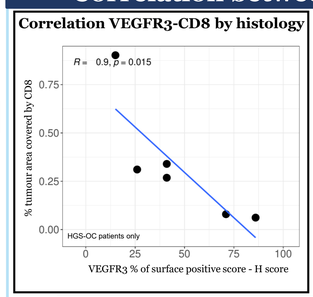
Correlation between VEGFR3 and CAIX expression

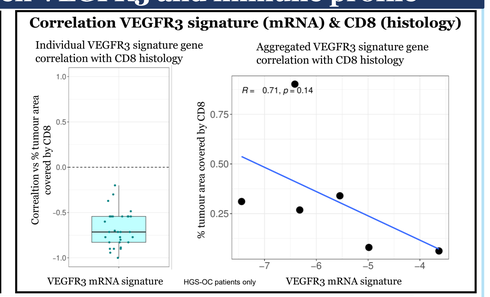




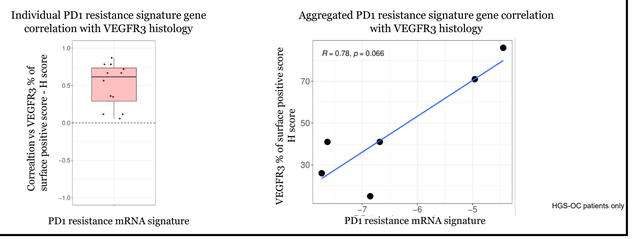
Moderate positive correlation between VEGFR3 expression and CAIX by histology

Correlation between VEGFR3 and immune profile



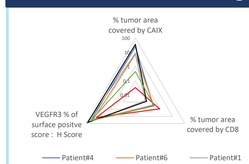


Correlation VEGFR3 (histology or mRNA signature) & PD1 mAb resistance signature



High inverse correlation between VEGFR3 expression & CD8 expression and positive correlation between VEGFR3 expression & PD1 mAb resistance signature

Conclusion and next steps



Radar chart illustrating the main analysed biomarkers for all HGS-OC patients in the study: CD8 infiltration, level of hypoxia (CAIX) and VEGFR3 expression in vessels are represented for all HGS-OC patients independently.

- **In HGS-OC patients enrolled, VEGFR3 expression tends to be positively correlated with hypoxia and PD1 resistance signature & negatively correlated with CD8^{pos} T-cells infiltration.**
- **The correlations in HGS-OC patients are highly encouraging and informational while aligning with the EVT801 mechanism of action**
- **Patients with hypoxic HGS-OC tumour poorly infiltrated with CD8^{pos} T-cells and with high VEGFR3 expression could benefit from EVT801 treatment**