Biomarkers analysis on samples from patients in EVT801 clinical trial: Patient characterization and immunomonitoring

Lise Davenne[1], Michael Fitzgerald[2], Pierre-Benoit Ancey[1], Oona Delpuech[1], Céline Poussereau-Pomié[1], Michael Esquerre[1], Michael Paillasse[1], Marie Mandron[1], Philippe Rochaix[3], Maha Ayyoub[3], Clara Maria Scarlata[3], Christine Caux[4], Christophe Caux[4], Philippe Cassier[4], Carlos Gomez Roca[3], Jean-Pierre Delord[3], John Friend[2] and Pierre Fons[1].

[1]Evotec, Toulouse, France ; [2]Kazia Therapeutics Ltd, Sydney, Australia ; [3]Institut Universitaire du Cancer Toulouse-Oncopole (IUCT-O), Toulouse France ; [4]Centre Léon Bérard, Lyon, France.

For researchers:

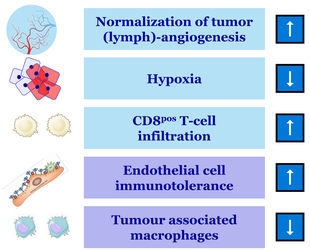
Abstract #1059

EVT801: A differentiating anti-tumour approach

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

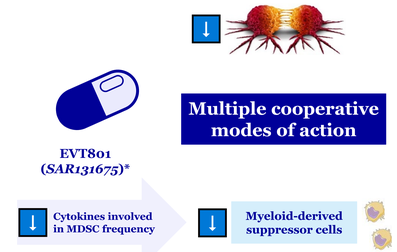
Cancer Research Communications (2022) 2 (11): 1504–1519.

EVT801 activity on tumour microenvironment



Data from Tacconi & al. with SAR131675

Tumour metastasis



*SAR131675, a close analogue of EVT801

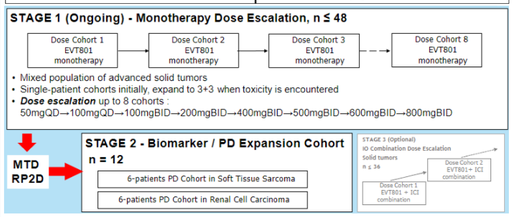
EVT801 MoA hypothesis: by destructing VEGFR3pos tumour blood vessels, EVT801 would induce tumour blood vessels normalization, reducing hypoxia and improving CD8 T-cells infiltration

EVT801 in Phase I clinical trial KZA-0801-101

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



NCT05114668

Approvals from regulatory bodies obtained in September 2021

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

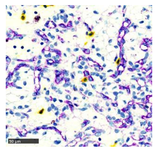
To date 32 patients enrolled in stage I

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

EVT801 Biomarkers strategy

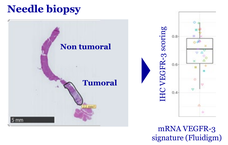
Patients characterization based on VEGFR-3 expression in archival tissues and/or biopsies

- 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

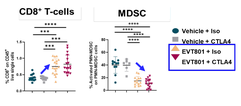
- Bulk RNA sequencing on blood cells at C1D1 vs C2D1 (Paxgene tube)

Safety biomarkers to control hypertension

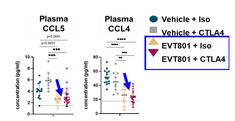
- Blood pressure measurement to control that EVT801 does not induce hypertension (as demonstrated in preclinical model)

Circulating endpoint biomarkers

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



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



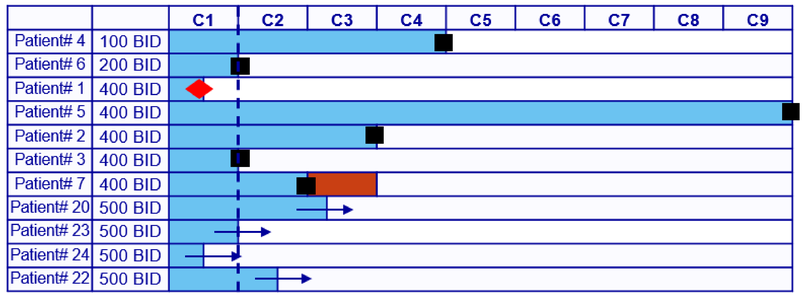
Resting samples will include

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

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**
- **Bioinformatics team has designed signatures based on VEGFR3 associated genes and genes regulated differentially in resistant versus sensitive patients to PD1 mAb therapy**

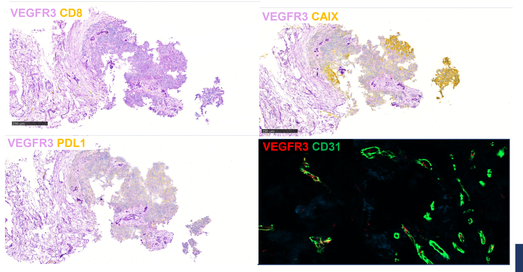
Ovarian cancer patients follow-up



Data Cut-off date = 21 Feb 2024

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

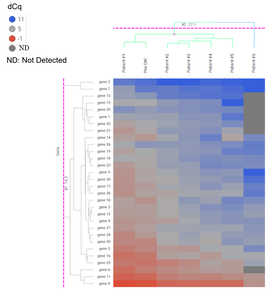
Example of histology staining on patient with High Grade Serous Ovarian Cancer (HGS-OC)



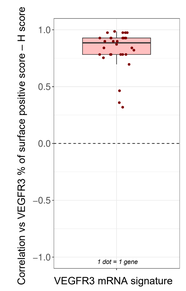
	Score	Status
VEGFR3 H-score (% of positive surface H-score)	71.0	High
CD8 quantification (% of tumour surface)	0.07	Immune desert
CAIX quantification (% of tumour surface)	35.2	High

Correlation of VEGFR3 expression detected by histology & mRNA

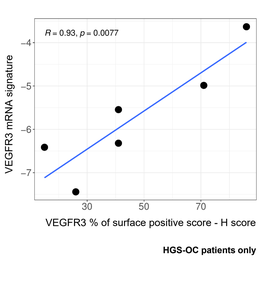
VEGFR3 gene signature heatmap of enrolled HGS-OC patients



Individual VEGFR3 gene signature correlation with VEGFR3 histology



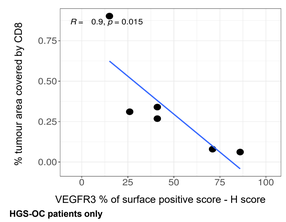
Aggregated VEGFR3 gene signature correlation with VEGFR3 histology



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

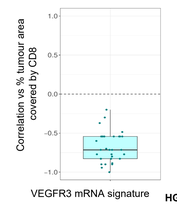
Inverse correlation between VEGFR3 and immune profile

Correlation VEGFR3-CD8 by histology

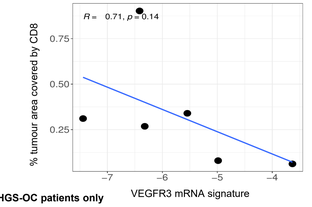


Correlation VEGFR3 gene signature (mRNA) & CD8 (histology)

Individual VEGFR3 gene signature correlation with CD8 histology



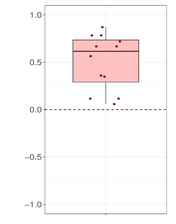
Aggregated VEGFR3 gene signature correlation with CD8 histology



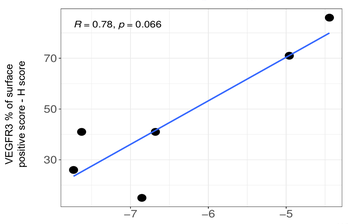
High inverse correlation between VEGFR3 expression & CD8 expression

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

Individual PD1 resistance gene signature correlation with VEGFR3 histology



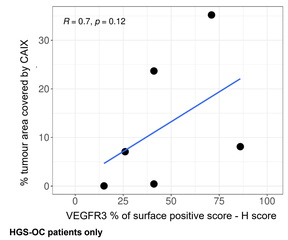
Aggregated PD1 resistance gene signature correlation with VEGFR3 histology



Positive correlation between VEGFR3 expression & PD1 mAb resistance signature

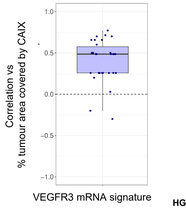
Correlation between VEGFR3 and CAIX expression

Correlation VEGFR3-CAIX by histology

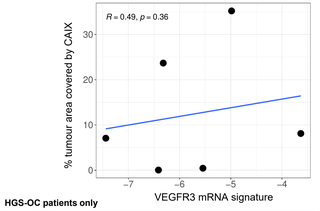


Correlation VEGFR3 gene signature (mRNA) & CAIX (histology)

Individual VEGFR3 gene signature correlation with CAIX histology

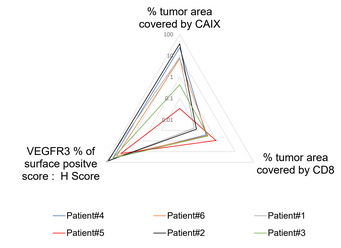


Aggregated VEGFR3 gene signature correlation with CAIX histology



Moderate positive correlation between VEGFR3 expression and CAIX by histology

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 inversely correlated with CD8pos T-cells infiltration and positively correlated with hypoxia and PD1 response signature.
- The results in HGS-OC patients are highly encouraging and informational while aligning with the hypothesized EVT801 mechanism of action
- Patients with hypoxic HGS-OC tumour poorly infiltrated with CD8pos T-cells and with high VEGFR3 expression could benefit from EVT801 treatment
- Stage 2 will be pivotal to consolidate our hypotheses